Single Technology Appraisal

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

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The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

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   a. Full submission

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3. **Patient group, professional group, and NHS organisation submissions** from:
   a. XLH UK

4. **Expert personal perspectives** from:
   a. Professor Kassim Javaid – clinical expert, nominated by XLH UK UK
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Burosumab for treating X-linked hypophosphataemia in adults

ID3822

Document B

Company evidence submission

26 April 2023

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List of abbreviations

Abbreviation	Definition
$1,25(OH)_2D$	1,25-dihydroxyvitamin D (calcitriol)
6MWT	Six-minute walk test
ADA	Anti-drug antibodies
AE	Adverse event
ALANEPE	Asociación Latinoamericana de Nefrología Pediátrica
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ATP	Adenosine triphosphate
BALP	Bone-specific alkaline phosphatase
BFI	Brief Fatigue Inventory
BL	Baseline
BMI	Body mass index
BNF	British National Formulary
BPI-Q3	Brief Pain Inventory-Short Form question 3
BPI-SF	Brief Pain Inventory-Short Form
cAMP	Cyclic adenosine monophosphate
CC	Complexity and comorbidity
CE	Conformité Européene
CEM	Cost-effectiveness model
CI	Confidence interval
CPRD	UK Clinical Practice Research Datalink database
CTx	Carboxy-terminal collagen crosslinks
DEXA	Dual-energy X-ray absorptiometry
DMP	Disease monitoring programme
EAP	Early Access Programme
EL	Elective inpatient
EMA	European Medicines Agency
ENT	Ear, nose, and throat
EPAR	European Medicines Agency public assessment report
EQ5D	EuroQol health-related quality of life questionnaire
EQ5D-5L	5-level EuroQol health-related quality of life questionnaire
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
EU	European Union
FAS	Full analysis set
FCE	Finished consultant episode
FGF23	Fibroblast growth factor 23
FOC	Free of charge
GEE	Generalised estimating equation
GFR	Glomerular filtration rate
GLM	Generalised linear model
GP	General practitioner
HES	Hospital Episode Statistics

HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly specialised technologies guidance
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
IFU	Information for use
IgG1	Immunoglobulin G subclass 1
IMD	Index of Multiple Deprivation
Int.	International
iPTH	Intact parathyroid hormone
KRN23	Burosumab
LLN	Lower limit of normal
LS	Least squares
LSM	Least squares mean
LYG	Life years gained
MCID	Minimum clinically important difference
MCS	Mental Component Summary
MEdDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMR	Mixed methods research
NEL	Non-elective long stay
NES	Non-elective short stay
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRS	Numerical rating scale
ONS	Office for National Statistics
OR	Odds ratio
P1NP	procollagen type 1 n-terminal propeptide
PAS	patient access scheme
PASS	Post-Authorisation Safety Study
PCNL	Percutaneous nephrolithotomy
PCS	Physical Component Summary
PD	Pharmacodynamics
PHEX	Phosphate-regulating endopeptidase X-linked
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTH	Parathyroid hormone
Q1	First quarter
QALY	Quality-adjusted life year
RCT	Randomised clinical trial
RIS	Research Information Systems
RWD	Real-world data
RWE/D	Real-world evidence/data

SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36v2	36-item Short Form Health Survey version 2
SmPC	Summary of Product Characteristics
SoC	Standard of care
SV	Study visit
SWL	Shock wave lithotripsy
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TIO	Tumour-induced osteomalacia
TmP/GFR	Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate
TRP	Tubular reabsorption of phosphate
TUG	Timed Up and Go test
UCLH	University College London Hospitals NHS Foundation Trust
UK	United Kingdom
ULN	Upper limit of normal
URS	Ureteroscopy
US	United States
VAS	Visual Analogue Scale
VITDT	1,25-dihydroxyvitamin D total
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphataemia

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission focuses on the adult population part of the technology's marketing authorisation. Burosumab has a marketing authorisation in the UK "for the treatment of X-linked hypophosphataemia (XLH) in children (aged 1 to 17 years) with radiographic evidence of bone disease, and in adults".[1]

This submission focuses on a sub-group of the licensed indication in adults, namely adults (aged ≥18 years) with a confirmed diagnosis of XLH who have chronic hypophosphataemia, symptoms that include a Brief Pain Inventory (BPI) "worst pain over the last 7 days" score of ≥4 (upper limit of mild pain), and for whom conventional therapy is unsuitable. Conventional therapy may be unsuitable due to ineligibility (e.g. patients with contraindications, such as presence of toxicities developed on conventional treatment such as renal or parathyroid toxicity), or intolerance, or insufficient efficacy (i.e. failure to normalise phosphate levels, or persistence of symptoms [e.g. fractures, pain, stiffness, fatigue] despite treatment). UK clinical experts have advised that BPI worst pain questionnaire can be feasibly used in clinical practice (see Appendix Q).

This population is the relevant population for NHS clinical practice because it is in line both with published clinical guidelines[2,3] and with draft clinical practice recommendations developed by UK clinicians for use in the NHS.[4] It is also in line with the population being treated in the NHS under the Early Access Programme (see p.8 of the application form).[5] **Burosumab would not be used in the whole population of adults with XLH, because clinical guidelines recommend that adults with XLH are only treated if they are highly symptomatic**.[2,3,6] **They state that routine treatment of asymptomatic patients is not recommended.** The guidelines define symptoms that warrant active treatment as musculoskeletal pain, pseudofractures, dental issues, planned orthopaedic or dental surgery or biochemical evidence of osteomalacia. The guidelines further recommend that patients are initially treated with conventional treatment, and that burosumab is considered if patients are intolerant to conventional therapy or conventional therapy is not effective. Clinical guidelines are described in Section 1.3.6.2 and the positioning of burosumab in Section 1.3.8.

Importantly, the requirement for BPI "worst pain in last 7 days" score of ≥4 in the submission population aligns with the population of the pivotal trial (study CL303).[7] Clinical experts in the

UK have confirmed that use of the BPI (measured using the BPI “worst pain” question with a recall period of 7 days), is feasible in clinical practice.

The population covered by the submission are highly symptomatic, with profound ongoing effects from this very rare disease on their physical and mental health, ability for everyday activities, social and economic participation and family life (see Sections 1.3.2 and 1.3.5 for details on the burden of XLH). They do not have any other intervention to treat XLH apart from burosumab. The decision problem is summarised in Table 1.

Table 1 The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with X-linked hypophosphataemia	The proposed population for submission is: adults (aged ≥18 years) with a confirmed diagnosis of XLH who have chronic hypophosphataemia, symptoms that include a Brief Pain Inventory (BPI) "worst pain in last 7 days" score of ≥4 (upper limit of mild pain), and for whom conventional therapy is unsuitable due to ineligibility (e.g. patients with contraindications, such as presence of toxicities developed on conventional treatment such as renal or parathyroid toxicity), or intolerance or insufficient efficacy (i.e. failure to normalise phosphate levels, or persistence of symptoms despite treatment).	This is in line with consensus statements on treatment of XLH, which recommend treatment of XLH in adults only if they are symptomatic.[2 3] It reflects the population that will receive treatment with burosumab in the NHS, and aligns with the criteria of burosumab's Early Access Programme (EAP) in England, which enabled access for adults "who are experiencing persistent and debilitating symptoms despite prior treatment with conventional therapy."[5] Draft clinical practice recommendations by expert UK clinicians also recommend burosumab for adults when conventional treatment is not tolerated or not effective.[6] The positioning also aligns with the trial population, in which adult patients had to have a worst pain score over the last 7 days of ≥4 on the BPI to be eligible.[7] Most patients (90.3%) had received prior therapy with both oral phosphate and active vitamin D metabolites or analogues, and almost all of the remainder had been treated with one or the other (3.0% had received only phosphate and 4.5% only vitamin D metabolites or analogues). In total, 82.8% had received conventional therapy after the age of 18 years.[8]
Intervention	Burosumab	In line with NICE scope	
Comparator(s)	Established clinical management without burosumab (including vitamin D analogues and phosphate supplementation)	The comparator is best supportive care. This corresponds to established clinical management without burosumab in the submission population, for whom conventional therapy is not suitable.	

Outcomes	The outcome measures to be considered include: • fractures • pain (including bone pain, joint pain and joint stiffness) • motor skills • tooth loss and pain • neurological complications (including problems with hearing and balance, and spinal cord compression) • renal function • parathyroid hormone levels • alkaline phosphatase levels • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).	The following outcomes (in bold) will be included in the base case economic analysis: • **Fracture incidence (including upper limb, vertebrae/spinal, foot, fibia/fibula, femur/pelvis, and other fractures)** • **Stiffness, pain and fatigue as reflected in WOMAC scores from the trial** • **Mortality** • **Health-related quality of life for patients. This is captured via mapping of WOMAC scores to EQ-5D utilities** • **Health-related quality of life for informal caregivers and close family** The following outcomes are considered to be largely the result of hypophosphataemia in utero and in childhood, and therefore unlikely to be reversible in adulthood. They will be modelled as scenario analyses: • Dental problems (tooth loss and pain) • Spinal stenosis and need for spinal surgery • Tinnitus and hearing loss The items above are in line with the draft NICE scope. There are, however, some differences from the draft scope. These are described below together with the rationale for the difference. • Serum phosphate levels are considered in the model rather than alkaline phosphatase levels, as serum phosphate level is the primary driver of morbidity in adults with XLH. Serum phosphate is modelled as normalised (≥ the lower limit of normal) or non-normalised. Alkaline phosphate results from the pivotal trial (study CL303) are reported but not modelled. • Joint stiffness and motor function (corresponding to 'motor skills' in the draft scope) are modelled via the WOMAC score as measured in the pivotal trial. Motor function was also assessed in the trial using the 6-minute walk test (6MWT) and the Timed Up and Go test (TUG). The 6MWT was an exploratory outcome. Patients on burosumab had a significant improvement at 24 weeks whereas those on placebo had a slight decrease in distance walked. This measure is not incorporated in the model because it is narrow in scope compared with WOMAC score, which was preferred as a more holistic measure. The TUG is subject to the same limitation, and anyway could not be modelled as few patients had a baseline value recorded. • Pain is modelled via WOMAC score, which includes pain in its questionnaire.

		• Parathyroid hormone levels are not modelled because hyperparathyroidism is largely an adverse effect of conventional treatment with oral phosphate supplements rather than a feature of XLH itself.[2,3] As conventional treatment is not a comparator in the model (because the submission population are patients who are currently untreated because conventional treatment is unsuitable), modelling of parathyroid hormone levels is not relevant. • Renal function is not modelled because renal dysfunction is not a common feature in adults with XLH who are not receiving conventional treatment.
Subgroups to be considered	None specified.	None.
Time horizon	As reference case	Lifetime time horizon.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances.	Several issues relating to equality are relevant to the submission. Adults with symptomatic XLH have a long-term disability, which is a protected characteristic under the Equality Act 2010. XLH is also a very rare disease. The UK Rare Disease Framework recognises four key priorities, including helping patients to get a faster diagnosis and improving access to specialist care, treatment and drugs.[9,10] It also cites the need to reduce the health inequalities faced by people living with rare conditions. Finally, people with XLH are more likely than the general population to suffer socioeconomic disadvantage, and are disproportionately located in the lowest two socioeconomic quintiles as measured by Index of Multiple Deprivation (IMD).[11]

1.2 Description of the technology being evaluated

In appendix C include the summary of product characteristics or information for use, and the UK public assessment report, scientific discussion or drafts.

Table 2 Technology being evaluated

UK approved name and brand name	Burosumab (UK approved name) CRYSVITA 10 mg solution for injection CRYSVITA 20 mg solution for injection CRYSVITA 30 mg solution for injection
Mechanism of action	Burosumab is a recombinant human monoclonal antibody (IgG1) that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23). By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney and increases serum concentration of 1,25 dihydroxy-Vitamin D.[1] As shown in Figure 2, (p. 20), burosumab addresses the underlying mechanism of XLH (excessive levels of FGF23) and restores phosphate homeostasis, resulting in increased serum phosphate levels.
Marketing authorisation/CE mark status	Burosumab received conditional marketing authorisation from the European Medicines Agency (EMA) in February 2018 for paediatrics, and in October 2020 received an extension of the licence to include the adult XLH population. The conditional marketing authorisation was converted to a standard marketing authorisation in the UK for the treatment of X-linked hypophosphataemia in children (ages 1-17) and in adults, on 14th October 2022.[1] Burosumab was granted orphan drug designation by the EMA in October 2014 for the treatment of XLH (designation EU/3/14/1351)[12]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Burosumab is indicated for the treatment of X-linked hypophosphataemia (XLH), in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.[1] Burosumab is contraindicated in the following groups: • Hypersensitivity to the active substance or excipients • Concurrent administration with oral phosphate, active vitamin D analogues. • Fasting serum phosphate above the normal range for age due to the risk of hyperphosphatemia. • Patients with severe renal impairment or end stage renal disease.
Method of administration and dosage	Treatment should be initiated by a physician experienced in the management of patients with metabolic bone diseases.[1] Oral phosphate and active vitamin D analogues (e.g. calcitriol) should be discontinued 1 week prior to initiation of treatment. Vitamin D replacement or supplementation with inactive forms may be started or continued as per local guidelines under monitoring of serum

	calcium and phosphate. At initiation, fasting serum phosphate concentration should be below the reference range for age.[1] **Dosing and administration** Burosumab is administered by subcutaneous injection in the upper arm, abdomen, buttock or thigh. • The recommended starting dose in adults is 1.0 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, given every 4 weeks.[1] **Monitoring and dose adjustment** After initiation of treatment, fasting serum phosphate should be measured every 2 weeks for the first month, every 4 weeks for the following 2 months and thereafter as appropriate. Fasting serum phosphate should be measured 2 weeks after the previous dose of burosumab. • If serum phosphate is within the normal range, the same dose should be continued. • If serum phosphate is above the upper limit of normal range, the next dose should be withheld, and the serum phosphate level reassessed within 2 weeks. The patient must have serum phosphate below the normal range before restarting burosumab. • Once serum phosphate is below the normal range, treatment may be restarted at half the initial starting dose up to a maximum dose of 40 mg every 4 weeks. Serum phosphate should be reassessed 2 weeks after any change in dose.[1] **Self-administration** Experience via the EAP has demonstrated that for the majority of patients, self/carer-administration may be suitable. Once no immediate dose modifications are anticipated, administration of burosumab can be performed by an individual who has been trained in injection techniques (training costs are paid by Kyowa Kirin). The first self-administered dose after drug initiation or dose change should be conducted under the supervision of a healthcare professional. Clinical monitoring of the patient, including monitoring of phosphate levels, must continue as required and as outlined above.[1] **Continuation and stopping of treatment** According to the proposed stopping rules for treatment used in the economic model, only patients achieving a clinically relevant benefit from burosumab remain on long-term treatment. Thus, continuation of treatment after year 1 in the model is based on a requirement of reaching serum phosphate levels above LLN after 24 weeks of treatment and an improvement in WOMAC total score at 12 months after starting treatment. Clinical experts have agreed that this is feasible to apply in clinical practice (see Appendix Q).
Additional tests or investigations	Burosumab does not require a companion diagnostic test or additional investigations beyond current standard practice for the diagnosis and assessment of XLH.
List price and average cost of a	Burosumab is presented as single-use vials of solution for injection at three different concentrations, with list prices per vial as follows:

course of treatment	• 10 mg solution for injection: £2,992 • 20 mg solution for injection: £5,984 • 30 mg solution for injection: £8,976 • Average cost of treatment for 1 year depends on patient weight. The average annual cost in the model is [redacted]
Patient access scheme (if applicable)	[redacted]

1.3 Health condition and position of the technology in the treatment pathway

Key points

- XLH is a very rare, life-long genetic disorder estimated to affect approximately 298 adults in England. Clinical presentation varies, and not all have severe symptoms that make them eligible for treatment with burosumab (see Budget Impact document for numbers eligible).
- XLH is characterised by low levels of phosphate in the blood caused by excess fibroblast growth factor-23 (FGF23).[14,15]
    - Phosphate plays a vital role in many key biological processes, and is essential for healthy development and maintenance of bone, the structure and function of muscle, and healthy development of teeth.[2,3,14]
    - Clinical manifestations of XLH usually begin in early childhood, causing soft, weakened bones (osteomalacia), lower limb deformities, pain and stiffness, short stature and dental abscesses.[14]
- The chronic and debilitating nature of XLH continues into adulthood and is life-long,[2,3,14,16,17] due to ongoing hypophosphataemia, and also to direct effects of FGF23.[14,15] Osteomalacia persists in adulthood and causes bone pain and increased risk of fractures.[2,15]
    - Painful, slow-healing/non-healing fractures are a common result of hypophosphataemia-driven osteomalacia: 43-47% in a sample of 336 adults with XLH had a history of fracture, and prevalence increased with age.[17]

- Hypophosphataemia in adulthood causes ongoing pain, stiffness and fatigue. For many adults with XLH these are highly burdensome and significantly affect their mobility and ability to perform daily activities, and limit their social, family and work life. [3,11,16,18]
    - An analysis of CPRD GOLD-ONS suggests that life expectancy for adults with XLH in the UK is significantly shortened (hazard ratio [HR] = 2.88; 95% CI 1.18-7.00).[19]
    - An additional, independent analysis found a similar HR (2.33 [95% CI: 1.16 – 4.67, P = 0.02], see Appendix R.
- Mental health is often profoundly affected:
    - A recent analysis of UK primary care data found that adults with XLH are almost three times more likely to suffer from depression than the general population (OR 2.95 [95% CI: 1.47, 5.92]).[11]
    - Adults with XLH commonly report low self-esteem, frustration and depression.[20,21]
- People with XLH have a disproportionately high prevalence of socioeconomic deprivation, likely due to the negative impact of the condition on educational and career opportunities and ability to work. This may compound the burden of the condition.
- Conventional therapy (oral phosphate and active vitamin D supplements) does not address the underlying cause of disease and cannot restore normal phosphate metabolism.
    - Conventional therapy has limited efficacy, is associated with serious adverse effects, and has a complicated treatment regimen.[22–24]
- There is a clear unmet, and urgent need for an effective treatment option for adults with highly symptomatic XLH for whom conventional therapy is not suitable.

1.3.1 XLH in adults: overview of the disease and its impact

X-linked hypophosphataemia (XLH) is a very rare, lifelong genetic disorder characterised by low levels of phosphate in the blood (hypophosphataemia), due to excessive production of the phosphate-regulating hormone fibroblast growth factor 23 (FGF23).[14,15] Production of the active form of vitamin D (calcitriol; also known as 1,25(OH)2D) is also reduced.[14,15] This pathology results in defective bone mineralisation, leading in childhood and adolescence to osteomalacia (softening and weakening of the bones), bone deformities, dental abnormalities and short stature.[14]

Adults with XLH are affected both by the legacy of childhood disease (short stature and lower limb and dental deformities) and by ongoing disease processes driven by hypophosphataemia.[3,14,15,17] It has been described as affecting people's "whole bodies, whole lives, and whole families".[25] In their Consensus Statement on management of XLH, Trombetti et al. noted that adults with XLH suffer from early development of osteoarthritis, osteomalacia, pseudofractures (painful, slow- or non-healing bone lesions), impaired muscle

function, chronic bone and joint pain, stiffness, impaired mobility and disability, depression and susceptibility to dental abscesses.[3] Patients typically experience musculoskeletal symptoms and complications at a much earlier age than the general population, often in young adulthood, and these accumulate over time.[17] Symptom patterns in adulthood vary, but for highly symptomatic individuals XLH has a profound impact on their physical and mental health and their day-to-day lives.[11,20,21,26,27] Career options and ability to work are significantly affected,[20,26,28] and people with XLH in the UK are more likely to experience social deprivation than the general population.[11] Data from the Clinical Practice Research Datalink (CPRD) database indicate reduced life expectancy: median age at death for people likely to have XLH was 64 years, compared with 72.5 years for matched controls.[19] The effects of XLH in children and adults are summarised in Figure 1.

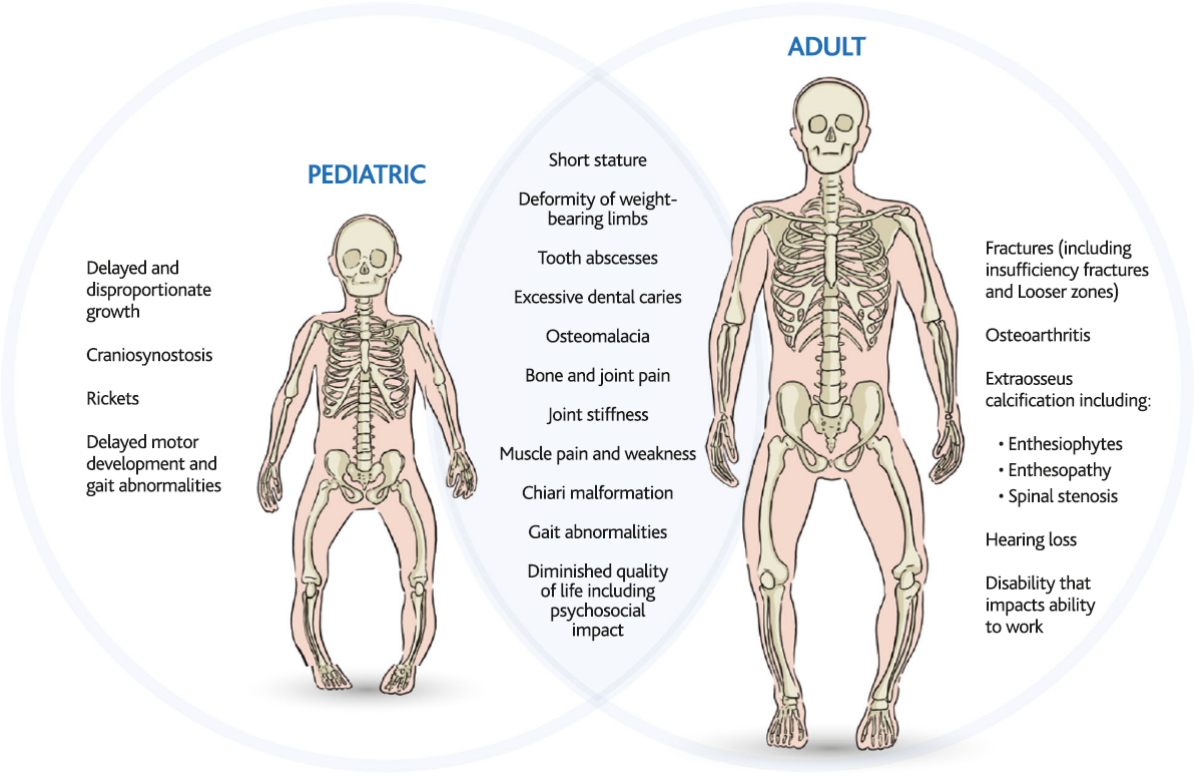


Figure 1 Symptomatology and pathophysiology of XLH. The signs, symptoms, sequelae, and long-term consequences of XLH in paediatric (left) and adult (right) patients.

Source: Beck-Neilsen 2019[14]

1.3.1.1 Epidemiology

XLH is an X-linked dominant genetic disorder,[2] meaning that both sons and daughters of an affected female have a 50% chance of inheriting it. Affected males cannot pass the gene to their sons (males inherit their X chromosome from their mother), but will pass it to all their daughters (females inherit an X chromosome from each parent).[29] Thus, the ratio of

females:males with XLH is approximately 2:1. XLH may affect multiple family members. However, in approximately 20-30% of patients XLH is thought to be caused by a de novo mutation rather than inherited, as there is no family history.[2,3]

Hawley et al. (2020) have estimated the UK-wide prevalence of XLH in adults using the CPRD database.[19] There is no agreed algorithm for identifying cases with XLH using real world data and no ICD (International Classification of Diseases) code for XLH, which is grouped with several other conditions under ICD code E83.3 (Disorders of phosphorus metabolism and phosphatases). Using a definition of 'at least likely' cases (those considered 'likely' or 'highly likely' to have XLH) gave an estimate of 0.67 per 100,000 adults (95% CI: 0.45-1.02) between 2012 and 2016. This suggests that in England there are approximately 298 adults with XLH in 2023. An estimate by specialist clinicians was similar at 305.[30] The numbers expected to be treated with burosumab are lower and are described in the Budget Impact document. Previous estimates of the prevalence of XLH have been varied due to differences in study populations and methods used, and comparisons with the UK-specific estimate by Hawley should be treated with caution.[19]

1.3.1.2 Diagnosis

XLH is diagnosed using a combination of clinical, radiological and biochemical findings, with confirmation via genetic testing (analysis of the *PHEX* gene).[2,3,6] Note that the element of uncertainty around diagnosis from database records in the Hawley paper (see above) is not applicable to the diagnosis of individual patients in clinical practice.

1.3.1.3 Pathophysiology and effects of hypophosphataemia in adults

XLH is caused by inactivating mutations in the *PHEX* gene, leading to excessive production (mainly in the bones) of a hormone known as fibroblast growth factor 23 (FGF23).[2,14] FGF23 plays a critical role in the regulation of phosphate and vitamin D homeostasis in the kidney. Raised serum FGF23 has two principal effects[14,31] (Figure 2):

- Increased excretion of phosphate in the urine, due to reduced re-absorption of phosphate in the kidney, resulting in hypophosphataemia (abnormally low phosphate levels in the blood, defined as serum phosphate below the lower limit of normal [LLN], i.e. <2.5 mg/dL [0.81 mmol/L][2]).

- Reduced production of the active form of vitamin D (calcitriol; also known as 1,25(OH)2D) resulting in impaired absorption of phosphate from the intestine.

Phosphate is a key component of bone mineralisation and also plays an essential role in metabolic processes and tissue structure and function throughout life.[2,14,31,32] It is a major component of bones and teeth in the form of calcium phosphate.[2] It is also a constituent of key molecules in metabolism (e.g. ATP) and cellular signalling (e.g. cAMP), and in the structure and function of muscles.[3,14] Chronic hypophosphatemia therefore affects multiple body systems,[3,14,31] and if unresolved will have lifelong and cumulative effects, resulting in impaired mobility and physical function and reduced health-related quality of life.[31]

Hypophosphataemia due to overproduction of FGF23 is the major pathophysiological mechanism in XLH.[14] Direct effects of FGF23 itself are also thought to contribute.[14] Downstream of FGF23 the pathophysiology of XLH is complex and not fully understood. However, it is well established that hypophosphataemia is the primary driving force behind the majority of the ongoing, cumulative morbidities experienced by adults with XLH.[3,14,31]

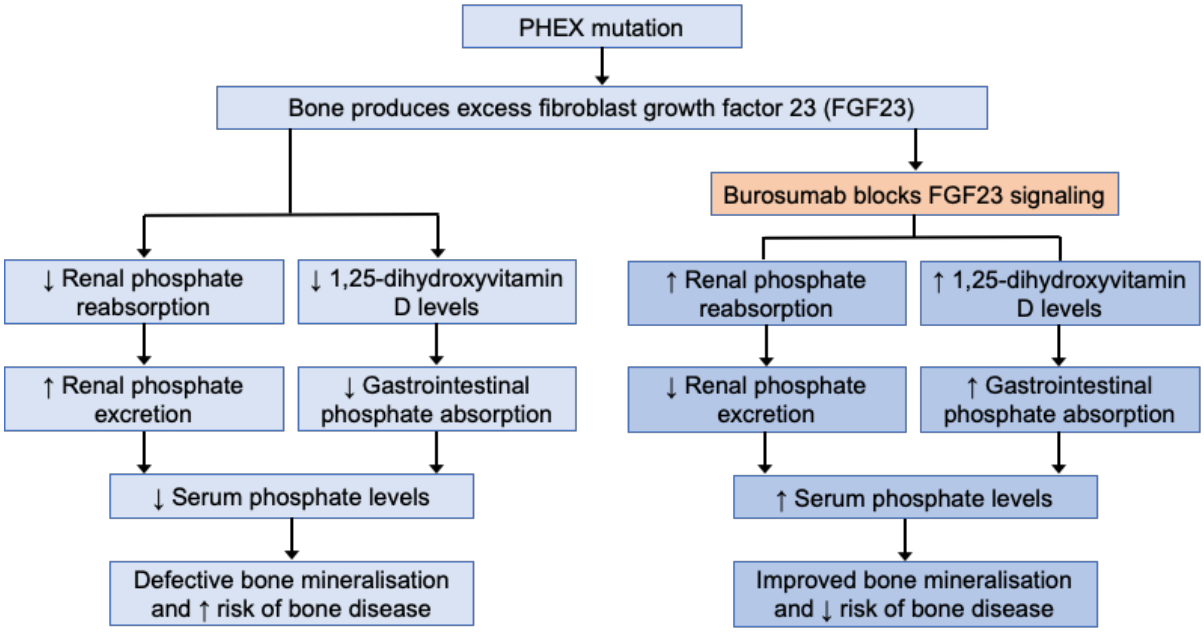


Figure 2 Pathophysiology of XLH, and mechanism of action of burosumab in its treatment

Source: adapted from Lyseng-Williamson 2018[33]

1.3.2 Clinical presentation

XLH has wide-ranging effects that begin in childhood and continue throughout life (Figure 1). Although skeletal and dental deformities are established in childhood, persistent hypophosphataemia leads to ongoing and lifelong morbidities.[14,17,34] The clinical features and severity of XLH vary between patients, and not all adults with XLH are symptomatic.[2]

However, for many affected adults, XLH has a profound impact on their physical and mental health and on their day-to-day lives.

The ongoing skeletal impact of XLH in adulthood is illustrated in Figure 3 and Figure 4. The radiographs show longstanding, painful stress and deformity fractures (also known as ‘pseudofractures’), which in many cases have developed despite conventional treatment, or have not responded to conventional treatment. Under current treatment, these painful lesions are typically slow- or non-healing.

Hx: history; OA: osteoarthritis

Figure 3 Radiographs of UK adults with XLH (1)

OA: osteoarthritis

Figure 4 Radiographs of UK adults with XLH (2)

A life course analysis, based on an XLH natural history study (see Section 2.3.3) and baseline data from Study CL303 (the pivotal study of burosumab vs. placebo presented in Section 2.3.1.5), has confirmed the lifelong, cumulative nature of XLH-related morbidities.[17] The analysis highlighted the prevalence of musculoskeletal events beginning as early as 20

years of age. For example, in the 18-29 year age band 27-40% had a history of fracture; this increased to 65-86% in those aged ≥60 years. The prevalence of osteoarthritis increased from 23%-37% among 18-29 year-olds to approximately 70% in those aged over 60. Similar patterns were seen for osteophytes and enthesopathy. Surgeries such as hip and knee arthroplasty were reported by adults in their 30s.

The effects of hypophosphataemia in adults with XLH are summarised in Table 3 below. As hypophosphataemia drives these morbidities, there is a strong rationale for treating symptomatic adults with burosumab in order to block the effects of excess FGF23 and restore phosphate homeostasis (see Section 2.6.1 for the clinical showing normalisation of serum phosphate and subsequent improvements to symptoms, physical functioning, fracture healing and HRQoL).

Table 3 Features of XLH in adults and their link to hypophosphataemia and/or FGF23

Morbidity	Role of hypophosphataemia and clinical manifestation
Osteomalacia (soft bone caused by defective mineralisation)	Phosphate is a key factor in the maintenance of bone health throughout life.[32] Osteomalacia is the hallmark of XLH in adults and is characterised by severe mineralisation defects that impair bone quality and bone remodelling. [7,35] Unlike in rickets, osteomalacia in XLH occurs in adults as well as children.[14] Thus, the effects of hypophosphataemia on bone in XLH do not cease once growth ends in adolescence. • Osteomalacia leads to bone pain, bone deformity and increased risk of pseudofractures and fractures.[2,15] • Bone pain from osteomalacia is distinct from bone pain caused by osteoarthritis,[2] though patients may have both.
Pseudofractures and fractures	Adults with XLH are at increased risk of painful pseudofractures and fractures due to a combination of osteomalacia and skeletal deformities in childhood.[36] Pseudofractures, also known as Looser zones, are incomplete fractures that involve only one cortex of the long bone, but may progress to complete fractures (i.e. fractures that extend across the entire cortex).[35] They usually appear in areas of high stress, such as the top of the thigh bone, lower hip, forearm and shoulder blade.[37] They typically occur in the absence of trauma or a fall:[35] everyday activities such as walking or climbing the stairs can cause pseudofractures in people with XLH. • In the global XLH natural history study, 44% of the 232 adult participants had a history of fracture.[18] In the 18- to 29-year-old age group, 27% of participants reported ever having a fracture; this increased to 68% among patients aged ≥60 years, showing the ongoing risk in adulthood.[17] • Fractures and pseudofractures are typically painful and slow- or non-healing in people with XLH and may require surgery (see Figure 6).

	• Figure 3 and Figure 4 show the burden of fractures and pseudofractures in adults with XLH.
Muscle weakness, pain and stiffness	Phosphate is important for muscle structure and function throughout life. Hypophosphatemia (and possibly also direct effects of FGF23) leads to altered muscle composition, resulting in muscle weakness, pain and stiffness in adults with XLH.[14] Reduced ATP levels due to lack of phosphate may contribute to muscle stiffness, weakness and cramping in patients with XLH.[3] In a survey of 232 adults with XLH, 60% reported muscle weakness.[18] Orlando et al. studied 26 adults with XLH recruited as part of a prospective cohort study, of whom 15 were taking conventional therapy (none were treated with burosumab at the time of this analysis).[38] They found a 55.4% reduction in muscle power (as measured by Esslinger Fitness Index) compared with reference values ($p<0.0001$). Stiffness is also a hallmark of XLH for many patients, as evidenced by patient surveys and WOMAC stiffness scores.[7,20,21] • Beck-Neilsen et al (2019) note that while abnormal skeletal development from childhood may play a part, patients with hypophosphatemia due to tumour-induced osteomalacia (TIO), who do not have skeletal abnormalities, also suffer from muscle pain and weakness. TIO is also driven by FGF23, indicating that FGF23 may contribute to the development of muscle manifestations either directly or via hypophosphatemia.[14] • They conclude that the available evidence indicates that FGF23-induced hypophosphatemia is associated with muscle weakness in XLH independently of skeletal abnormalities, and that FGF23 may also play a direct role through its effect on skeletal muscle.[14]
Impaired physical functioning	Adults with XLH experience varying degrees of impaired physical functioning, including mobility issues and difficulties with activities of daily living.[7,20,21] The study by Orlando et al. (described above) found that 10 of 26 participants (38.6%) had a short physical performance battery (SPPB) score of ≤8, indicating impaired mobility. Functional capacity assessed by 6-minute walk test (6MWT) was reduced and almost three-quarters had low physical activity as measured by the International Physical Activity Questionnaire (IPAQ).[38] Skeletal deformity is compounded by bone and muscle pain, muscle stiffness and weakness, osteoarthritis and enthesopathy in impairing physical functioning.[38] Many of the causes of impaired functioning can be expected to improve with blockade of excess FGF23 and normalisation of phosphate homeostasis, and this was shown to be the case in the pivotal trial of burosumab[7] (study CL303, Section 2.6.2.2).
Pain	In the global XLH natural history study, 97% of the 232 adult participants said they had experienced pain during the last year and 67% said their pain was bad enough to require the use of medication at least once a week.[18] Clinical experts have noted that in highly symptomatic individuals, pain can persist despite use of analgesics, including opioids (see Appendix Q).

	• Many of the sources of pain in XLH (bone pain from osteomalacia, pseudofractures, muscle pain and potentially pain from enthesopathy and osteoarthritis) can be expected to be improved or prevented by normalisation of phosphate homeostasis. This is confirmed by the improvements in pain scores seen with burosumab (see Section 2.6.2.3). • Other sources of pain (dental pain, osteoarthritic pain attributable to skeletal misalignment) arise from abnormalities that are fixed in childhood and are unlikely to be addressed by phosphate normalisation in adults.[7]
Fatigue	Adults with XLH commonly report fatigue. Abnormalities in muscle structure and function as described above, and reduced ATP levels due to lack of phosphate, may contribute to fatigue. Patients also report that living with chronic pain and stiffness contribute to their fatigue, including sleep disturbance caused by pain.[20,21]
Osteoarthritis	Adults with XLH are at high risk of osteoarthritis, with onset commonly seen at a much younger age than in the general population. • In the global XLH natural history study, approximately a quarter of adult participants who were aged between 18 and 29 years already had osteoarthritis; this increased to almost 50% of those aged in their thirties.[17] • In Study CL303, 37% of participants who were aged between 18 and 29 years already had osteoarthritis; this increased to 74% of those aged in their thirties.[17] • Osteoarthritis results partly from abnormal loading of the joints due to skeletal misalignments developed in childhood. However, Trombetti et al. (2022) note that this cannot fully explain early osteoarthritis in XLH, and that further investigation of a possible role for FGF23 is required.[3]
Enthesopathy	Patients with XLH can develop excessive mineralisation of the fibrocartilage of the entheses (the point where tendons insert into bone). This causes spurs (enthesophytes), leading to joint stiffness and pain (enthesopathy).[14] • The pathophysiology of enthesopathy in XLH is not fully understood, and it is not notably influenced by conventional therapy.[3] • It may be a secondary effect of reduced mineralisation and osteomalacia of the long bones making them weaker and more bendable and placing more strain on the entheses and their attachments.[14]
Dental abscesses	Painful dental abscesses are common in XLH but result primarily from abnormalities of tooth architecture developed in utero and in childhood, rather than ongoing hypophosphataemia.[14] However, improvements to bone quality resulting from burosumab treatment may improve the quality of the jaw bone, which may result in improvement to dental health.
Hearing loss	Hearing loss is also a feature of XLH for some adults. Its aetiology is complex and poorly understood, and any link with FGF23 and phosphate levels in its development or progression in adulthood is

	unclear.[14] Therefore, due to lack of evidence it is unclear whether treatment of XLH in adulthood will have an impact on hearing.

1.3.3 Adverse effects of conventional treatment

Adults with XLH have a raised prevalence of kidney stones, nephrocalcinosis and hyperparathyroidism. However, these are largely adverse effects from conventional treatment, rather than features of XLH itself.[3] Nausea and diarrhoea are other common adverse effects of conventional therapy.[3] Current treatment and its adverse effects are discussed further in Section 1.3.6.3.

1.3.4 Life expectancy and mortality

An analysis by Hawley et al. (2020) using data from the UK Clinical Practice Research Datalink (CPRD) database found that XLH is associated with significantly increased mortality. In individuals classed as 'at least possible' XLH cases (N=122), the HR was 2.93, 95% CI 1.24–6.91 compared with matched controls without XLH. The median age at death was approximately 8 years younger at 64 years (IQR 58-74) vs. 72.5 (IQR 52-91) years.[19] [NB this is a correction to the published IQR for the 72.5 year median, by personal communication from the authors.] In individuals considered 'likely or highly likely' to have XLH (N=62), HR was 6.65 (95% CI 1.44–30.72). Median age at death was 61 years (IQR 56-66) for cases compared with 68 (IQR 29-71) for controls. In the economic modelling, a HR of 2.88 (95% CI 1.18-7.00) is applied, derived from a sensitivity analysis in the Hawley paper (see Section 3.2.2.1). An additional, independent analysis found a similar HR (2.33 [95% CI: 1.16 – 4.67, P = 0.02], see Appendix R.

There is a lack of published evidence on causes of death in people with XLH or the mechanisms which might lead to increased mortality. Hawley et al. noted that the mechanism for the increased mortality was not known, but cited differences in incidence of comorbidities and direct effects of FGF23 as potential contributors. However, a range of factors that affect adults with XLH are known or hypothesised to be associated with reduced life expectancy, as shown in Figure 5 and detailed in Table 4 below. Clinical experts agree it is plausible that this constellation of interconnected risk factors would result in increased mortality, as observed in the Hawley analysis (see Appendices P and Q for minutes of expert consultations).

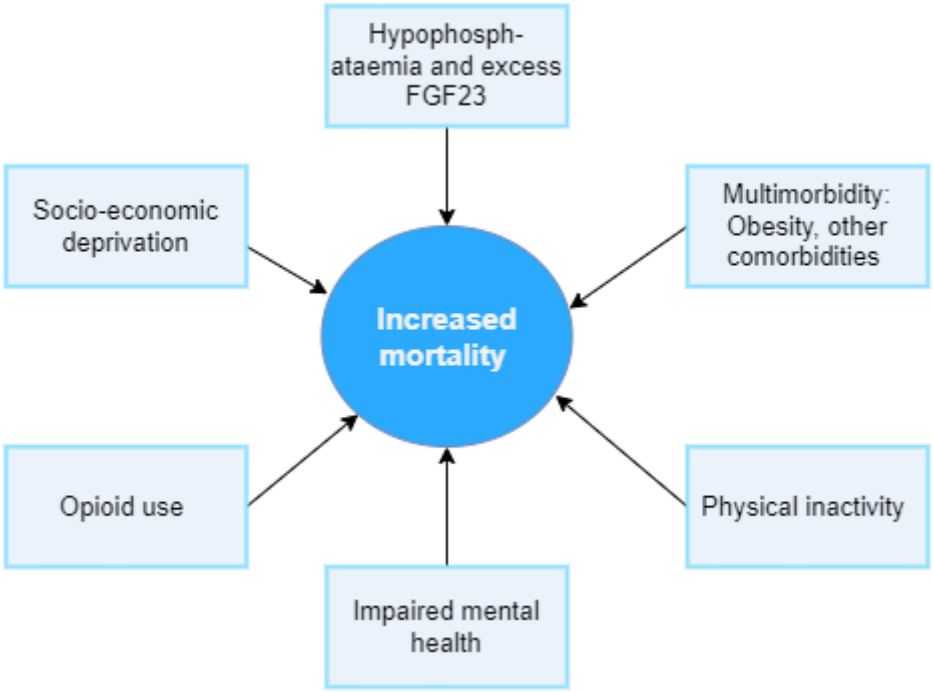


Figure 5 Potential contributors to increased mortality in adults with XLH

Based on Hawley 2020[19] and clinical expert opinion (see Appendices P and Q)

Table 4 Potential contributors to increased mortality in adults with XLH

Contributing factor	Rationale
Hypophosphataemia and excess FGF23	As described in Section 1.3.1.3 above, phosphate plays an essential role in metabolic processes and tissue structure and function throughout the body.[2,14,31,32] Excess FGF23, which is the root cause of hypophosphataemia, is also thought to have adverse effects independently of hypophosphataemia.[14] Life-long phosphate insufficiency, together with reduced production of active vitamin D and an excess of FGF23, may have systemic effects that predispose patients to earlier death. Excess FGF23 levels have been associated with shortened life expectancy in dialysis patients, though the authors note that this may not be generalisable to other groups.[39,40]
Multimorbidity, including obesity	Adults with XLH live with multiple, often complex, co-morbidities, as evidenced in the life course analysis study by Javaid et al.[17] Multimorbidity is associated with increased all-cause mortality.[41] Obesity: adults with XLH have a higher prevalence of obesity than the general population.[3] Obesity is a well-established risk factor for diabetes and a range of other morbidities associated with reduced life expectancy. Other comorbidities: The consensus statement by Trombetti et al. notes that XLH may be associated with hypertension and possibly left ventricular hypertrophy.[3] More recently, a study of 50 adults with hereditary hypophosphataemia

	(including XLH) by Espersen et al. found their blood pressure (BP) was significantly higher than matched controls (systolic BP 128 [95%CI: 124-133 mmHg] versus 118 [95% CI: 114-121 mmHg], p<0.001; diastolic BP was also significantly higher).[42] In the UK, Maronga et al. (2023) analysed 64 patients with XLH, including children, identified through the CPRD database. They identified 'a strong signal indicating higher prevalence of hypertension' compared with controls (OR=2.31, p=0.2).[43] People with XLH have a higher prevalence of kidney stones and other renal abnormalities, and hyperparathyroidism; these are adverse effects of conventional treatment.[3]
Physical inactivity	The pain, stiffness, fatigue and impaired physical function associated with XLH lead to an increased prevalence of physical inactivity. In a study of 26 UK adults with XLH, almost three-quarters reported a low level of physical activity.[38] Physical inactivity is associated with a higher risk of mortality: Lear et al. 2017 studied 130,000 people from 17 countries and found that compared to low physical activity levels, those with moderate and high activity levels had lower mortality (hazard ratios of 0.80 and 0.65, respectively).[44]
Impaired mental health	Hawley et al. found that adults with XLH in the UK were three times as likely to have a diagnosis of depression compared to the general population.[11] Patient testimonies (see Section 1.3.5.4) and clinical consensus statements[3] confirm that living with XLH exerts a toll on mental health for many adults. A study of 68,222 community-dwelling adults aged 35+ in the UK found that psychological distress was associated with an increased risk of mortality, which rose with increasing distress scores: HR (age and sex adjusted) versus General Health Questionnaire-12 score 0 ranged from 1.20 (95% CI 1.13 to 1.27) to 1.94 (95% CI 1.66 to 2.26; P<0.001 for trend). This association remained after adjustment for somatic comorbidity and behavioural and socioeconomic factors.[45]
Opioid use	Many adults with XLH are long-term users of prescription opioids in order to manage their pain. In the CL001 natural history study, 67% reported taking opioids at least once a week, and 22.4% of participants in CL303 were taking opioids at baseline.[7] Chronic opioid use is associated with adverse effects including fractures, breathing problems during sleep, hyperalgesia, immunosuppression, chronic constipation, bowel obstruction and myocardial infarction.[46] Inoue et al. 2022 analysed data on 13,884 US adults of whom 2168 suffered from chronic pain. Opioid prescriptions significantly increased the risk of all-cause mortality (Odds ratio = 1.5 [95% CI 1.1, 1.9] at 3 years and 1.3 [1.1, 1.6] at 5 years.[47]
Socio-economic deprivation	As described in Section 1.4, people with XLH in the UK face disproportionately high levels of social deprivation compared with the general population, with 65% falling below the Index of Multiple Deprivation (IMD) national average. [11] A 2018 analysis of 328,594 participants in the UK Biobank aged 40–

	69 years found that deprivation was associated with increased mortality risk: each one-quintile increment in deprivation was associated with a HR for trend of 1·11 (95% CI 1·08–1·13) for all-cause mortality (see Figure 8 for distribution of IMD quintiles in people with XLH).[48]

The potential effects of burosumab treatment on the excess mortality associated with XLH are discussed in Section 3.3.1.3.

1.3.5 Burden on patients and families: effects on health-related quality of life

Living with symptomatic XLH as an adult significantly affects HRQoL.[2,20,21] As previously noted, it affects people's "whole bodies, whole lives, and whole families".[25] Adults with XLH may face a lifetime of pain, stiffness and fatigue that significantly impacts their mobility and ability to perform daily activities, limits their social, family and work life and affects their mental health.[2,16,20,21] Patient testimonies illustrating the effects of XLH are provided in Appendix M. The impact on day-to-day life was summed up by the Chair of XLH UK as follows (see Appendix M for full document):

"*XLH can affect people throughout their day to day life. Ranging from difficulties from being able to get out of the bath, being unable to put on your socks, to being unable to do chores around the home. XLH adults find it difficult to climb their own stairs and difficultly going down their stairs. Parents have described being unable to carry their babies/children while walking. Adults have presented with balance issues and have difficulty in using public transport. The emotional toll XLH has on anyone with XLH is significant and presents various social challenges. XLH has shown to limit those to engage with work/study, social events, hobbies, intimacy, sleep and driving a car."*

"The impact of XLH is a whole-body whole life disease. That is [it] progressively worsens, and affects multiple family members for generations."

These impacts are explored further below. People with XLH are also disproportionately affected by socio-economic deprivation, which is likely to compound the overall burden of the condition for individuals.[19]

1.3.5.1 Mobility and daily activities

- Mobility problems caused by pain and stiffness affect daily activities such as work, housework, shopping, getting in and out of bed, going up and down stairs, and self-care.[20,21] Some adults with XLH require modifications to their home and use walking aids or other equipment to improve mobility.[21,26]

- In a European qualitative study of 30 adults with XLH aged ≥26 years (n=18 from the UK),[20] participants described the negative impact of XLH on their ability to do housework (e.g. standing for long to cook, grocery shopping); caregiving (e.g. carrying children, walking quickly or for long with children); and social, leisure or work activities that required walking or standing for long periods. Many were unable to run. Some reported use of assistive devices or modified living/working environments to because of mobility issues and short stature.

1.3.5.2 Impact of pain and stiffness

- In the same study, many patients reported that pain was the most salient symptom of XLH. Pain was commonly reported to affect physical functioning and to exert a psychological burden.[20] A thematic analysis of free-text responses in the XLH Burden of Disease Survey found that pain was a dominant theme throughout the life course of people with XLH, with bone pain, joint pain and generalised pain all frequently reported.[16]

- Parents often described the impact of pain on caregiving and being able to play with their children as one of the most challenging aspects of their condition.[20] They also reported that fatigue sometimes impacts their ability to care for their children and forces them to rely on their partners for caregiving duties.[20]

Pain can also affect sleep, with individuals reporting difficulty getting to sleep and waking in the night because it hurts to lie down.[20,21] The impact of pain, stiffness and fatigue is illustrated in the following quotes from adults with XLH:

- *"…it's extremely tiring having pain all the time. It affects my social, wanting to do things or being able to go out and do things and I am limited sometimes, as to what I can actually do. I've organised to do something and then I'm just in too much pain on that day so I don't do it…"* [20]
- *"I have a lot of stiffness. And it makes doing simple things hard. Like cooking and cleaning and just being active with my children."* [21]
- *"You don't really want to go out and do things and see friends… you do not want to do anything at all on the weekend… You'll just be very absent minded; you can't focus on anyone else… I can't focus on my other half."* [20]

1.3.5.3 Need for surgeries

Adults with XLH typically undergo multiple orthopaedic surgeries to repair fractures, replace joints and manage other skeletal complications.[26] In the global XLH natural history study, 94% of the 232 adult participants reported that they had undergone surgery, including osteotomy, knee replacement and cartilage repair.[18] A series of 59 adults with XLH in the UK reported by Chesher et al. reported that 27 had a history of bone surgery, with a range of procedures reported through childhood and adulthood.[34]

Surgeries are typically extensive, and gruelling for patients. Trombetti et al. note in relation to complex XLH surgeries that: “The burden of recovery (an inability to walk and being wheelchair-bound), combined with dependency on medication (opiates such as oxycodone) and loss of freedom and mobility has major emotional and mental effects”. The Chair of XLH UK described the impact on patients of “knowing that surgery is often extremely challenging” and cited long-term effects of surgery related to healing, muscle loss, loss of confidence and fear of falling (see Appendix M). Figure 6 Illustrates extensive surgery required for fractures in a young adult man with XLH, which was necessary despite conventional treatment.

Figure 6 Radiographs from adult male XLH patient from the UK on conventional therapy, showing surgeries for fractures

1.3.5.4 Effects on mental health

Living with a very rare disease substantially impacts mental health, both through the effect of physical symptoms and through lack of understanding among others and uncertainty about the future.[49] In the England survey of 18 burosumab-naïve adults with XLH, mental health was rated as one of the three most bothersome challenges of living with XLH, along with pain and fatigue (see Appendix O).

- Adults with XLH commonly report low self-esteem, frustration and depression.[20,21] A UK study of 64 adults graded 'likely' or 'very likely' to have XLH using the Clinical Practice Research Datalink (CPRD) GOLD found they were three times as likely to have a diagnosis of depression compared with matched controls (OR 2.95 [95% CI: 1.47, 5.92]).[11]

- Concern about worsening symptoms in the future is common. Patients worry about what will happen as the impacts of XLH accumulate, particularly if they have witnessed deteriorating health in older relatives with XLH.[20,26]

The psychological impact of XLH is illustrated by the following quotes:

"…I have suffered pain, deformity and I have been ostracised by society because of the effects of XLH. Imagine walking down a busy high street with hundreds of people and only you walk like you, everyone turning and staring in horror, the polite few turn away, some laugh, some point, some throw stones or spit at you. That is my reality." [27]

"…The worry that I might, that my legs might get worse, that I'm going to suffer with arthritis, that I might at some point in the future be in a wheelchair. All these things really. It's the worry of the condition worsening over time." [20]

Donna, a 36-year-old female with XLH from England, states that she has not been offered any mental health support and continues to battle with her mental health alone (see Appendix M). Sally, a 30-year-old female from England, states that XLH has made her self-conscious, less outgoing and less able to develop meaningful relationships. She is anxious about the likelihood of a child inheriting XLH and worries how her partner and his family would react to potentially having children with XLH. Further details of Sally's story are available in Appendix N.

1.3.5.5 Impact on career and productivity

No quantitative data on the impact of XLH on work productivity were identified from the literature, but qualitative studies are available. Unemployment and early retirement are more common among adults with XLH than in the general population.[26] In an English survey of burosumab-treated adults carried out in conjunction with XLH UK of 20 adults who received burosumab via an Early Access Programme, 88% of the 17 who had not retired were in some form of employment. Of the 6 working part time, [redacted] see Appendix O, Survey 2 for full details of this patient survey). [redacted]

Adults with XLH who are able to work feel that their condition disrupts their work life, as they frequently need time off to attend appointments,[26] and they may be overlooked for promotion as a result.[28] Symptoms such as fatigue can cause loss of concentration at work,[20] resulting in presenteeism (reduced productivity while at work).

Adults with XLH report that it has affected their career choices.

- Donna, a 36-year-old female with XLH from England, wanted to become an endocrinology nurse but the demanding training meant that she was physically unable to pursue this. She has also had to give up jobs in retail and in a care home, which has been very frustrating as she enjoys working. Instead, she has focused on educational courses. Further details of Donna's story are available in Appendix M.

- Adrian, a 44-year old male with XLH from England, aspired to be a football player or firefighter, but due to the morbidities and fatigue caused by XLH he had to choose an office-based career instead. Even in his office-based job Adrian faced issues. He had to take time off due to starting a new treatment. This absence was not understood by his then employer and he lost his job. Further details of Adrian's story are available in Appendix M.

The (often multigenerational) effect of XLH on educational participation and attainment, career opportunities and ability to work mean that adults with XLH are disproportionately located in the lowest two quintiles of the Index of Multiple Deprivation (IMD). This is further discussed in Section 1.4 (Equality Considerations).

1.3.5.6 Effect on informal caregivers and family

The disutility associated with a patient's health state also affects the quality of life of caregivers and family. Patient advocates have described the impact of XLH on the family unit as "catastrophic" (see Appendix M). As XLH is primarily an X-linked heritable disease, several members of the same family are often affected. Adults with XLH may find themselves caring for children with the same condition, adding to the burden they face from their own experience of living with XLH.

Close family of adults with XLH are affected by the impact of XLH, regardless of whether or not they take a 'caregiver' role and regardless of whether they have the condition themselves. This has been confirmed by patient advocates (see Appendix M) and by a research study looking specifically at family impact, reported below and in Appendix S.

Study of family and caregiver burden in XLH

A targeted literature review commissioned by Kyowa Kirin found no published papers on the effects of XLH on informal caregivers and close family members, highlighting the lack of information on the family impact of this condition.[50] A mixed methods study was therefore commissioned to interview carers or family members of adults (aged 18+) in the UK with an XLH diagnosis about their experiences, and interim data for 19 participants (3 who also had a diagnosis of XLH themselves, and 16 without a personal diagnosis of XLH) are available at the time of writing. The interim study report is provided in Appendix S; a final report will be available at Technical Engagement.

This was the first study to explore the impacts and experiences of caring for, supporting, or living with an adult patient with XLH, focusing specifically on spillover effects. The study found that carers and family members provide considerable support for adult patients with XLH that increases over time as the disease progresses, and that this results in a broad range of impacts to carers and family members' lives. Notably, the study's qualitative findings highlight areas of carer-burden that may not be well captured by the quantitative findings, particularly for carers without XLH, with small impacts to EQ-5D utilities observed despite qualitative data suggesting large impacts to HRQoL. Conversely, for carers with XLH, large impacts were demonstrated in both quantitative and qualitative data.

Quantitative survey data were collected which captured: (1) patients' treatments and background demographics and personal characteristics of family members who were study participants; (2) the EQ-5D-5L; (3) the Work Productivity and Activity Impairment (WPAI) questionnaire. EQ-5D-5L data were mapped to the EQ-5D-3L using the Hernandez et al.

(2020) mapping function[51] to generate utility weights. Qualitative data were collected via one-to-one semi-structured interviews (completed by telephone or online).

Carers of adults with XLH had lower HRQoL compared with the UK general population. The mean EQ-5D utility for the total sample was 0.668 (95% CI: 0.508 – 0.828). Mean EQ-5D utilities for participants with and without a personal diagnosis of XLH were 0.116 (95% CI: -0.678 – 0.910) and 0.772 (95% CI: 0.658 – 0.886) respectively. Across the total sample, the mean difference in observed versus expected EQ-5D utilities was -0.184 (95% CI: -0.339 – -0.029), when compared with age-linked UK general population utility data. Mean differences for participants with and without XLH were 0.737 (95% CI: -1.401 – -0.073) and -0.081 (95% CI: -0.190 – 0.029) respectively.

Results from the Work Productivity and Activity Impairment Questionnaire (WPAI) found that of the 11 participants who had worked in the previous 7 days, the mean percentage of work missed over the last week due to caring responsibilities (absenteeism) was 4.3%. Average presenteeism (impairment of work activities due to caring responsibility) was 31.8%. Overall work productivity loss was 29.1% on average. Across the total sample (N=19) overall activity impairment was 41.6%.

The qualitative interviews revealed five principal areas of support provided by family members and carers:

- Support with medical care and management of XLH
- Physical support
- Emotional and mental support
- Support with daily activities
- Financial support.

Participants reported how they needed to provide increasing amounts of support over time. Partners of individuals with XLH described how providing support for an adult with XLH meant "*always planning ahead*", "*having more responsibility to do things and help*" and "*always needing to be available, even when [they] were working*". They also described how their routine differs from others as "*with somebody that doesn't live with somebody that has XLH, the workload is shared between the couples more*".

Participants described spending considerable time providing care or support, which ranged from a "*couple of hours a day*" to "*15-hours a week*" and "*four or five [full] days a week*". For some participants, this involved using all their "*spare time*" to provide care and support, with

one participant describing it as "*another work shift*". Many participants identified or described themselves as 'carers', as opposed to just relatives or partners.

Participants identified the impact of providing support on six areas of their lives:

1. All but one participants described a negative impact on their emotional wellbeing. For many, this was expressed as feeling overwhelmed and "*anxious about them being alone when they go out by themselves*", as well as worried for the future and how "*they're [adult with XLH] going to cope*" if the participant is not able to provide support. Participants also expressed feeling guilt, with some experiencing guilt when taking time for themselves, for feeling that the support they provide "*stretches [them] a little bit far*", or for feeling that they're not "*doing enough*". Guilt was also expressed by carers with an XLH status due to feeling that they "*passed it onto them*".
2. A significant impact on daily activities, experiencing "*an impact on [their] freedom*" with no time left for themselves: "*I don't know who I am anymore … little things I used to do like listen to music … I don't really get a chance to anymore*".
3. An impact on their work. Participants described having to work more or less hours, having to work in ways they would have otherwise not chosen or preferred, and having to stop working altogether in order to be able to provide support for the adult with XLH. Examples included having to work night shifts to ensure they are home during the day to provide support, which took "*a big toll*".
4. Financial impacts, with contributing factors including transport costs, medical costs, having to work less hours, and giving up "*all financial stability to look after [them]*" by quitting work.
5. Social and relationship impacts. Participants reported limitations in their ability to socialise with friends and other family members due to factors associated with supporting an adult with XLH. For example, participants expressed how their partner's mobility issues limit them from being able to take part in social activities together, and missing out on social events due to not being able to "*leave [them] for that amount of time [three days]*". Relationship impacts also extended to participants' relationship with the adult with XLH, with negative and positive impacts reported.
6. Impacts on their physical wellbeing were also noted, including experiencing body aches as a result of the support they provide, feeling tired, and not getting enough sleep.

1.3.6 Current treatment and clinical pathway of care

1.3.6.1 Goals of treatment

The goals of treatment in adults with XLH include normalising serum phosphate levels, correcting osteomalacia, preventing and/or healing pseudofractures and fractures, and relieving bone pain.[15]

Expert clinicians in the UK suggest that individualised patient-centred goals might include [redacted][6]. Because of the variety of symptoms that can be involved, patients should be treated using an interdisciplinary, patient-centred approach.[3]

1.3.6.2 Treatment guidelines

There are no NICE or UK-specific treatment guidelines or clinical pathway of care for adults with XLH. Clinical practice recommendations were published by Haffner et al. (a group of European experts including UK authors) in 2019.[2] These were followed by a Consensus Statement published by a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) in 2022 (Trombetti et al.).[3] The latter takes into account additional evidence published since the Haffner guideline, including evidence relating to burosumab. Recommendations from both publications for the treatment of adults are summarised in Table 5.

A working document (as yet unpublished) of clinical practice recommendations has been proposed by a group of expert clinicians in the UK.[6] A brief summary is provided in Table 6, focusing on aspects most relevant to the decision problem. Consideration of burosumab is recommended in symptomatic patients (with musculoskeletal pain and stiffness, or pseudofractures), if conventional therapy with phosphate supplementation is not tolerated, not beneficial, or has already been tried in the last 24 months for similar symptoms.

Table 5 Published treatment recommendations for XLH in adults

Guideline	Recommendations (summary)*
Haffner et al. 2019[2]	**Conventional treatment** Treatment is recommended in symptomatic adult patients, i.e. those with musculoskeletal pain, pseudofractures, dental issues, planned orthopaedic or dental surgery or biochemical evidence of osteomalacia with an increase in serum levels of bone-specific ALP. Routine treatment of asymptomatic adults with XLH is not recommended. Conventional treatment with active vitamin D and oral phosphate improves pain, osteomalacia and oral health (with respect to periodontitis and the

	frequency of dental abscesses) but does not prevent or improve hearing loss or enthesopathies. Taking daily active vitamin D and at least twice- daily oral phosphate supplements is burdensome for many adults and has potential adverse effects. It is recommended to stop phosphate supplements in patients with markedly increased parathyroid hormone levels.
	Burosumab Consideration of burosumab is recommended in adults with persistent bone and/or joint pain due to XLH and/or osteomalacia that limits daily activities; pseudofractures or osteomalacia- related fractures; and insufficient response or refractory to conventional therapy. Consideration is also recommended in patients who experience complications related to conventional therapy.
	Follow-up Patients should be seen regularly by a multidisciplinary team, with team composition and frequency of monitoring tailored to patient's needs. Serum ALP is a reliable biomarker of osteomalacia in adults but bone-specific ALP is preferred. Elevated ALP levels indicate under-treatment of osteomalacia. PTH should be measured regularly as secondary hyperparathyroidism is promoted by oral phosphate supplementation. Measurement of serum and urinary levels of calcium is required to evaluate the safety of active vitamin D. Regular measurement of serum FGF23 in treated patients is not recommended as it does not guide therapy. In patients treated with burosumab, fasting serum phosphate level is a biomarker of efficacy and should be monitored to exclude hyperphosphataemia. It is suggested that TmP/GFR should be analysed together with fasting serum phosphate. Serum levels of $1,25(OH)_2$ vitamin D might increase under burosumab therapy; it is suggested to measure these every 6 months and analyse them together with the urinary calcium excretion as safety parameters.
Trombetti 2022[3]	**Conventional treatment** Treatment of asymptomatic adults is not recommended unless they develop pseudofractures (even without symptoms). Treatment in adults should include: vitamin D analogues (alfacalcidol 0–1.5 µg per day, once per day, or calcitriol 0–1.0 µg per day, in one or two doses) alone or with phosphate supplements (ideally smaller doses than in children), which are evenly distributed across the day, 0–2,000 mg per day. When growth is completed, the dose of oral phosphate must be progressively decreased down to the lowest dose consistent with relief of symptoms. The doses of alfacalcidol or calcitriol should be adjusted to the required dose of phosphate to ensure normal mineral metabolism. Adverse effects of conventional treatment include intestinal discomfort due to phosphate supplements, with nausea, diarrhoea, hypercalciuria and nephrocalcinosis. Secondary and tertiary hyperparathyroidism can occur due to long-standing stimulation of parathyroid glands by phosphate supplements and further suppression of $1,25(OH)_2D$ production by FGF23.

	Burosumab Burosumab could be suggested as a second-line therapy in adults with XLH with overt osteomalacia, with pseudofractures that are not responding to conventional treatment or in patients intolerant to conventional treatment. Burosumab is well tolerated.
	Follow-up Patients should be seen by a multidisciplinary team, at least every 3 months after initiation of therapy, and at least every 6 months in patients showing positive response to treatment and/or stable condition. In patients receiving burosumab: Monitor fasting serum levels of phosphate together with the TmPi/GFR, every 2 weeks during the first month after treatment initiation, every 4 weeks for the following 2 months (and thereafter as appropriate); Measure fasting serum levels of phosphate 4 weeks after any dose adjustment. Measure serum levels of 1,25(OH)2D every 6 months, analysed together with the urinary calcium excretion as safety parameters.

* Only recommendations pertinent to the decision problem are summarised

Table 6 Summary of working document on recommended management of XLH in adults in the NHS (selected aspects relevant to submission)

Topic	Recommendations
Goal of treatment	[redacted]
Work-up	[redacted]
Treatment of musculoskeletal pain and stiffness	[redacted]

	[redacted]
Treatment of pseudofractures	[redacted]
Complete fragility fracture	[redacted]
Other elective orthopaedic surgery	[redacted]

Source: Summarised from Mohsin et al. 2022

1.3.6.3 Conventional treatment

Limited efficacy: Conventional treatment in adults consists of active vitamin D analogues and phosphate supplements (see Table 5). Treatment attempts to replace lost phosphate and vitamin D but does not address the underlying pathophysiology of XLH and does not restore phosphate homeostasis. Conventional therapy has not been evaluated in controlled

trials and there is limited evidence on its effectiveness.[22] Small uncontrolled studies have shown modest benefits with respect to pain, bone softening (osteomalacia) and dental health.[22,52,53] However, it is inadequate for some patients. One statement submitted by an adult with XLH as part of the consultation process for the HST8 appraisal of burosumab in children stated that:[27] “Although I was diagnosed early and have taken the currently available phosphate and calcitriol treatment religiously my whole life, I have still required multiple surgeries and have experienced disabling pain, spinal stenosis and dental problems as a direct result of my XLH." The radiographs in Figure 3, Figure 4 and Figure 6 show the high burden of fractures and surgeries in some adult patients despite conventional treatment.

Adverse effects: Phosphate supplements are frequently associated with gastro-intestinal discomfort, nausea and diarrhoea. Long-term treatment with phosphate supplements and decreased production of calcitriol due to excess FGF23 can cause hyperparathyroidism (excessive production of parathyroid hormone (PTH).[2,3] Trombetti et al. note that “Adults with XLH are particularly prone to developing secondary and eventually tertiary hyperparathyroidism with hypercalcaemia, which affected 25% and 10% of patients with XLH respectively, in one study[54]”.[3] In the global XLH natural history study, 29% of the 232 adult participants reported hyperparathyroidism associated with the use of conventional therapy, 21% reported nephrocalcinosis, 14% reported kidney stones, and 8% reported impaired renal function.[18]

Hyperparathyroidism can aggravate phosphate wasting and promote bone resorption. Symptoms of hyperparathyroidism include osteoporosis, kidney stones, abdominal pain, fatigue and weakness, depression, memory problems, bone and joint pain, nausea or vomiting and loss of appetite.[55] In tertiary hyperparathyroidism, the parathyroid gland enlarges and excess PTH secretion cannot be managed by medical treatment; surgery to remove parathyroid tissue (parathyroidectomy) may then be required.[2,55]

Treatment burden: oral phosphate is taken 2 to 4 times a day and vitamin D once-daily.[2,3] These supplements have an unpleasant taste. Some patients experience chronic diarrhoea from treatment: for example, one patient in the XLH Burden of Disease Survey states: "*In order to avoid the chronic diarrhoea during work or social functions, I skip my medication.”*[16] For these reasons, some adults find conventional treatment inconvenient and burdensome.

Poor adherence and persistence: adherence to conventional therapy among adults appears to be low, due to difficulties in persevering with the regimen, leading to limited engagement with treatment and eventual treatment discontinuation.[23]

1.3.7 Unmet therapeutic need

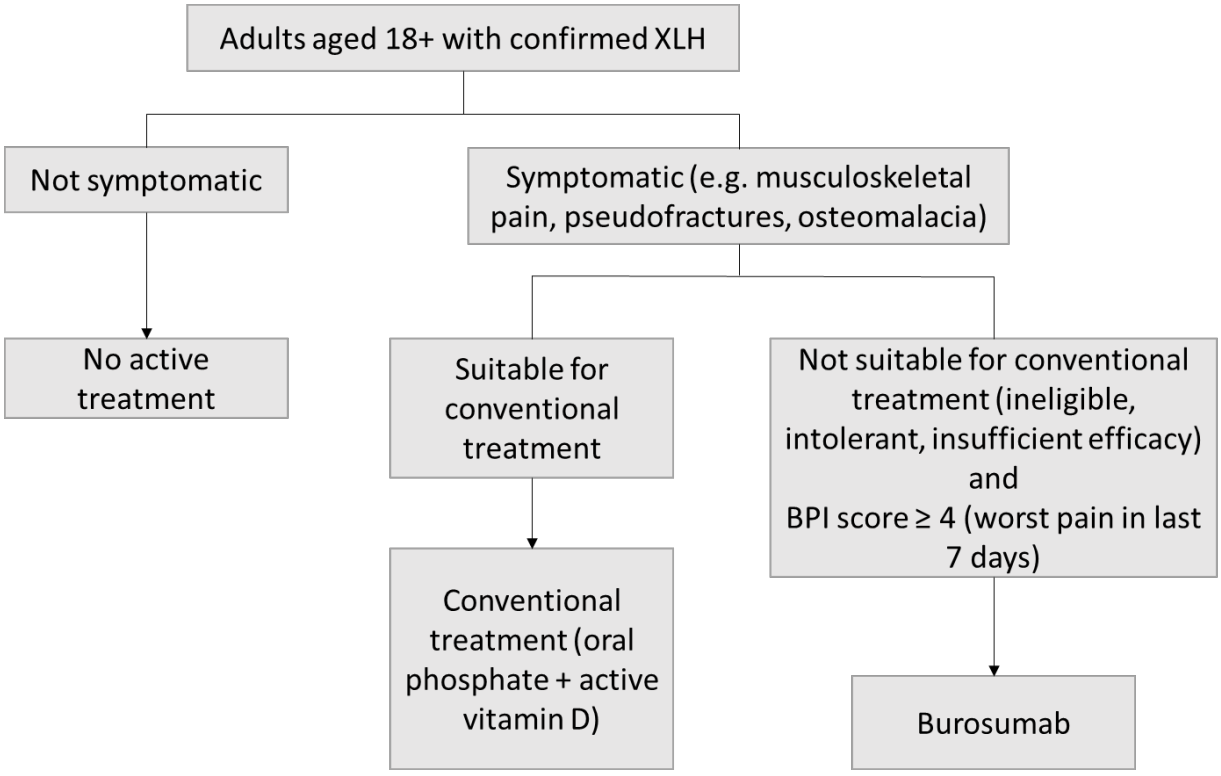
There is a clear need for a well-tolerated therapy that corrects the underlying cause of disease and restores phosphate homeostasis, thereby normalising serum phosphate levels and improving symptoms, physical functioning and HRQoL for adults with highly symptomatic XLH whose needs are not met by conventional therapy.

As described above, conventional therapy with oral phosphate does not address the underlying pathophysiology of XLH (FGF23-induced hypophosphatemia), lacks compelling evidence of efficacy, is poorly tolerated, and has long-term adverse effects that may require discontinuation. It therefore fails to meet the treatment needs of a significant proportion of adults with symptomatic XLH. Chesher et al. (2018), reporting natural history and outcomes for a series of 59 adult patients treated at a UK centre from 1998, and before the availability of burosumab, concluded that “Currently available treatments for XLH do not appear to fully address the long-term complications of the condition, which is associated with considerable morbidity in adulthood”.[34]

1.3.8 Position of burosumab in the treatment pathway

Burosumab is the first and only disease-modifying treatment that treats XLH by targeting the pathophysiology of the condition. Burosumab restores phosphate homeostasis by binding to and inhibiting FGF23, normalising serum phosphate in 94% of patients in the pivotal RCT (study CL303) after 24 weeks.[7] This improves bone mineralisation and bone physiology,[7,35] and improves pain, stiffness, fatigue, physical functioning and fracture healing.[7,56] This in turn is expected to slow the ongoing accumulation of morbidities caused by chronic hypophosphataemia in adults with XLH.

Burosumab is expected to be used in highly symptomatic adult patients who meet the criteria for active pharmacological treatment of their XLH set out in clinical guidelines, but for whom conventional treatment is not suitable due to ineligibility, intolerance or insufficient efficacy. As described in Sections 1.1 and 1.3.6.2, clinical guidelines and UK clinical experts indicate that patients would initially be considered for conventional therapy, and would be considered for burosumab if conventional therapy is not suitable for the reasons outlined above. Further details of the rationale for this positioning are given in Section 1.1 and Table 1.



BPI: Brief Pain Inventory

Figure 7 Pathway of care and position of burosumab in therapy

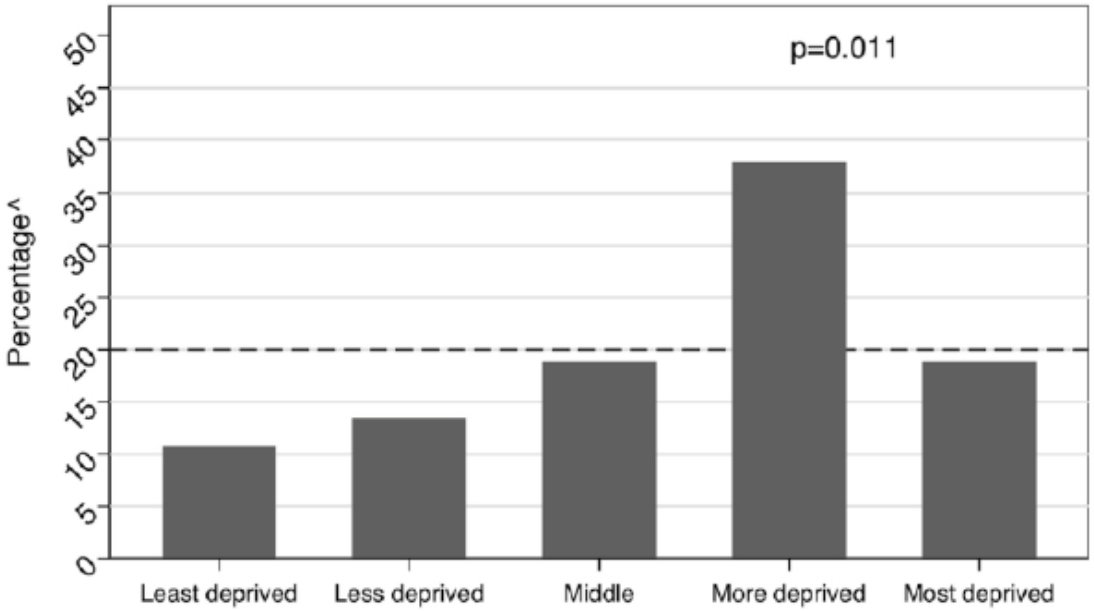
1.4 Equality considerations

Adults with symptomatic XLH have a long-term disability, which is a protected characteristic under the Equality Act 2010.

XLH is also a very rare disease. The UK Rare Disease Framework recognises four key priorities, including helping patients to get a faster diagnosis and improving access to specialist care, treatment and drugs.[9,10] The Framework also cites the need to reduce the health inequalities faced by people living with rare conditions.

People with XLH in the UK are more likely to experience higher levels of social deprivation than the general population.[11] In an analysis by Hawley et al. of 37 XLH adults with linked Index of Multiple Deprivation (IMD) data, 25 (65%) were below the national IMD average (Figure 8).[11] More than one-third of XLH patients fell into the 'more deprived' quintile, which is the second highest level of social deprivation. This is likely to be due to the negative impact of XLH on educational and career options and ability to work, as described in Section 1.3.5.5. The hereditary nature of XLH is likely to worsen deprivation and add to the cumulative multigenerational burden of XLH on families.

Figure 8: Adults with XLH by IMD quintile (n=37)



Dotted reference line represents the hypothetical distribution if XLH prevalence were independent of IMD
IMD, Index of Multiple Deprivation; XLH, X-linked hypophosphataemia
Source: Hawley et al. (2021) [11]

In summary, decision-making on the availability of burosumab directly and exclusively affects individuals with a disability due to a very rare inherited disease, who are also likely to be living with significant socioeconomic deprivation.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

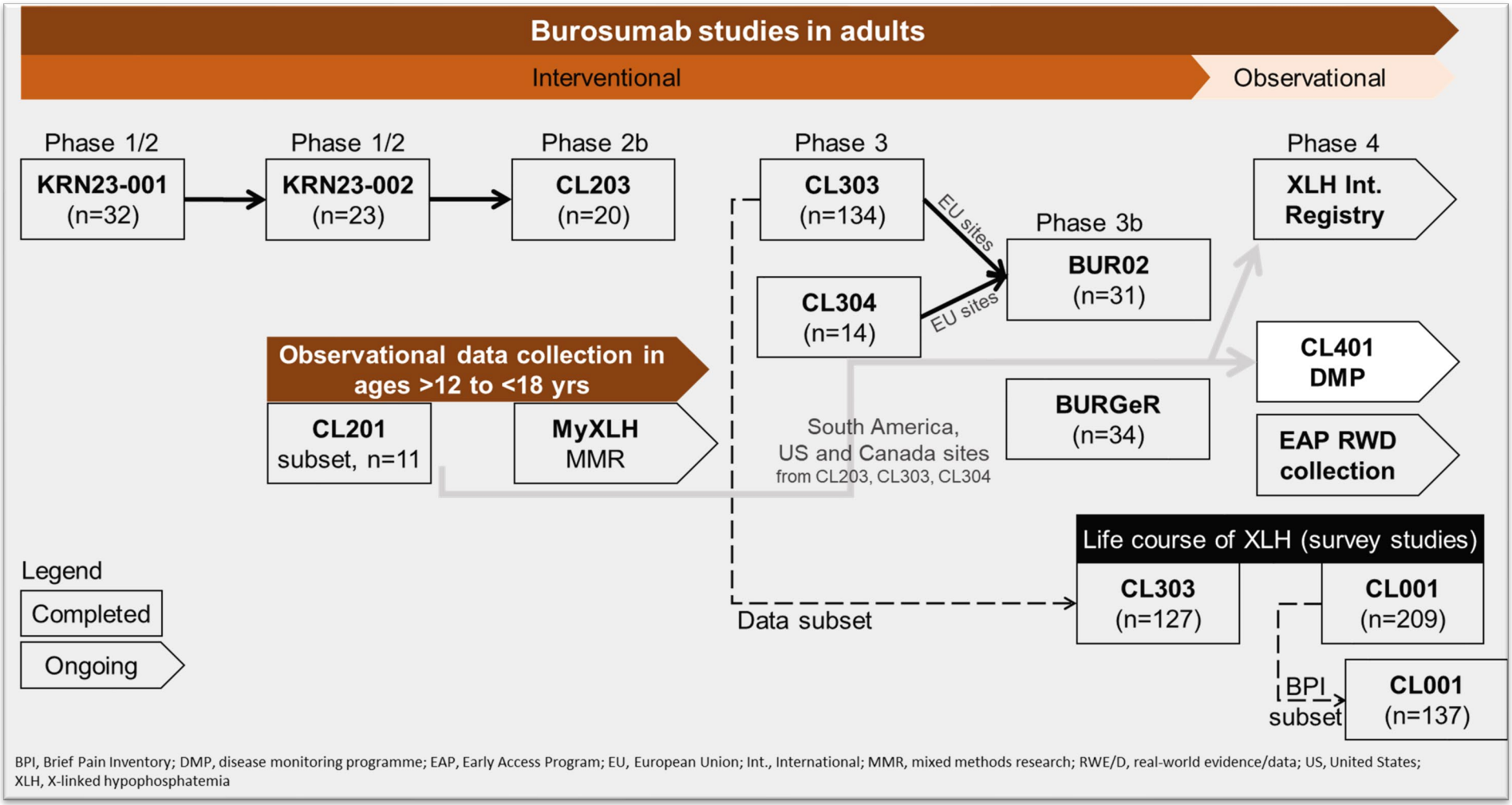
A systematic literature review was carried out to identify relevant studies. See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

Evidence on the clinical effectiveness of burosumab in adults with XLH is available from a number of clinical studies. The studies presented in the submission are listed in Table 7, Table 8 and Figure 9. In addition, supporting real-world evidence is available from a UK centre (see Section 2.6.6).

Table 7 Overview of studies presented in the submission

Study number	Brief description	Outcomes used in the model
Studies of burosumab that inform the base case economic model		
CL303[7,8,57]	Phase 3 randomized, double-blind, placebo-controlled (the pivotal trial) Evaluates: safety and efficacy	Serum phosphate levels WOMAC scores Morbidity rates in non-burosumab-treated patients
BUR02[58,59]	Phase 3b international, multicentre open label extension study Evaluates: long-term safety and efficacy	WOMAC scores
Other studies that inform scenarios in the economic model		
CL001[18]	Global natural history survey	Morbidity rates in non-burosumab-treated patients
Other studies presented in the submission		
CL203[56]	A Phase 2b, open-label, long-term extension study Evaluates: Long-term safety and pharmacodynamics	Not included in the economic model because it does not provide comparative data: all patients received open label burosumab.
CL304[35]	Phase 3, open-label, single-arm, multicentre study Evaluates: effects on bone quality and osteomalacia	Not included in the economic model because the outcomes measured (e.g. osteoid volume) are not suitable for modelling
Life course analysis[17]	Based on CL001 and CL303 Evaluates: development of XLH morbidities associated with the use of conventional therapy as a function of age	-Not included in the economic model as CL001 was deemed more suitable
Early phase studies not presented in the submission		
KRN23-001	Phase 1/2 dose escalation study	-
KR223-002	Long-term extension of KRN23-001	-



BPI, Brief Pain Inventory; DMP, disease monitoring programme; EAP, Early Access Program; EU, European Union; Int., international; MMR, mixed methods research; RWE/D, real-world evidence/data; US, United States; XLH, X-linked hypophosphataemia
CL001 is also known as the global XLH natural history study

Figure 9. Overview of clinical programme for burosumab

Table 8. Overview of the clinical development programme for burosumab in adults

Study	Registry code	Study title/design	Patient population	Duration of treatment	Treatment arms	Primary endpoint
KRN23-001	NCT01340482	A Phase 1/2 open-label, repeat-dose, dose-escalation study of KRN23 in adult subjects with XLH	Adult patients ≥18 years n=32	120 days	Escalating doses of KRN23 (0.05, 0.10, 0.30 and 0.60 mg/kg) administered SC every 28 days (up to 4 doses)	Safety and efficacy of repeated SC injections of KRN23 from baseline as assessed by serum phosphate levels, immunogenicity, adverse events and clinically significant changes in vital signs and laboratory testing
KRN23-002	NCT01571596	An open-label, long-term extension study to evaluate the safety and efficacy of KRN23 in adult subjects with XLH	Adult patients ≥18 years n=23	12 months	Escalating doses of KRN23 (0.05, 0.10, 0.30 and 0.60 mg/kg) administered SC every 28 days (up to 12 doses)	Safety and efficacy of repeated SC injections of KRN23, from baseline, as assessed by serum phosphate levels, immunogenicity, adverse events and clinically significant changes in vital signs and laboratory testing
UX023-CL203	NCT02312687	A Phase 2b, open-label, long-term extension study to evaluate the safety and pharmacodynamics of KRN23 in adult subjects with XLH	XLH patients ≥18 years n=20	144 weeks	All patients received open-label burosumab (0.3, 0.6 or 1.0 mg/kg every 4 weeks)	Long-term safety and efficacy of burosumab, assessed by serum phosphate levels in the normal range (2.5–4.5 mg/dL [0.81–1.45 mmol/L]), PD and immunogenicity
UX023-CL303	NCT02526160	A randomised, double-blind, placebo-controlled, Phase 3 study to assess the efficacy and safety of KRN23 in adults with XLH	Adult patients ≥18 years n=134	RCT period (0–24 weeks) Open-label Treatment Continuation period (24–48 weeks) Open-label Treatment Extension period I (48–96 weeks) Open-label Treatment Extension period II – US only (96–149 weeks)	Burosumab 1.0 mg/kg administered via SC injection every 4 weeks Placebo administered via SC injection every 4 weeks	Proportion of patients achieving mean serum phosphate levels above the LLN

Study	Registry code	Study title/design	Patient population	Duration of treatment	Treatment arms	Primary endpoint
UX023-CL304	NCT02537431	Open-label, single-arm, multicentre study to establish the effects of burosumab on bone quality and osteomalacia associated with XLH in adult patients (Phase 3)	Adult patients ≥18 years n=14	Open-label treatment period (0–48 weeks) Open-label treatment extension period (48–96 weeks)	Burosumab 1.0 mg/kg administered via SC injection every 4 weeks	Percent change from baseline at Week 48 in osteoid volume
BUR02	NCT03920072	Phase 3b open-label, international, multicentre study to continue to monitor the long-term safety and efficacy of burosumab in adults	EU patients who participated in in UX023-CL303 or UX023-CL304 n=35	Open-label treatment period (0-48 weeks)	Burosumab 1.0 mg/kg administered via SC injection every 4 weeks	Proportion of patients achieving mean serum phosphate levels above the LLN

EU, European Union; KRN23, burosumab; LLN, lower limit of normal; RCT, randomised clinical trial; SC, subcutaneous; US, United States; XLH, X-linked hypophosphataemia

2.2.1 Summary of clinical studies used in the model

Summaries of the two clinical studies used in the economic model (CL303 and BUR02) are given in Table 9 and Table 10. Bold indicates outcomes used in modelling. Methods for all studies presented are given in Section 2.3.

Table 9 Study CL303 (pivotal trial)

Study	**Pivotal trial UX023-CL303 (NCT02526160)**
Study design	Phase 3, randomised, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of burosumab in adults with XLH
Population	Adults aged 18 to ≤65 years with confirmed XLH diagnosis (N=134)
Intervention(s)	Burosumab 1.0 mg/kg every 4 weeks administered via subcutaneous injection.
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	n/a
Reported outcomes specified in the decision problem	*Primary outcome* **Proportion of participants achieving a mean serum phosphate concentration above the lower limit of normal (LLN) of 2.5 mg/dL (0.81 mmol/L).** A single value was calculated as the average of values at the midpoints of the 4-weekly dosing intervals (i.e. at Weeks 2, 6, 10, 14, 18 and 22). *Secondary outcomes* **Change from baseline to Week 24 in BPI worst pain score** **Change from baseline to Week 24 in WOMAC stiffness subscale score** **Change from baseline to Week 24 in WOMAC physical function subscale score** Adverse effects of treatment *Exploratory outcomes* Mobility (6-minute walk test, Timed Up and Go) Active fractures and pseudofractures
All other reported outcomes	Additional measures to assess serum phosphate between baseline and Week 24 Change and percentage change from baseline to post-baseline visits in serum phosphate, serum 1,25(OH)2D, urinary phosphate, TmP/GFR and TRP Change and percentage change from baseline to post-baseline visits in biochemical markers of bone remodelling, including P1NP, CTx and BALP

	Change from baseline to post-baseline visits in BPI worst pain score Change from baseline to post-baseline visits in BPI pain severity score Change from baseline to post-baseline visits in BPI pain interference score Change from baseline to post-baseline visits in BFI worst fatigue score Change from baseline to post-baseline visits in BFI global fatigue score Change from baseline to post-baseline visits in WOMAC stiffness subscale score Change from baseline to post-baseline visits in WOMAC physical function subscale score *Relevant exploratory outcomes are listed in the row above. A full list of exploratory outcomes is available in the Clinical Study Report.*

Sources: Clinical trial registry entry (NCT02526160, ClinicalTrials.gov); Insogna et al., 2018;[7] Clinical study report[8]

Table 10. BUR02 (NCT03920072)

Study	BUR02 (NCT03920072)
Study design	Phase 3b open-label, international, multicentre extension study to continue to monitor the long-term safety and efficacy of burosumab in adults
Population	EU patients who participated in in UX023-CL303 or UX023-CL304 N=35
Intervention(s)	Burosumab 1.0 mg/kg every 4 weeks administered via subcutaneous injection.
Comparator(s)	N/A – open label
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	Yes
Rationale if study not used in model	*n/a*
Reported outcomes specified in the decision problem	**Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)** Brief Pain Inventory (BPI-SF) Brief Fatigue Inventory (BFI) Short Form 36 Version 2 (SF-36v2) Walking ability as measured by 6-Minute Walk Test (6MWT) (optional) Mobility as measured by Timed Up and Go (TUG) test completion time (optional)
All other reported outcomes	Proportion of patients achieving mean serum phosphate levels above the LLN

Sources: Clinical trial registry entry (NCT03920072, ClinicalTrials.gov); Clinical study report[59]; Kamenicky 2023[60]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

This section details the methodology of the presented studies. Statistical analysis and baseline patient characteristics are also described here for ease of reference. In addition, a comparative summary of the studies that inform the economic model (CL303 and BUR02) is provided in Table 18.

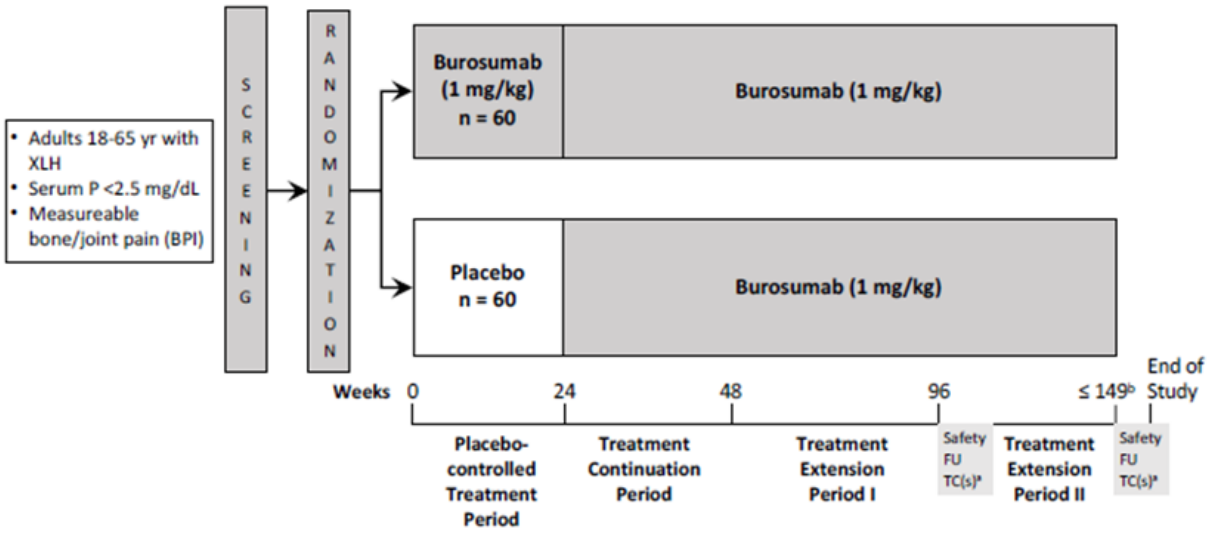
2.3.1 CL303 (Pivotal trial)

The pivotal trial was study UX012-CL303, hereafter referred to as CL303. This was a randomised, double-blind, placebo-controlled, Phase 3 study with open-label extension to

assess the efficacy and safety of KRN23 (burosumab) in adults with X-linked hypophosphataemia (XLH) (NCT 02526160). Information on this trial is taken from the study publication by Insogna et al. 2018,[7] supplemented by the EMA public assessment report (EPAR)[61] and the Clinical Study Report[8] where additional detail is required. Additional study publications describe long-term results.[57,62]

Figure 10 shows the study design. After screening, participants were randomised 1:1 to either burosumab or placebo and entered the 24-week placebo-controlled treatment period. At the end of this period, participants entered an open-label treatment continuation period (Weeks 24 to 48), during which they all received burosumab. There were then two open-label treatment extension periods, the first from Week 48 to 96 and the second (in the US only) from Week 96 to 149. After Week 96, participants in the EU had the option to enter the open-label Study BUR02, which is described later in this section.

Figure 10: Study design: CL303



[a]Safety follow-up telephone calls took place after completion of treatment or early discontinuation if the patient did not continue treatment with burosumab via another route
[b]Treatment Extension Period II only took place in the US. Its length varied between patients but could be no longer than 53 weeks.
Source: EMA public assessment report[61]

The protocol specified that randomisation was to be stratified by mean Brief Pain Inventory (BPI) worst pain score for the 7 days before the baseline visit. However, an error meant that BPI average pain data were used instead. Owing to the correlation between BPI worst pain score and average pain score, it was accepted by the EMA that this did not affect the outcome of the primary endpoint and had minimal impact on the PRO results.[61] Randomisation was also stratified by region (North America/European Union, Japan, or South Korea).

2.3.1.1 Eligibility criteria

The key inclusion and exclusion criteria for Study CL303 are shown in Table 11.

Table 11: Inclusion and exclusion criteria: Study CL303

Key inclusion criteria	Key exclusion criteria

• Age 18 to ≤65 years
• XLH diagnosis supported by classic clinical features and at least one of the following at screening:
  ○ Documented *PHEX* mutation in the patient or a directly-related family member with appropriate XC-linked inheritance
  ○ Serum intact FGF23 level >30 pg/mL by Kainos assay
• Biochemical findings associated with XLH:
  ○ Serum phosphate <2.5 mg/dL (0.81 mmol/L)
  ○ Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR) of <2.5 mg/dL
• Brief Pain Inventory (BPI) worst pain score ≥4 (see Section 2.3.1.3 for recall period)
• If taking chronic pain medications, must have been on a stable regimen for >21 days before screening and willing to maintain the same dose (maximum 60 mg/day oral morphine equivalent) and schedule during the placebo-controlled treatment period
	• Corrected serum calcium ≥10.8 mg/dL (2.7 mmol/L)
	• Serum intact parathyroid hormone (iPTH) ≥2.5-fold ULN and/or use of medication to supress parathyroid hormone in the 60 days before screening
	• Recent history (≤6 months) of traumatic fracture or orthopaedic surgery

Source: Insogna et al. (2018)[7]

2.3.1.2 Study medicines

During the placebo-controlled treatment period, participants received either burosumab 1.0 mg/kg or matching placebo every 4 weeks. During the subsequent open-label periods, all participants received burosumab 1.0 mg/kg every 4 weeks. Each dose was rounded up to the nearest 10 mg, up to a maximum of 90 mg to reach serum phosphate levels within the lower limits of normal. Treatment was administered via subcutaneous injection.

Permitted and disallowed concomitant medications

- Participants who were receiving therapies that affect phosphate metabolism (such as oral phosphate, active vitamin D metabolites, or analogues) could only enrol in the study after a wash out period of at least 2 weeks.

- If a participant's serum level of 25-hydroxyvitamin D fell below 20 ng/mL during the study, they were allowed to take oral supplementation (e.g. cholecalciferol, ergocalciferol).
- If a participant was receiving pain medication, the regimen had to be stable for at least 21 days before screening and the participant had to agree to stay on the same dose (maximum 60 mg/day oral morphine equivalent) and schedule during the double-blind period.
- Participants could have received burosumab previously as part of another clinical trial; however they were not allowed to enrol in Study CL303 within 90 days of receiving burosumab or any other monoclonal antibody.[8]

2.3.1.3 Endpoints and outcome measures

Pre-specified primary and secondary outcomes are listed in Table 12, followed by explanatory details of the outcome measures used.

Table 12 CL303: Outcome measures

Endpoint
Primary efficacy endpoint
Proportion of participants achieving a mean serum phosphate concentration above the lower limit of normal (LLN) of 2.5 mg/dL (0.81 mmol/L). A single value was calculated as the average of values at the midpoints of the 4-weekly dosing intervals (i.e. at Weeks 2, 6, 10, 14, 18 and 22).
Key secondary endpoints
• Change from baseline to Week 24 in BPI worst pain score • Change from baseline to Week 24 in WOMAC stiffness subscale score • Change from baseline to Week 24 in WOMAC physical function subscale score
Other secondary endpoints
• Additional measures to assess serum phosphate between baseline and Week 24 • Change and percentage change from baseline to post-baseline visits in serum phosphate, serum 1,25(OH)2D, urinary phosphate, TmP/GFR and TRP • Change and percentage change from baseline to post-baseline visits in biochemical markers of bone remodelling, including P1NP, CTx and BALP • Change from baseline to post-baseline visits in BPI worst pain score • Change from baseline to post-baseline visits in BPI pain severity score • Change from baseline to post-baseline visits in BPI pain interference score • Change from baseline to post-baseline visits in BFI worst fatigue score • Change from baseline to post-baseline visits in BFI global fatigue score • Change from baseline to post-baseline visits in WOMAC stiffness subscale score • Change from baseline to post-baseline visits in WOMAC physical function subscale score
Relevant exploratory endpoints
• Active fractures and pseudofractures • Six-minute Walk test • Timed Up and Go test

$1,25(OH)_2D$, 1,25-dihydroxy vitamin D; BALP, bone-specific alkaline phosphatase; BFI, Brief Fatigue Inventory; BPI, Brief Pain Inventory; CTx, carboxy-terminal cross-linked telopeptide of type I collagen; P1NP, procollagen type 1 n-terminal propeptide; TmP/GFR, ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; TRP, tubular reabsorption of phosphate; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index
Source: Insogna et al. (2018)[7]; EMA public assessment report[61]

Patient-reported outcomes were assessed in Study CL303 using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Brief Pain Inventory-Short Form (BPI-SF) and the Brief Fatigue Inventory (BFI). All these instruments are validated for use in XLH.[63–65] An overview of their characteristics is given below and in **Table 13**.

WOMAC score: The Western Ontario and McMaster Universities Osteoarthritis Index **(**WOMAC) is a patient-reported questionnaire that is well established in evaluation of osteoarthritis.**[66]** Two domains were used in the study: Stiffness (2 questions) and Physical Function (17 questions), which evaluate symptoms over the previous 48 hours. The WOMAC is administered in a 5-point Likert-scale format using descriptors of none, mild, moderate,

severe, and extreme corresponding to an ordinal scale of 0-4. Higher scores on the WOMAC indicate worse stiffness and functional limitations. Scores are normalized to a 0-100 metric where 0 was the best health state and 100 the worst.[67]

Brief Pain Inventory (BPI): The BPI evaluates pain over the previous 24 hours. Two dimensions are measured: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Question 3 of the short-form BPI (BPI-Q3) asks subjects to rate their pain at its worst in the last 24 hours on a scale of 0 (no pain) to 10 (pain as bad as you can imagine). Pain interference in the last 24 hours is rated on a scale of 0 (does not interfere) to 10 (completely interferes). [67] The average BPI score was calculated from 8 scores (pain diaries from the 7 days prior to the visit and the score at the visit), except for the randomization stratification, which was based on 7 scores (pain diaries from the prior 7 days).[7]

Brief Fatigue Inventory (BFI): The BFI is a self-reported questionnaire consisting of 9 items related to fatigue that are rated on a numerical scale with a recall period of 24 hours. Two dimensions are measured: fatigue severity and the interference of fatigue on daily life (activity, mood, walking ability, work, relations with others, and enjoyment of life). BFI Global Fatigue score was calculated by averaging all 9 items on the BFI. Global scores range from 0 to 10, with higher score indicating worse fatigue severity and interference.[67]

Table 13 Patient-reported outcome instruments used in Study CL303

	WOMAC	BPI-SF	BFI
Number of items	24	15[a]	
Response format	5-point scale: none, mild, moderate, severe, extreme	0-10 NRS (where 10 = worst pain severity/interference)	0-10 NRS (where 10 = worst fatigue severity/interference)
Scores reported	Pain (5 items) Stiffness (2 items) Physical function (17 items) Total score (24 items)	Worst pain (average) (1 item)[b] Worst pain (greatest (1 item)[b] Pain severity (4 items) Pain interference (7 items)	Worst fatigue (average) (1 item)[c] Worst fatigue (greatest (1 item) [c] Fatigue severity (3 items) Fatigue interference (6 items) Global fatigue (9 items)
Recall period	48 hours	24 hours	24 hours
XLH-specific meaningful change (MCID)[d]	≥-11.0 pain ≥-10 stiffness ≥-8 physical function ≥-10 total score [65]	≥-1.72 worst pain ≥-1.0 pain interference [64]	≥-1.5 worst fatigue ≥-1.2 global fatigue ≥-1.2 fatigue interference [63]

[a]BPI-SF has 15 items in total; 11 items contribute to the scores reported in this submission. [b]BPI-SF Question 3 asks subjects to rate pain at its worst in the last 24 hours on a scale of 0 (no pain) to 10 (pain as bad as you can imagine). The analysis described in this submission reports worst pain (average score for Question 3 over 8 days) and worst pain (greatest score for Question 3 over 8 days (82, 84, 85). [c]BFI Question 3 asks subjects to rate fatigue at its worst in the last 24 hours on a scale of 0 (no fatigue) to 10 (fatigue as bad as you can imagine). The analysis described in this submission reports worst fatigue (average score for Question 3 over 8 days) and worst fatigue (greatest score for Question 3 over 8 days) (83). [d]A guide for interpreting the mean in a group of subjects rather than in an individual.
BFI, Brief Fatigue Inventory; BPI-SF, Brief Pain Inventory-Short Form; MCID, minimal clinically important difference; NRS, numerical rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; XLH, X-linked hypophosphataemia.
Source: Briot et al. (2021)[57]

2.3.1.4 Statistical analysis and definition of study groups

Table 14 Statistical analyses of study CL303

	CL 303
Hypothesis objective	The primary hypothesis was that treatment with 1.0 mg/kg burosumab every 4 weeks is more effective than placebo in increasing serum phosphate levels in adults with XLH.
Analysis sets	For the primary analysis of the primary outcome, efficacy analyses were carried out on the primary analysis set (i.e. all randomised participants who received at least one dose of study drug during the placebo-controlled treatment period). This population was used for the analysis as each specific milestone (i.e. Weeks 24, 48 and 96).[61]

Sample size, power calculation	A sample size of 60 per group (total sample size of 120) was determined to provide >95% power to detect a 50% difference between treatment groups in the proportion of participants achieving a mean serum phosphate concentration above the lower limit of normal (LLN) of 2.5 mg/dL (0.81 mmol/L) at the midpoint and end of the dose intervals between Baseline and Week 24 at the two-sided level of significance of 0.05. With a total sample size of 120 subjects, this study design also had ≥ 80% power to detect a mean difference of 1.0 in change from Baseline between the burosumab and placebo groups in BPI Worst Pain, assuming a mean change from Baseline of 2.0 in the burosumab group and 1.0 in the placebo group, a common standard deviation (SD) of 1.8, and a 10% drop-out rate.[61]
Statistical analysis of primary endpoint	The primary endpoint was analysed with the Cochrane-Mantzel-Haenzel test, adjusted for randomisation stratification factors (BPI average pain score and region), tested at the two-sided alpha level of 0.05. A sensitivity analysis was performed on the primary endpoint using the planned randomisation stratification factors (i.e. BPI worst pain score and region).[61]
Statistical analysis of secondary endpoints	If the primary endpoint was shown to be statistically significant, the key secondary endpoints were analysed as a group using a generalised estimating equation (GEE) repeated-measures analysis, with the Hochberg adjustment applied for multiple testing. Treatment, the actual randomisation stratification factor based on BPI average pain, region, visit and interaction of treatment-by-visit were included as fixed factors, adjusted for baseline measurements. Compound symmetry was used as the covariance structure in the model to allow constant variance for the assessment and constant covariance between the assessments over time. A sensitivity analysis was performed on the key secondary endpoints using the planned randomisation stratification factors (i.e. BPI worst pain score and region). Other continuous secondary endpoints were analysed using similar GEE models. The fracture analysis used a generalised linear mixed model for binomial distribution with the logit link function that included treatment, visit, treatment-by-visit and fracture type as fixed factors, accounting for nesting of fractures within patients.[7,61] Further analyses of the key secondary PRO outcomes were undertaken at the request of the EMA, using a repeated measures ANCOVA. These analyses were accepted by the EMA.[61]
Data management and patient withdrawals	134 subjects were enrolled and randomized 1:1 to burosumab (68 subjects) or placebo (66 subjects). All 134 subjects (100%) received at least 1 dose of study drug and were included in the Primary and Safety Analysis Sets.[7] Instances of missing or uninterruptable data were resolved in coordination with the investigator. No imputation on missing data was made, unless stated otherwise.

2.3.1.5 Baseline characteristics and patient disposition

All 134 participants (100.0%) received at least 1 dose of study drug and were included in the Primary and Safety Analysis Sets. All but 1 participant, who was in the burosumab group, completed the 24-week Placebo-controlled Treatment Period. A total of 133 participants received at least 1 dose of open-label burosumab and were included in the Treatment Continuation Analysis Set, including 126 (94.0%) who completed the Treatment Continuation Period. The CONSORT diagram for the 24-week period is provided in Appendix D and details of disposition in the Treatment Extension Period are available in the CSR, Table 12.

Table 15 shows participants' baseline demographics and disease characteristics for study CL303, which were similar between the treatment groups. A substantial disease burden was apparent at baseline, even though most had received conventional therapy at some point during their disease course. Nearly all participants had enthesopathy at baseline and more than half had active fractures and/or pseudofractures. Approximately 70% of participants reported their pain as severe at baseline.

Table 15 Demographics and baseline characteristics (CL303)

	Burosumab (n = 68)	**Placebo (n = 66)**	**Total (n = 134)**
Demographics			
Age (years)			
Mean ± SD	41.3 ± 11.6	38.7 ± 12.8	40 ± 12.2
Range	20.0-63.4	18.5-65.5	18.5-65.5
Female, n (%)	44 (64.7)	43 (65.2)	87 (64.9)
Race, n (%)			
White	55 (80.9)	53 (80.3)	108 (80.6)
Asian	12 (17.6)	9 (13.6)	21 (15.7)
Black	0	3 (4.5)	3 (2.2)
Other	1 (1.5)	1 (1.5)	2 (1.5)
Region, n (%)			
North America/Europe	58 (85.3)	58 (87.9)	116 (86.6)
Japan	6 (8.8)	5 (7.6)	11 (8.2)
South Korea	4 (5.9)	3 (4.5)	7 (5.2)
Height[a], mean ± SD			
Centimetres	152 ± 9.5	153 ± 11.8	152 ± 10.7
Z-score[b]	-2.3 ± 1.2	-2.3 ± 1.3	-2.3 ± 1.3
Percentile	6.4 ± 12.9	7.2 ± 12.1	6.8 ± 12.5
BMI[a] (kg/m^2), mean ± SD	30.0 ± 7.5	30.6 ± 7.8	30.0 ± 7.6
Genetic status			
PHEX mutation, n (%)			
Pathogenic	45 (66.2)	50 (75.8)	95 (70.9)
Likely pathogenic	8 (11.8)	7 (10.6)	15 (11.2)
Variant of unknown significance	9 (13.2)	8 (12.1)	17 (12.7)

	Burosumab (n = 68)	Placebo (n = 66)	Total (n = 134)
No mutation	6 (8.8)	1 (1.5)	7 (5.2)
Laboratory measurements			
Serum phosphate (mg/dL)[c], mean ± SD	2.0 ± 0.30	1.9 ± 0.32	2.0 ± 0.31
TmP/GFR (mg/dL)[c], mean ± SD	1.7 ± 0.40	1.6 ± 0.37	1.6 ± 0.39
Serum 1,25(OH)2D (pg/mL)c, mean ± SD	32.4 ± 13.0	33.5 ± 15.6	33.0 ± 14.3
Serum calcium (mg/dL)c, mean ± SD	9.2 ± 0.49	9.1 ± 0.41	9.2 ± 0.45
Serum iPTH (pg/mL)c, mean ± SD	98.9 ± 60.8	95.2 ± 38.8	97.0 ± 50.9
Prior conventional therapy			
Conventional therapy ever, n (%)			
Phosphate + vitamin D metabolites or analogues	59 (86.8)	62 (93.9)	121 (90.3)
Phosphate alone	3 (4.4)	1 (1.5)	4 (3.0)
Vitamin D metabolites or analogues alone	3 (4.4)	3 (4.5)	6 (4.5)
Conventional therapy before age 18 years, n (%)			
Phosphate + vitamin D metabolites or analogues	45 (66.2)	48 (72.7)	93 (69.4)
Phosphate alone	5 (7.4)	2 (3.0)	7 (5.2)
Vitamin D metabolites or analogues alone	5 (7.4)	4 (6.1)	9 (6.7)
Conventional therapy duration (years), mean ± SD			
Phosphate[d]	16.8 ± 10.7	16.2 ± 10.2	16.5 ± 10.4
Vitamin D metabolites or analogues[e]	19.0 ± 10.0	17.5 ± 11.9	18.2 ± 11.0
Pain scores and medication			
BPI worst pain >6.0, n (%)	53 (77.9)	43 (65.2)	96 (71.6)
Any pain medication at baseline, n (%)	47 (69.1)	44 (66.7)	91 (67.9)
Any opioid at baseline, n (%)	17 (25.0)	13 (19.7)	30 (22.4)
XLH manifestations			
Enthesopathy on X-ray, n (%)	68 (100.0)	65 (98.5)	133 (99.3)
Nephrocalcinosis score >0[f], n (%)	34 (50.0)	39 (59.1)	73 (54.5)
Medical history			
Orthopaedic surgery, n (%)	45 (66.2)	47 (71.2)	92 (68.7)
Osteoarthritis, n (%)	47 (69.1)	38 (57.6)	85 (63.4)
Fractures			
Unhealed fracture/pseudofracture at baseline, n (%)	32 (47.1)	38 (57.6)	70 52.2)
Number of fractures/pseudofractures	65	91	156
Fractures	14	13	27
Pseudofractures	51	78	129

[a]Height and BMI not recorded at baseline for one patient in each group. [b]Z-score adjusted for sex.
[c]Normal ranges: phosphate, 2.5-4.5 mg/dL; 1,25(OH)2D, 18-72 pg/mL; calcium, 8.6-10.2 mg/dL; iPTH,

14-72 pg/mL; TmP/GFR, 2.5-4.2 mg/dL. [d]Among patients with any prior use of phosphate (n = 62 burosumab, n = 63 placebo). [e]Among patients with any prior use of vitamin D metabolites or analogues (n = 62 burosumab, n = 65 placebo). [f]On a 5-point scale where 0 = normal and 4 = stone formation solitary focus of echoes at the tip of the pyramid
BMI, body mass index; BPI, Brief Pain Inventory; iPTH, intact parathyroid hormone; SD, standard deviation; TmP/GFR, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate
Source: Insogna et al. (2018);[7] Portale et al. (2019)[62]

At baseline, [redacted][68] regardless of whether they were taking phosphate supplements at screening, before washout period (a washout period was required for participants taking oral phosphate and active Vitamin D supplements) (Table 16).

Table 16: Serum phosphate levels by record of phosphate supplement intake at screening visit 1 (before washout): Study CL303

	No record of phosphate supplement [redacted]	**Record of phosphate supplement** [redacted]	**p-value (exact chi-squared)**
Below LLN, n (%)	[redacted]	[redacted]	
Above LLN (or equal), n (%)	[redacted]	[redacted]	[redacted]
Mean, mmol (SD)	[redacted]	[redacted]	
Min, max	[redacted]	[redacted]	
Below LLN, n	[redacted]	[redacted]	
Mean, mmol (SD)	[redacted]	[redacted]	
Min, max	[redacted]	[redacted]	
Above LLN, n	[redacted]	[redacted]	
Mean, mmol (SD)	[redacted]	[redacted]	
Min, max	[redacted]	[redacted]	

LLN, lower limit of normal (2.5 mg/dL); SD, standard deviation
Source: Kyowa Kirin Ltd Data on file, 2022[68]

2.3.2 Study BUR02

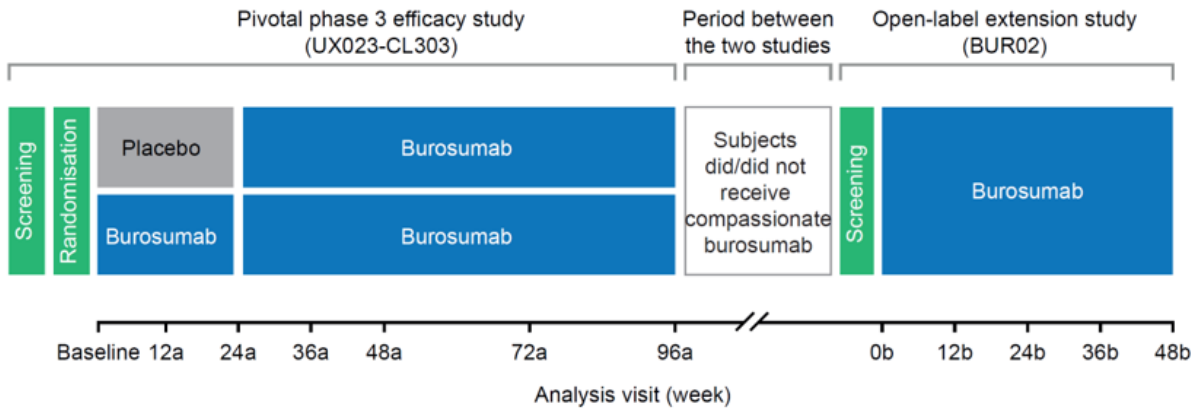
2.3.2.1 Eligibility criteria and study design

Study BUR02 (NCT03920072) was a Phase 3b, multicentre open label extension study to monitor the long-term safety and efficacy of burosumab in adults (18 to 70 years old). Participants from European sites in Studies CL303 and CL304 were invited to take part and received burosumab every 4 weeks at the dose they were receiving at the end of CL303, for up to a further 48 weeks (giving a total study duration of up to 144 weeks) (Figure 11).[60]

Participants were transitioned to BUR02 as soon as possible after the completion of CL303 or CL304. During the gap between these studies and BUR02, interim burosumab treatment

was provided via an Early Access Programme to those participants for whom this was accessible. In those countries where early access was not permissible, patients had a gap in treatment (see below).

The primary efficacy outcome was the serum phosphate concentration at the end of each dose cycle (mean trough serum phosphate). Secondary outcomes included the same patient-reported outcomes and functional assessments as in Study CL303. Post-hoc exploratory analyses were conducted to evaluate the impact of treatment interruption on clinical laboratory values and PROs. [69]



Analysis visits in the phase 3 study and open-label extension study are suffixed a and b, respectively Source: Kamenicky et al. 2023[60]

Figure 11: Time course and treatment in CL303 and BUR02

2.3.2.2 Statistical analysis

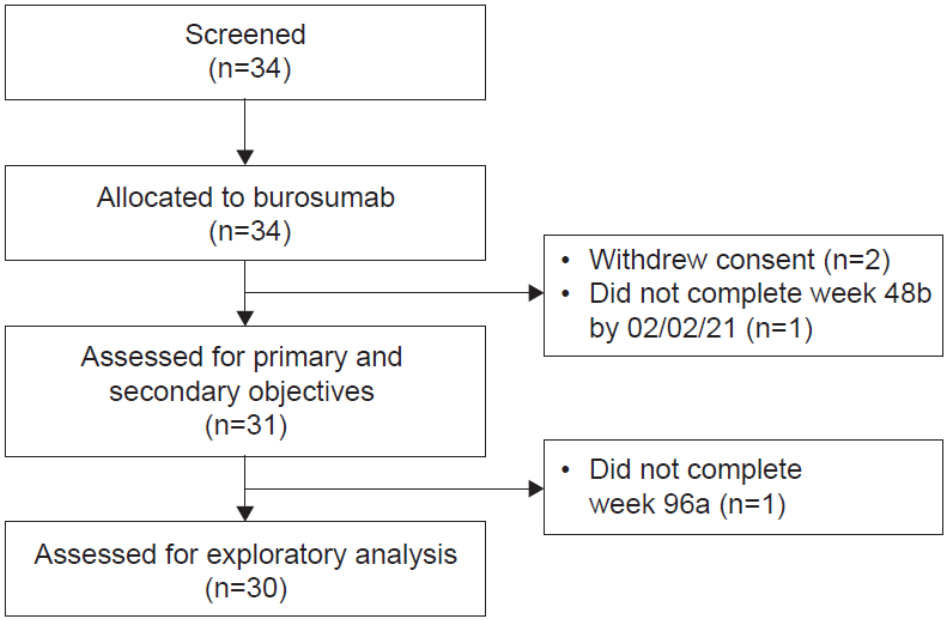
The population for the primary analysis comprised all participants who enrolled in the CL303 and BUR02 open-label extension studies and who recorded at least one measurement after CL303 baseline in the latter. PROs and functional endpoints were evaluated as change from CL303 baseline to each analytical time point through to week 96 in CL303 and in the open-label extension through to week 48. To maintain consistency with the analysis for CL303, a generalised estimating equation repeated-measures analysis was also performed. The model included treatment, actual randomisation stratification factor based on BPI Average Pain (except the model for BPI Worst Pain), region, visit and interaction of treatment-by-visit as fixed factors, adjusted for CL303 baseline measurements. Compound symmetry was used as the covariance structure for the model, which specified constant variances for the assessments and constant covariances between the assessments over time. There were no statistical adjustments for multiplicity.

For the exploratory analysis on the impact of interruption to burosumab treatment, Fisher's exact test was used to compare the numbers of participants in the two groups with values above the LLN at the start of the open-label extension study. To assess the impact of

burosumab treatment on PROs and ambulatory function, changes in PRO score/6MWT distance from CL303 baseline to the start of the open-label extension study in the two groups were compared using the Mann-Whitney U test.

2.3.2.3 Patient disposition and baseline characteristics

34 patients from CL303 met the eligibility criteria and were enrolled but 2 subsequently withdrew. At the published data cut in January 2021, 31 participants had received up to 48 weeks' further burosumab treatment in BUR02. The publication by Kamenicky et al. reports the results for these 31 participants from the phase 3 study baseline to week 96a and through the open-label extension study to week 48b.[60] Patient disposition is shown in Figure 12. No further publication is expected due to the small amount of additional data reported in the final CSR.[59]



Week 96a is the end of the randomized study; week 48b is the end of the open-label extension

Figure 12 Flow of patients through CL303 and BUR02 open label extension study

Table 17 shows demographics and baseline characteristics for the BUR02 study. Of note, 8 patients received continuous burosumab for 6–16 months and eight missed only one dose during 6–7 months' treatment. The remainder experienced treatment interruptions before beginning BUR02.

Table 17: Demographic and baseline characteristics, BUR02

	BUR02 (n=31)
Mean (SD) age (years) Range	40.1 (12.1) 18.5-59.9
Female (n, %)	21 (67.7)
Height (mean [SD]), cm	154.4 (13.0)
Body mass index (kg/m^2)	27.7 (5.5)
BPI-SF worst pain score	6.7 (1.2)
Any pain medication at baseline	25 (80.6)
Any opioid at baseline	8 (25.8)
Medical history Orthopedic surgery Osteoarthritis	 20 (64.5) 20 (64.5)

Source: Kamenicky et al.[60]

2.3.3 Study CL304

2.3.3.1 Summary of methods

Study CL304 (NCT02537431) was a 96-week, Phase 3, open-label, single-arm multicentre study to investigate the efficacy of burosumab in improving osteomalacia in adults with XLH who had not been treated for at least 2 years.[35] Osteomalacia is associated with poor bone quality that can result in pseudofractures, fractures, impaired fracture healing, and bone and joint pain. The key inclusion criteria were confirmed XLH; age 18-65 years; a fasting serum phosphate and renal tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR) <2.5 mg/dL; and skeletal pain defined as a “worst pain” score of 4 on the Brief Pain Inventory.

Participants received burosumab 1 mg/kg every four weeks. If the baseline biopsy did not reveal osteomalacia, they continued treatment but did not underdo a second biopsy at Week 48. After Week 48, all participants continued treatment for an additional 48 weeks.

The primary endpoint was the improvement in osteoid volume/bone volume assessed by transiliac bone biopsies taken at baseline and Week 48. Other endpoints included serum phosphate, markers of bone turnover, fracture/pseudofracture healing and safety. Active (unhealed) fractures and pseudofractures were identified at baseline and fracture healing was assessed by follow-up targeted X-rays of those fractures/pseudofractures.[35] Histomorphometric endpoints were analysed using a two-sided t test. If the normal assumption was not met, a sign test for median was used. For other selected endpoints, the least squares (LS) mean and standard error (SE) for the change from baseline to week 48 were provided using the generalized estimating equation (GEE) repeated measures analysis,

including time as the categorical variable adjusted for baseline measurement in the model with compound symmetry covariance structure.

2.3.3.2 Patient disposition and baseline characteristics

Patient disposition is shown in Figure 13.

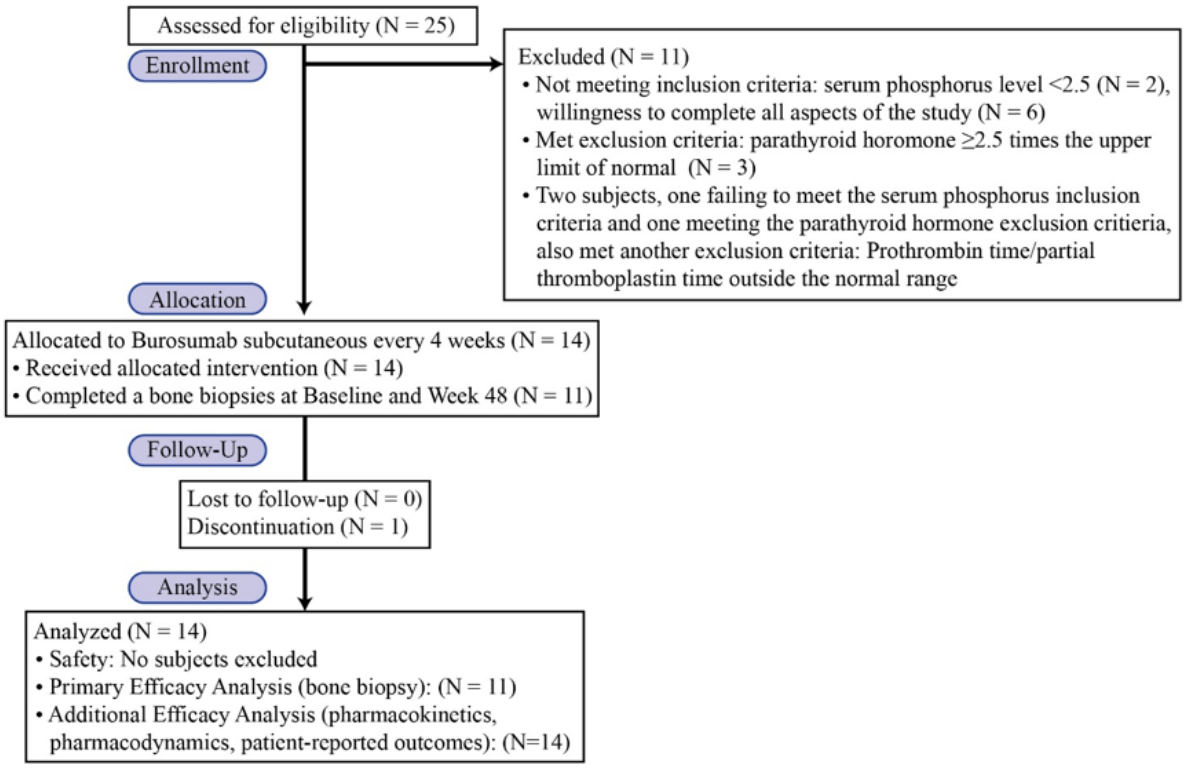


Figure 13 Study CL304, patient disposition

Source: Insogna 2019[35]

In the 14 patients analysed, mean age was 40.1 years (SD 8.7) and 57.1% were female. There was radiographic evidence of a healed fracture in six (43%), active pseudofractures in four (29%), osteoarthritis in eight (57%), and prior orthopaedic surgery in 11 (79%). At some point in the past that was at least 2 years before enrolment, 12 (86%) had taken conventional therapy.

2.3.4 Study CL001: natural history study

This was a cross-sectional online survey. Adults with XLH and parents/caregivers of children with XLH were recruited through The XLH Network Inc. (a disease-specific patient advocacy organization which was the study sponsor), and clinicians with an interest in XLH. The survey included multiple-choice and open-ended questions on demographics, disease manifestations, treatment history, assistive device use, and age-specific patient-reported outcomes.[18] The adult version included the WOMAC questionnaire, Brief Pain Inventory (short form), and the 36-Item Short Form Health Survey version 2 (SF-36v2).

Data were collected from 232 adults with XLH (mean age, 45.6 years; 76% female). At the time of survey, 64% of were receiving oral phosphate, active vitamin D, or both.

2.3.5 Life course analysis

To evaluate the burden of musculoskeletal features and associated surgeries across the life course of adults with XLH, Javaid et al. (2022) analysed data for participants in Study CL303 (baseline data), participants in the natural history study (CL001),[17] and a subgroup of participants from CL001 who were considered comparable to Study CL303 participants (by having BPI worst pain scores ≥4). Adults who reported previously participating in a clinical trial of burosumab were excluded; thus no adults in the analysis had prior burosumab exposure. Rates of five prespecified musculoskeletal features and associated surgeries (history of fractures, OA, osteophytes, enthesopathies, and spinal stenosis; plus hip and knee arthroplasty and spinal surgeries) were investigated across the following age bands: 18-29, 30-39, 40-49, 50-59 and ≥60 years. Data on dental abscesses were also collected. Features were described as having ever been present or as absent, but age of diagnosis was not recorded. Full details of methodology are available in the study publication.[17]

Data from 336 adults were analysed. The analysis highlighted the prevalence of musculoskeletal events beginning as early as age 20 years accumulating with age. For example, across all three groups, 43% to 47% had a history of fracture. In the 18–29-year age band 27% to 40% had a history of fracture; this increased to 65% to 86% in those aged ≥60 years. The overall prevalence of osteoarthritis was >50% in all three groups; again this increased with age from 23% to 37% among 18-29 year-olds to approximately 70% in those aged over 60 years. Similar patterns were seen for osteophytes and enthesopathy. Surgeries such as hip and knee arthroplasty were reported by adults in their 30s.

2.3.6 Comparative summary of methods of studies used in model

A comparative summary of the clinical studies used in the model is provided in Table 18.

Table 18 Comparative summary of trial methodology

Trial number (acronym)	**CL303 (NCT02526160)**	**BUR02 (CL303 extension study) (NCT03920072)**
Settings and locations where the data were collected	25 study centres in the following locations: United States (8 sites), United Kingdom (5 sites), Japan (5 sites), France (3 sites), South Korea (2 sites), Ireland (1 site), Italy (1 site)	Conducted in Europe, at 10 sites in France, Italy, Ireland and UK. Burosumab was administered by a health care professional every 4 weeks at the subject's home or local clinic and subjects were to attend visits to the clinic every 12 weeks (additional home or clinic visits were required every 12 weeks [-2 weeks] to test peak phosphate levels.
Trial design	Randomized, double-blind, placebo-controlled, phase 3 study to assess the efficacy and safety of burosumab in adults with XLH. **RCT period** (0-24 weeks) **Open-label Treatment Continuation period** (24–48 weeks) **Open-label Treatment Extension period I (BUR02)** (48-96 weeks) **Open-label Treatment Extension period II – US only** (96-149 weeks)	Phase 3b multi-centre, open-label extension study to evaluate and continue monitoring long-term safety and efficacy of burosumab in adult subjects with XLH, who had participated in either study CL303 or study CL304.
Key eligibility criteria for participants	**Inclusion criteria:** • Age 18 to 65 years (inclusive) • Diagnosis of XLH supported by classical clinical features and at least one of PHEX mutation (in patient or direct family member) or serum iFGF23 level > 30 pg/mL by Kainos assay • Presence of skeletal pain attributed to XLH/osteomalacia, as defined by a score of ≥ 4 on BPI Worst Pain at SV1 • Biochemical findings consistent with XLH at SV2 following overnight fasting (min. 8 hours): • Serum phosphorus < 2.5 mg/dL (0.81 mmol/L)	Participated and completed study CL303 or CL304, including the final study visit. Any subject who did not complete study CL303 or study CL304, was included on a case-by-case basis. Enrolment was not dependent on any response to primary or secondary endpoints in studies CL303 or CL304. Participants who discontinued treatment from studies CL303 or CL304 due to either a grade ≥3 treatment-related hypersensitivity reaction or a burosumab-related hypersensitivity reaction reported as a serious adverse event (SAE) were excluded from the study.

	• Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR) of < 2.5 mg/dL **Exclusion criteria:** • Use of vitamin D metabolite or analog, or oral phosphate (within 14 days prior to screening visit 2) • Use of burosumab, or any other therapeutic monoclonal antibody, within 90 days prior to screening visit 1 • Planned or recommended orthopedic surgery within the first 24 weeks of the clinical trial period • History of traumatic fracture or orthopedic surgery within 6 months prior to SV1	

Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	During the placebo-controlled treatment period, participants received either burosumab 1.0 mg/kg or matching placebo every 4 weeks. During the subsequent open-label periods, all participants received burosumab 1.0 mg/kg every 4 weeks. Each dose was rounded up to the nearest 10 mg, up to a maximum of 90 mg to reach serum phosphate levels within the LLN. Treatment was administered via subcutaneous injection.	Subjects began treatment at the same dose as they received in the previous study or in the early access program; the total dose was rounded to the nearest 10 mg. For subjects with an interruption in burosumab treatment longer than 8 weeks, the starting dose for this study was to be confirmed by the investigator. The dose remained fixed for the duration of the study, provided serum phosphate levels did not exceed the upper limit of normal (ULN) or fall below the LLN, as measured by the central laboratory, and body weight did not change by >20% from the baseline measurement. The dose was recalculated to account for the new body weight if it changed by >20%. **Dose increase:** If fasting serum phosphate was below the LLN, the subject was asked to visit the study centre 12 days (±2 days) later to undergo further serum phosphate blood sampling. If the concentration remained below LLN then the investigator was asked to consider a dose increase. The dose was to be increased stepwise by 0.4 mg/kg up to a maximum dose of 2.0 mg/kg (maximum dose of 90 mg). Fasting serum phosphate was measured 12 days (±2 days) after any dose increase to ensure that the subject was not hyperphosphatemic. Burosumab was not adjusted more frequently than every 4 weeks. **Dose decrease:** If fasting serum phosphate was above the ULN for adults, the next dose was halved, and the fasting serum phosphate was reassessed within 2 weeks.
Permitted and disallowed concomitant medication	• Participants who were receiving therapies that affect phosphate metabolism (such as oral phosphate, active vitamin D metabolites, or analogues) could only enrol in the study after a wash out period of at least 2 weeks. • If a participant's serum level of 25-hydroxyvitamin D fell below 20 ng/mL during the study, they were	The following were disallowed: • Pharmacologic active vitamin D metabolites or analogs (e.g., calcitriol, doxercalciferol, and paricalcitol) • Oral phosphate • Aluminum hydroxide antacids, acetazolamides and thiazides • Bisphosphonate therapy • Denosumab therapy (no use in the 6 months prior to screening visit 1)

	allowed to take oral supplementation (e.g. cholecalciferol, ergocalciferol). • If a participant was receiving pain medication, the regimen had to be stable for at least 21 days before screening and the participant had to agree to stay on the same dose (maximum 60 mg/day oral morphine equivalent) and schedule during the double-blind period. • Participants could have received burosumab previously as part of another clinical trial; however, they were not allowed to enrol in Study CL303 within 90 days of receiving burosumab or any other monoclonal antibody	• Teriparatide therapy (no use in the 2 months prior to screening visit 1) • Parathyroid hormone suppressors (e.g., cinacalcet; 60-day washout required) • Any other monoclonal antibody therapy (other than study drug; 90-day washout required)
Primary outcomes (including scoring methods and timings of assessments)	The proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dose interval (ie, Weeks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between Baseline and Week 24.	The proportion of subjects achieving mean trough serum phosphate level above the LLN
Other outcomes used in the economic model/specified in the scope	• Change from Baseline to Week 24 in BPI Worst Pain score • Change from Baseline to Week 24 in WOMAC Stiffness score • Change from Baseline to Week 24 in the WOMAC Physical Function score	• Pre-existing (identified during CL303 or CL304) pseudofracture healing and enthesopathy • Six Minute Walk Test (6MWT) • Timed Up and Go (TUG) test • WOMAC score • Brief Pain Inventory – short form (BPI-SF) • Brief Fatigue Inventory (BFI) • Short Form 36 version 2 (SF-36 v2)

Sources: Kyowa Kirin Ltd. Study UX203-CL303 final clinical study report. 2021.;[8] Kyowa Kirin Ltd. Study BUR02 Clinical Study report. 2022.[59] Kamenicky 2023[60]

2.3.7 Expert elicitation

Opinion was obtained from expert clinicians practising in the UK to support and validate various aspects of the submission. Details of the validation exercises are given Appendices P and Q and are discussed in Section 3.13.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical analysis and definition of study groups in the clinical studies are described in the respective sections on trial methodology in Section 2.3 above.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Risk of bias assessment for the RCT (CL303) is provided in Appendix D. No problems were identified. The primary analysis was based on all randomised patients who received at least one dose of study treatment, rather than a true ITT analysis. However, all randomised patients were contained in this primary analysis group. BUR02 was an open label, single-arm long term extension study rather than an RCT. The route of patients into study BUR02, their treatment history and their disposition are well explained in the publication. A limitation is that patient-reported outcomes from open label studies are potentially subject to bias resulting from patients being aware that they are receiving active treatment. Neither study has any major barriers to generalisability to UK clinical practice. Generalisability is discussed in Section 2.12.

2.6 Clinical effectiveness results of the relevant studies

Key points

- Burosumab treatment normalises serum phosphate levels for the great majority of patients, and the increase in phosphate is sustained over time. In the pivotal trial (CL303):
    - 94.1% of participants who received burosumab had achieved serum phosphate levels above the lower limit of normal (LLN) across the midpoint of dosing intervals at Week 24, compared with 7.6% of those who received placebo (P<0.001).[7]

    - Between Weeks 24 and 48, 83.3% of participants who continued to receive burosumab achieved serum phosphate levels above the LLN. After crossing over to burosumab, 89.4% participants in the placebo-burosumab group achieved serum phosphate levels above the LLN.[62]
    - Between Weeks 48 and 96, [redacted].[8]

- Increases in serum phosphate levels in CL303 were accompanied by reductions in stiffness, pain and fatigue that were sustained over time (see Section 4.2).
    - At Week 24, patients had statistically significant improvements from baseline in WOMAC stiffness, BPI worst pain (average and greatest), BPI pain interference, and BFI worst fatigue (average and greatest), compared with placebo.[7]
    - At Week 48, statistically significant improvements from baseline were maintained for all WOMAC and BPI-SF scores.[57]
    - At Week 96, statistically significant improvements from baseline were maintained for all patient-reported outcome measures.[57]
- Participants receiving burosumab had statistically significant improvements from baseline in 6MWT distance walked (p=0.018) and percent predicted (p=0.021) at Week 24, compared with slight decreases with placebo.[57]
- Burosumab was associated with improved fracture healing in an exploratory analysis and improved bone quality (as assessed by markers of bone remodelling)
    - After 24 weeks of treatment, the odds of complete fracture healing were almost 17-fold greater with burosumab than with placebo.[7]
- The benefits of burosumab were maintained with continued treatment beyond 96 weeks in an open label extension (Study BUR02).[60]
- In an open-label, single arm study (CL304), burosumab substantially and consistently improved osteomalacia in adults with XLH (n=14).[35]

- Of four active pseudofractures identified at baseline, two had healed completely and two had partially healed by week 12; by week 48, three of the four had healed (the fourth was not evaluable).

Clinical effectiveness results are presented by outcome measure. For each outcome measure, the results of the pivotal study (CL303) are presented, followed by the relevant results from other studies.

2.6.1 Serum phosphate levels

2.6.1.1 Pivotal trial (CL303)

Burosumab treatment resulted in significant and clinically meaningful increases in serum phosphate levels. After 24 weeks of treatment, 94.1% of participants receiving burosumab had achieved a mean serum phosphate level above the LLN across the midpoints of the dose intervals (i.e. the time of peak pharmacodynamic effect), compared with 7.6% of participants receiving placebo (primary study endpoint; Table 19).[7]

Table 19 Proportion of participants with serum phosphate levels above LLN through Week 24 (Study CL303)

	Burosumab (n = 68)	**Placebo (n = 66)**
Achieved mean serum phosphate >LLN, n (%)	64 (94.1)	5 (7.6)
95% CI	85.8, 97.7	3.3, 16.5
P-value	<0.0001	

CI, confidence interval; LLN, lower limit of normal
Source: Insogna et al. (2018);[7] EMA public assessment report.[61]

The increase in serum phosphate levels with burosumab was sustained over time. Between Weeks 24 and 48 (the open-label treatment continuation period), 83.8% of participants in the burosumab-burosumab group had a mean serum phosphate level above the LLN across the midpoints of the dose intervals.[62] After crossing over to burosumab treatment, 89.4% of participants in the placebo-burosumab group had a mean serum phosphate level above the LLN across the midpoints of the dose intervals.[62] [redacted] Figure 14 [redacted]

[redacted][8]

Figure 14 Serum phosphate concentrations over time: midpoint of the dosing interval (Study CL303)

Data are mean ± SE. Dashed lines indicate the upper and lower limits of normal. KRN23 = burosumab. SE, standard error
Source: Study CL303 final clinical study report[8]

Pre-specified subgroup analyses produced results similar to the analysis for the overall population (see Section 2.7).[61] The overall consistency of the results of these subgroup analyses demonstrates the robustness of the results for the primary endpoint.

A prespecified sensitivity analysis adjusting for region and the original planned randomisation stratification based on BPI worst pain produced results similar to the primary analysis, indicating that the misclassification of the randomisation stratification (described in Section 2.3.1) had minimal impact on the results for the primary endpoint.[61]

Trough serum phosphate: Trough serum phosphate levels were a secondary endpoint in study CL303. The majority of participants in the burosumab group (67.6%, versus 6.1% for placebo) maintained a mean serum phosphate concentration above the LLN just before the next dose.

Figure 15 shows mean trough serum phosphate levels (i.e. levels across the end of the dose intervals, 4 weeks after a dose).

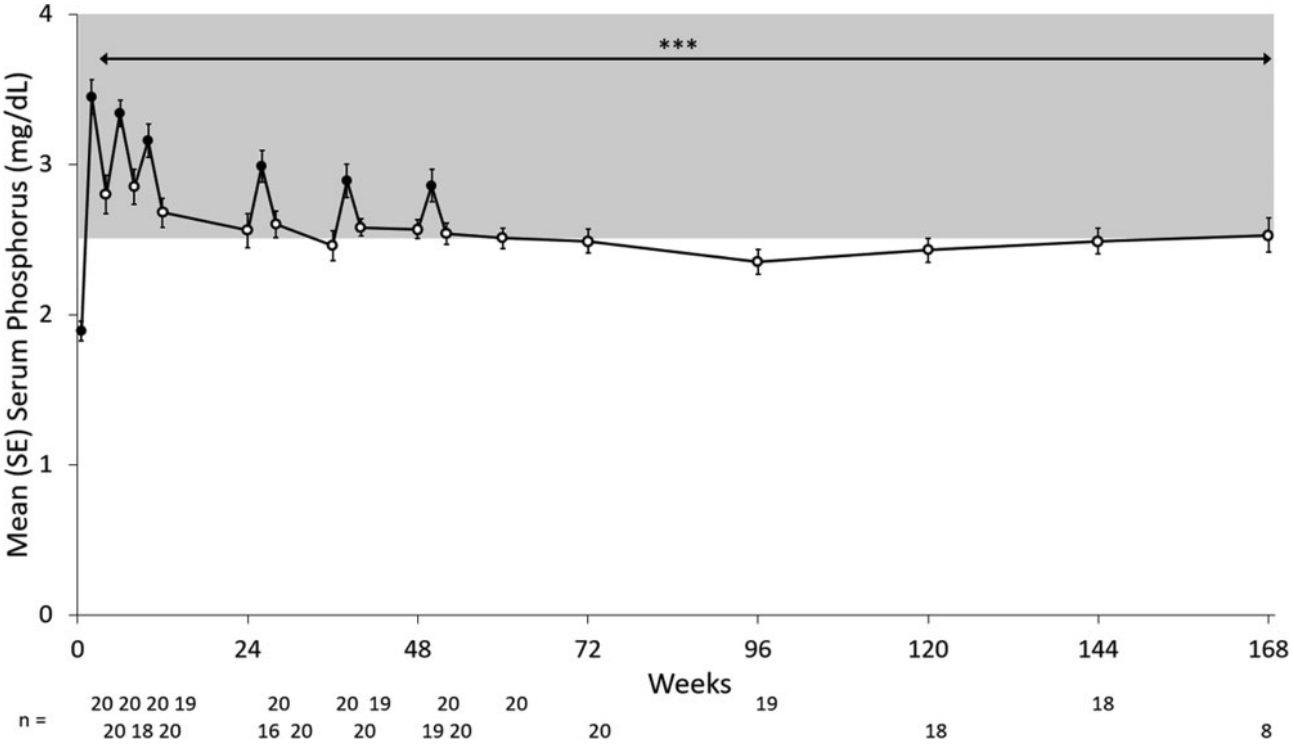
Figure 15 Trough serum phosphate concentrations over time: end of the dosing interval (Study CL303)

Data are mean ± SE. Dashed lines indicate the upper and lower limits of normal. KRN23 = burosumab. SE, standard error
Source: Study CL303 final clinical study report[8]

2.6.1.2 Additional data on long-term control of phosphate levels

Mean fasting serum phosphate above LLN at the end of the dosing period was maintained above LLN with burosumab treatment throughout the BUR02 open-label extension study to week 48b (see Figure 11 for explanation of time course).[60]

A publication by Weber et al 2022[56] contained data on 20 patients from UX023-CL203 (NCT02312687), a Phase 2b, open-label, single-arm, long-term extension study of adults who participated in the KRN23-INT-001 or KRN23-INT-002 studies. At weeks 24, 48, 72, 96, 120, 144, and 168, and End of Treatment Visit, fasting serum phosphate levels at the midpoint of the dosing interval (2 weeks post dose, the time of peak effect) were within the normal range in 85% to 100% of patients. Mean values are shown in Figure 16, showing the maintenance of effect across the 168 weeks.



Statistical analysis examined change from baseline using trough values from Weeks 24, 48, 72, 96, 120, 144, and 168 from baseline (***P < .0001). Closed markers represent expected peaks of burosumab activity 2 weeks after the previous dose. Open markers represent expected troughs of burosumab activity 4 weeks after the previous dose and immediately prior to dosing. Gray shading indicates normal range (2.5-4.5 mg/dL). Source: Weber 2022.[56]

Figure 16 Mean (SE) serum phosphate to 168 weeks, study CL203

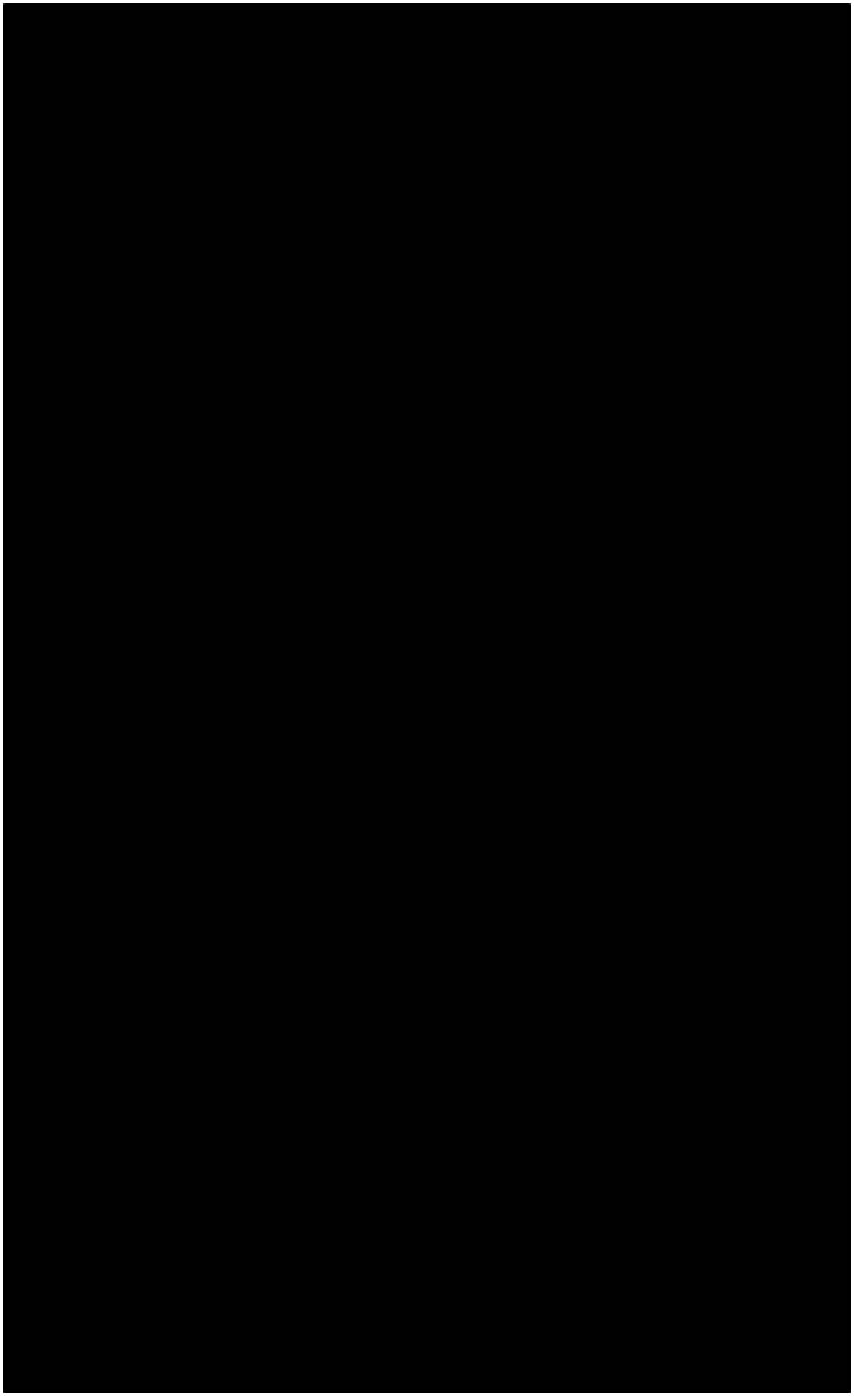
2.6.1.3 Vitamin D and laboratory markers of phosphate homeostasis and bone remodelling

1,25(OH)$_2$D (active vitamin D) levels, TmP/GFR (ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate), and tubular reabsorption of phosphate (TRP) were all secondary endpoints in the pivotal trial (study CL303).

- Serum 1,25(OH)$_2$D, TmP/GFR and TRP increased in the burosumab group but showed minimal change in the placebo group through Week 24 (Figure 17).[7]
- Between Weeks 24 and 48, both serum 1,25(OH)$_2$D levels and TmP/GFR were maintained in the burosumab-burosumab group. In the placebo-burosumab group, serum 1,25(OH)$_2$D levels and TmP/GFR increased after initiation of burosumab (Figure 17).[62] [redacted].[8]

- The changes in these outcomes confirmed that by inhibiting FGF23, burosumab increases tubular reabsorption of phosphate and synthesis of $1,25(OH)_2D$, thereby restoring phosphate homeostasis.

Figure 17 Serum 1,25(OH)2D levels (A) TmP/GFR (B) and TRP (C) over time: Study CL303



Dashed lines are lower and upper limits of normal. KRN23, burosumab; TmP/GFR, ratio of renal tubular maximum reabsorption phosphate to glomerular filtration rate; TRP, tubular resorption of phosphate; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; VITDT, 1,25-dihydroxyvitamin D
Source: Study CL303 final clinical study report[8]

2.6.2 Patient-reported outcomes (stiffness, pain, fatigue, physical functioning)

Key points

- Participants treated with burosumab had significant improvements in stiffness, pain, fatigue and physical functioning. [7,57]
    - At Week 24, participants had statistically significant improvements from baseline in WOMAC stiffness, BPI worst pain (average and greatest), BPI pain interference, and BFI worst fatigue (average and greatest), compared with placebo.[7]
    - At Week 48, statistically significant improvements from baseline were maintained for all WOMAC and BPI-SF scores.[57]
    - At Week 96, statistically significant improvements from baseline were maintained for all patient-reported outcome measures.[57]
- Mapping of WOMAC scores from the CL303 and BUR02 studies to EQ-5D is described in Section 3.4.2. Improvements in WOMAC subscales over time due to burosumab translated into improvements in estimated EQ-5D utilities.
- Real-world evidence from a NHS centre of excellence shows a significant improvement in HRQoL with burosumab. For the 40 patients reported, the mean baseline EQ-5D visual-analogue scale (VAS) score was 55.9 (on a scale of 0-100, with 0 'the worst health you can imagine and 100 'the best health you can imagine'). After 1 year this increased to 63.9 (P=0.03).[4]

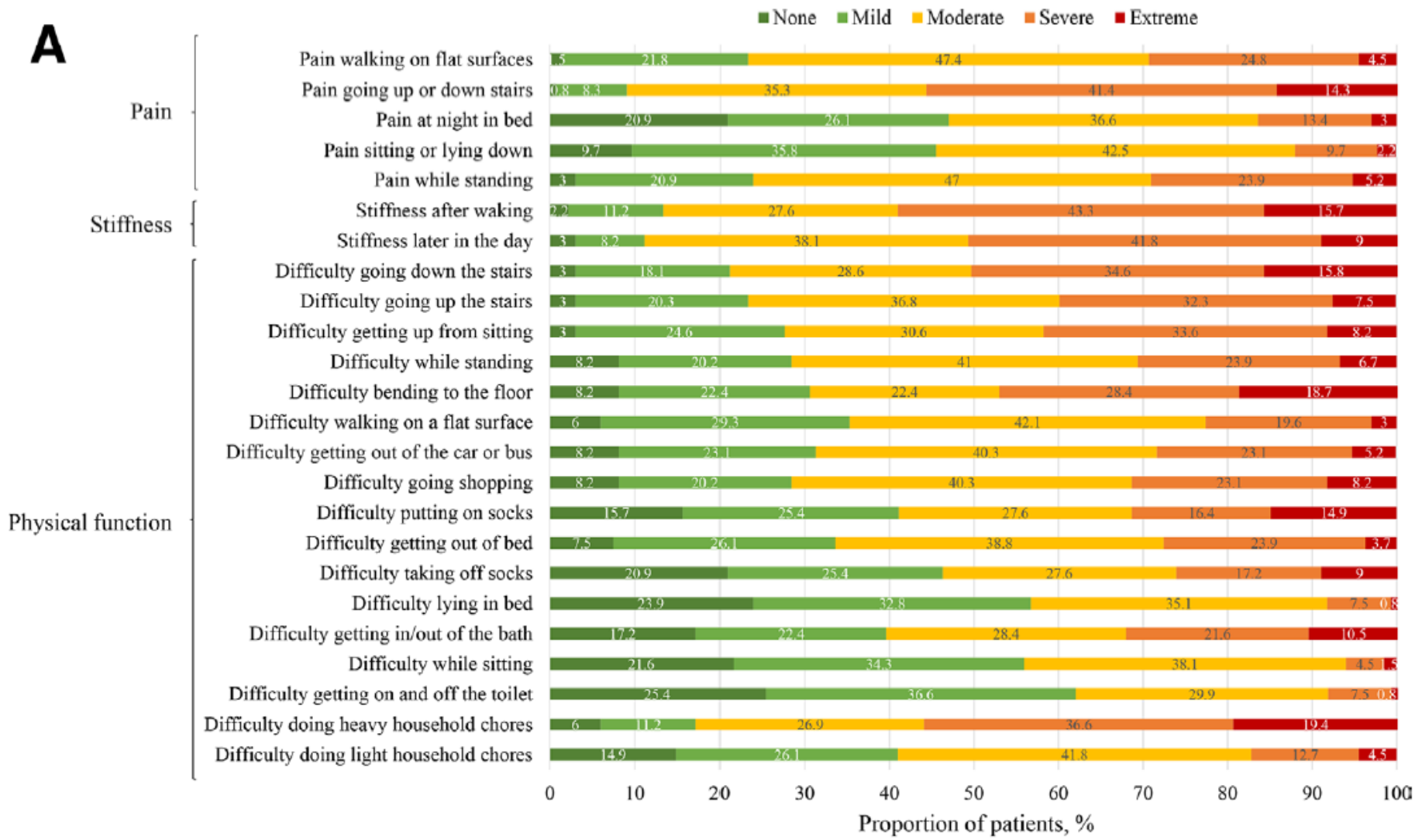
WOMAC, BPI-SF and BFI data up to Week 96 are published and are presented below. All endpoints were prespecified, with the exception of WOMAC total score, BPI-SF worst pain (greatest), BFI worst fatigue (greatest) and BFI fatigue interference, which were *post-hoc.* A total of 119 participants completed 96 weeks of treatment; the analysis presented here included all 134 participants who were enrolled and randomised to treatment. Note that data presented here are taken from the Week 96 publication (Briot et al. 2021);[57] owing to reanalysis of certain endpoints for the placebo-controlled period, some of the datapoints may differ from those reported in the earlier 24-week[7] and 48-week[62] publications.

2.6.2.1 Baseline impairment

Physical function and stiffness: At baseline, participants in the pivotal study (CL303) reported significantly impaired physical function and stiffness (Table **20**). Approximately half had severe or extreme impairment going down the stairs and 56% reported severe or extreme pain when using the stairs. The ability to do household chores was severely or extremely impaired in 56% of participants and 59% reported severe or extreme stiffness after waking.[57]

Pain and fatigue: Most participants (72%) reported severe pain at baseline.[57] In general, pain was considered to have a moderate impact on activities of daily living. However, 8-12% of participants reported that severe pain when walking, during general activity and during normal work completely interfered with daily life. Participants also reported that fatigue interfered with their walking ability, normal work and enjoyment of life.

Baseline PRO scores are shown in Table 20. The severity of patients' impairment, pain and fatigue at baseline is shown visually in Figure 18, which also shows the questions associated with each PRO instrument.



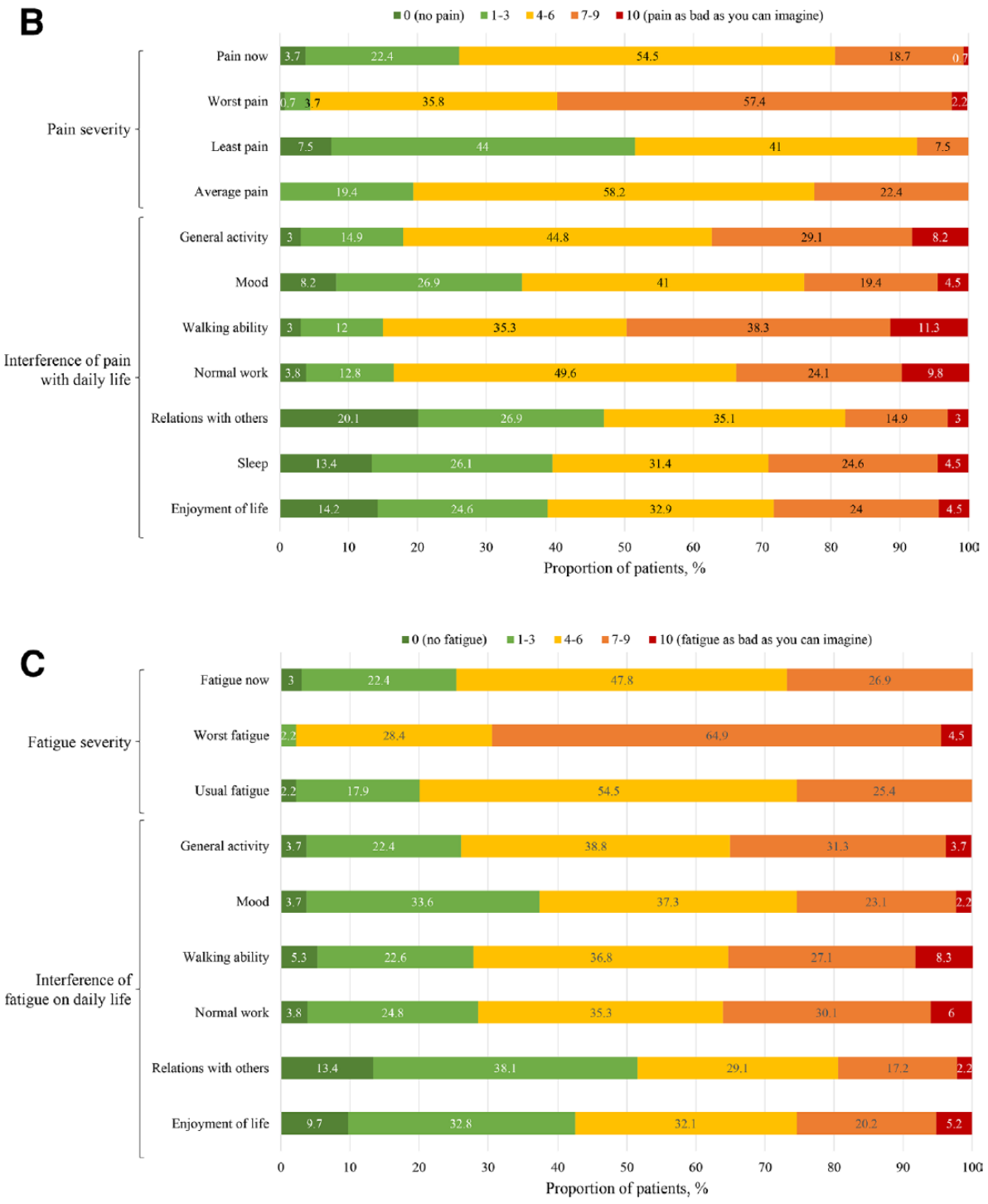


Figure 18 Proportion of adults reporting (A) WOMAC, (B) BPI-SF and (C) BFI item level scores at baseline (N=134).

Interference of pain on walking ability and normal work were not recorded at baseline for one participant in each group. BFI, Brief Fatigue Inventory; BPI-SF, Brief Pain Inventory-Short Form; WOMAC, Western Ontario and the McMaster Universities Osteoarthritis.

Source: Briot 2021[57]

Table 20 Baseline patient reported outcomes (CL303)

	Burosumab (n = 68)	Placebo (n = 66)	All participants (n = 134)
WOMAC[a], mean (SD)			
Total score	51.8 (18.3)	46.2 (17.7)	49.1 (18.2)
Physical function	50.8 (19.7)	43.9 (19.9)	47.4 (20.0)
Stiffness	64.7 (20.3)	61.4 (20.8)	63.1 (20.5)
Pain	50.7 (18.0)	48.0 (15.5)	49.3 (16.8)
BPI-SF[b] worst pain (average)			
Mean (SD)	6.8 (1.3)	6.5 (1.4)	6.7 (1.4)
≤6.0, n (%)	15 (22.1)	23 (34.8)	38 (28.4)
>6.0, n (%)	53 (77.9)	43 (65.2)	96 (71.6)
BPI-SF[b] worst pain (greatest)			
Mean (SD)	8.1 (1.2)	8.0 (1.5)	8.0 (1.3)
BPI-SF[b] pain interference, mean (SD)	5.2 (2.2)	4.8 (2.2)	5.0 (2.2)
BFI[c] scores, mean (SD)			
Global fatigue	5.4 (2.0)	4.9 (1.9)	5.1 (2.0)
Worst fatigue (average)	6.9 (1.7)	6.7 (1.5)	6.9 (1.6)
Worst fatigue (greatest)	8.2 (1.4)	8.2 (1.3)	8.2 (1.4)
Fatigue interference	5.0 (2.3)	4.5 (2.3)	4.8 (2.3)

[a]WOMAC range 0-100, where 0 represents best health. [b]BPI-SF range 0-10, where 10 indicates worst pain. [c]BFI range 0-10, where 10 represents worst fatigue BPI-SF, Brief Pain Inventory-Short Form; WOMAC, Western Ontario and McMasters Universities Osteoarthritis Index. Source: Briot et al. (2021)[57]

2.6.2.2 Effect of burosumab on stiffness, pain and physical function (WOMAC scores)

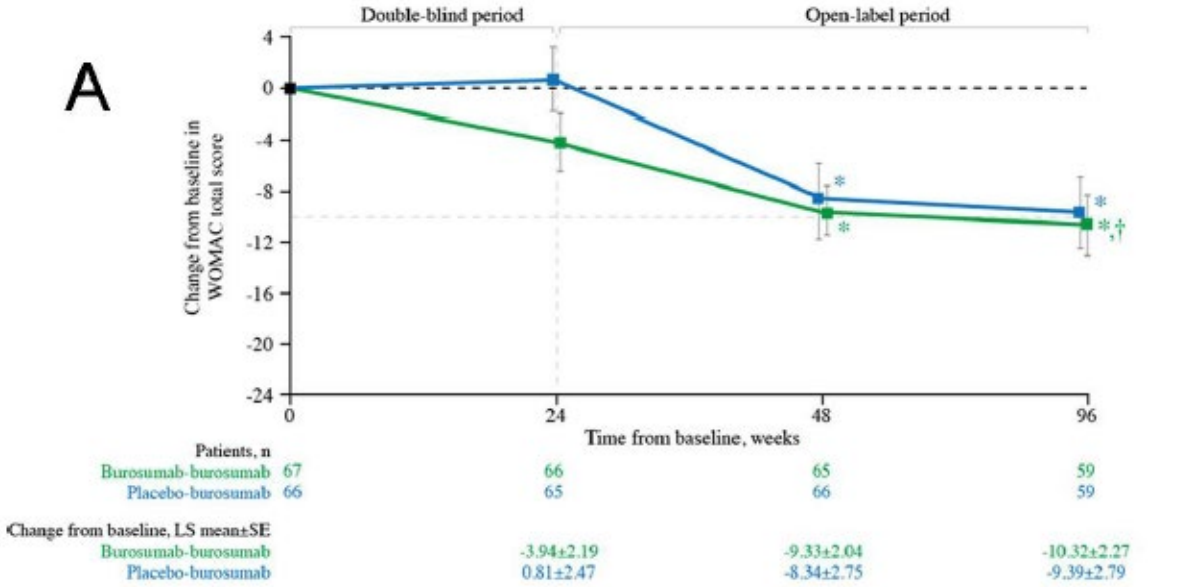
Treatment with burosumab was associated with statistically significant and clinically meaningful improvements in WOMAC scores in CL303 (lower scores indicate improvement).

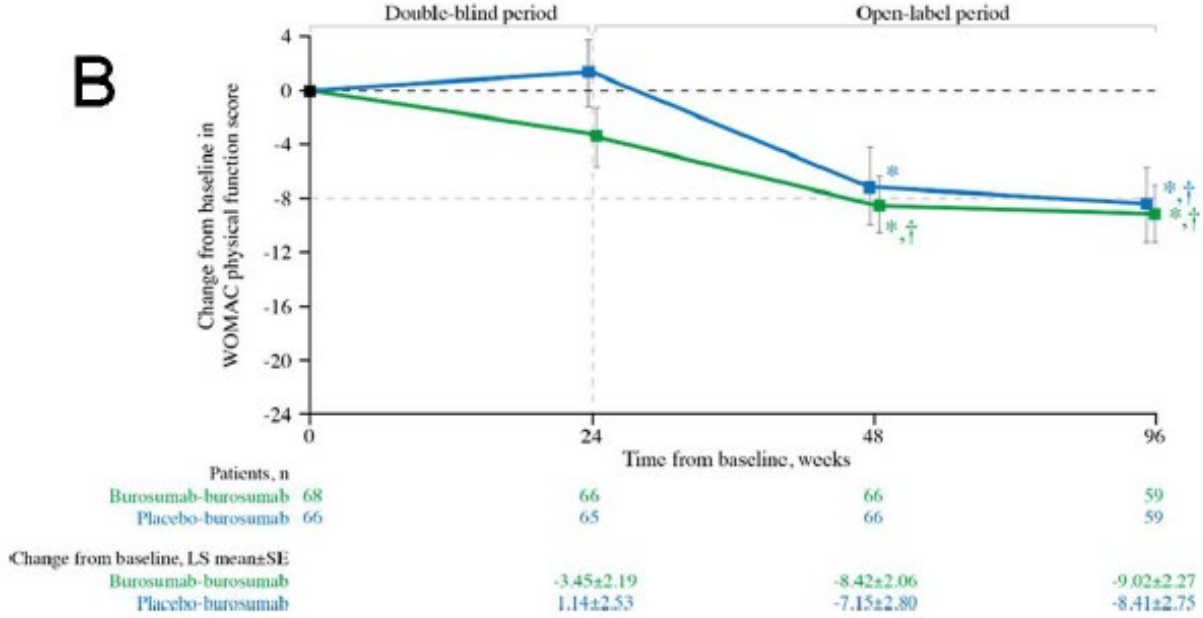
- Participants who received burosumab had statistically significant improvements from baseline in WOMAC stiffness scores at Week 24 compared with placebo (P<0.007).[7]
- At Week 48 (after patients initially randomised to receive placebo had crossed over and received burosumab for 24 weeks) there were significant improvements from baseline in all WOMAC scores in both the burosumab-burosumab and placebo-burosumab groups (all P<0.05). These improvements were maintained at Week 96 (all P<0.05 for change from baseline).[57]
- At Weeks 48 and 96, the improvements in WOMAC stiffness score in burosumab-treated patients (both groups) met the suggested XLH-specific estimate of minimal clinically important difference (MCID; see Table **20**).[57]

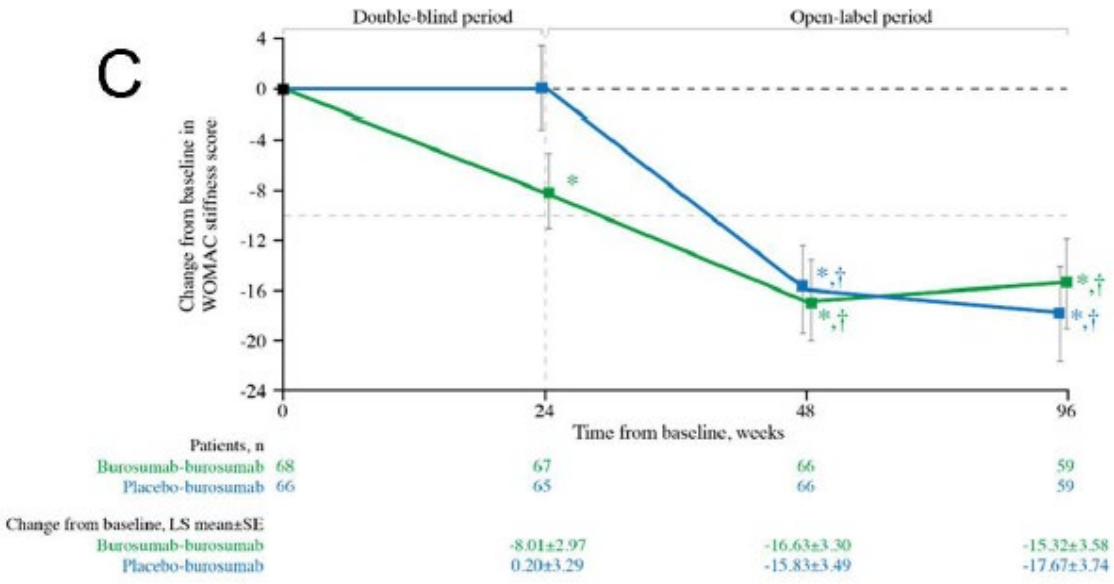
- The suggested MCID for WOMAC physical function score was achieved in the burosumab-burosumab group at Week 48 and in both groups at Week 96.
- The MCID for WOMAC total score and WOMAC pain score were met in the burosumab-burosumab group at Week 96.

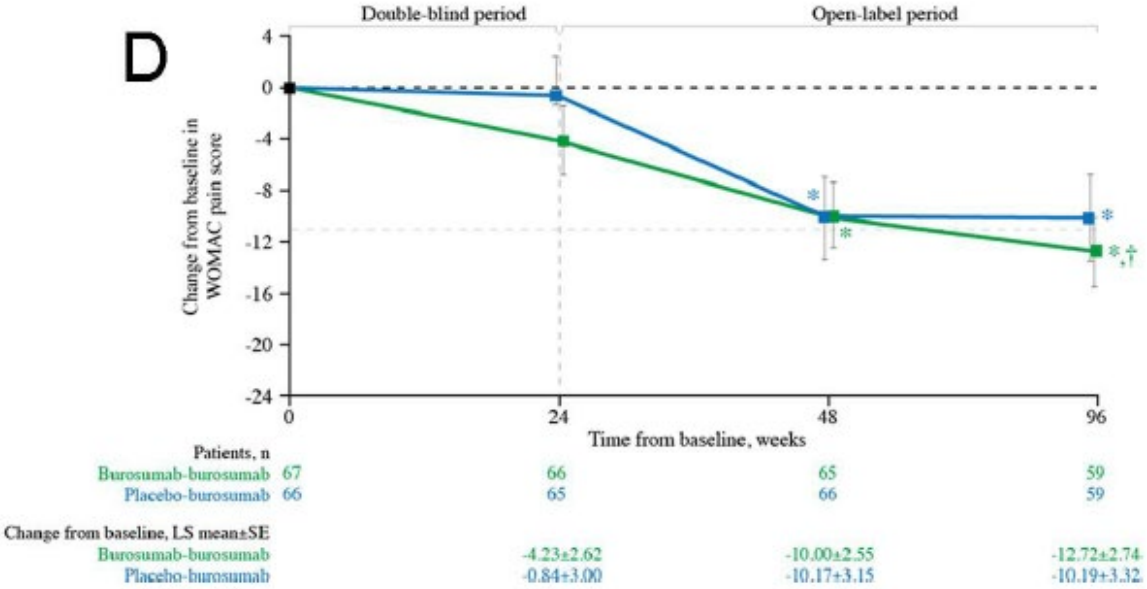
- [redacted][8]

Figure 19 Change from baseline in WOMAC (A) total score, (B) physical function, (C) stiffness and (D) pain







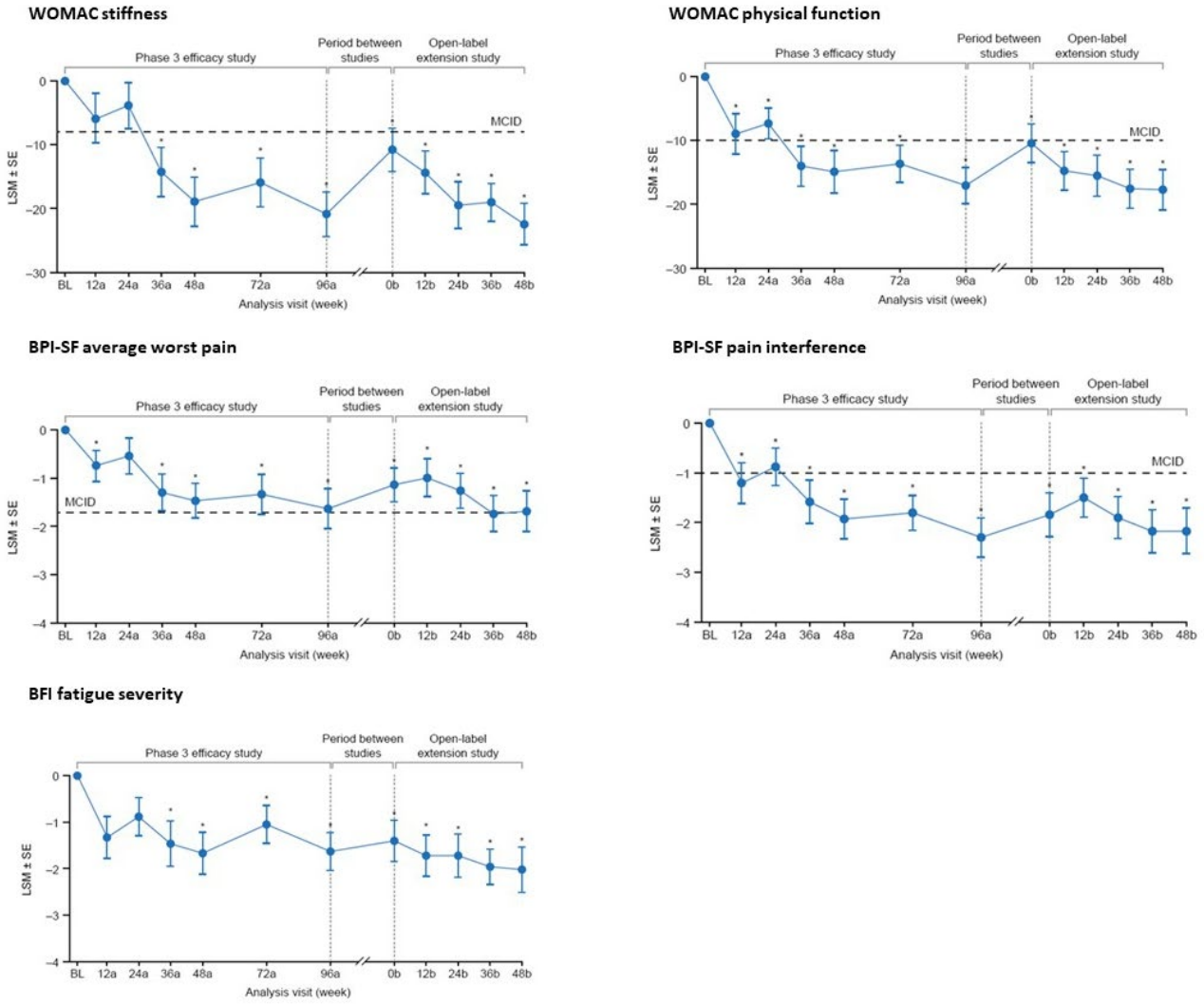


Data are LS mean (SE) change from baseline; lower scores indicate better health. *P<0.05 for LS mean change from baseline. †Meets MCID threshold; the MCID value is indicated by the pale grey horizontal dashed line. LS, least squares; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
Source: Briot et al. (2021)[57]

Burosumab was associated with sustained improvements in patient-reported outcomes over Studies CL303 and the BUR02 long-term extension (see Figure 20). Improvements from baseline in WOMAC stiffness scores met the MCID threshold (≥8-point decrease) from Week 36a in Study CL303 through to the end of Study BUR02. For WOMAC physical function scores, improvements meeting the suggested MCID threshold (≥10-point decrease)

were seen at Week 12a in Study CL303 and from Week 36a in Study CL303 through to Week 48b in Study BUR02.[60]

Figure 20: Effect of burosumab on patient-reported outcomes during Studies CL303 and BUR02 open label extension (N=31)



Lower values indicate improvement. *Statistically significant change from baseline. BL, baseline; LSM, least squares mean; MCID, minimum clinically important difference; SE, standard error; WOMAC, Western Ontario McMasters Universities Osteoarthritis Index
Source: Kamenicky et al. (2023)[60]

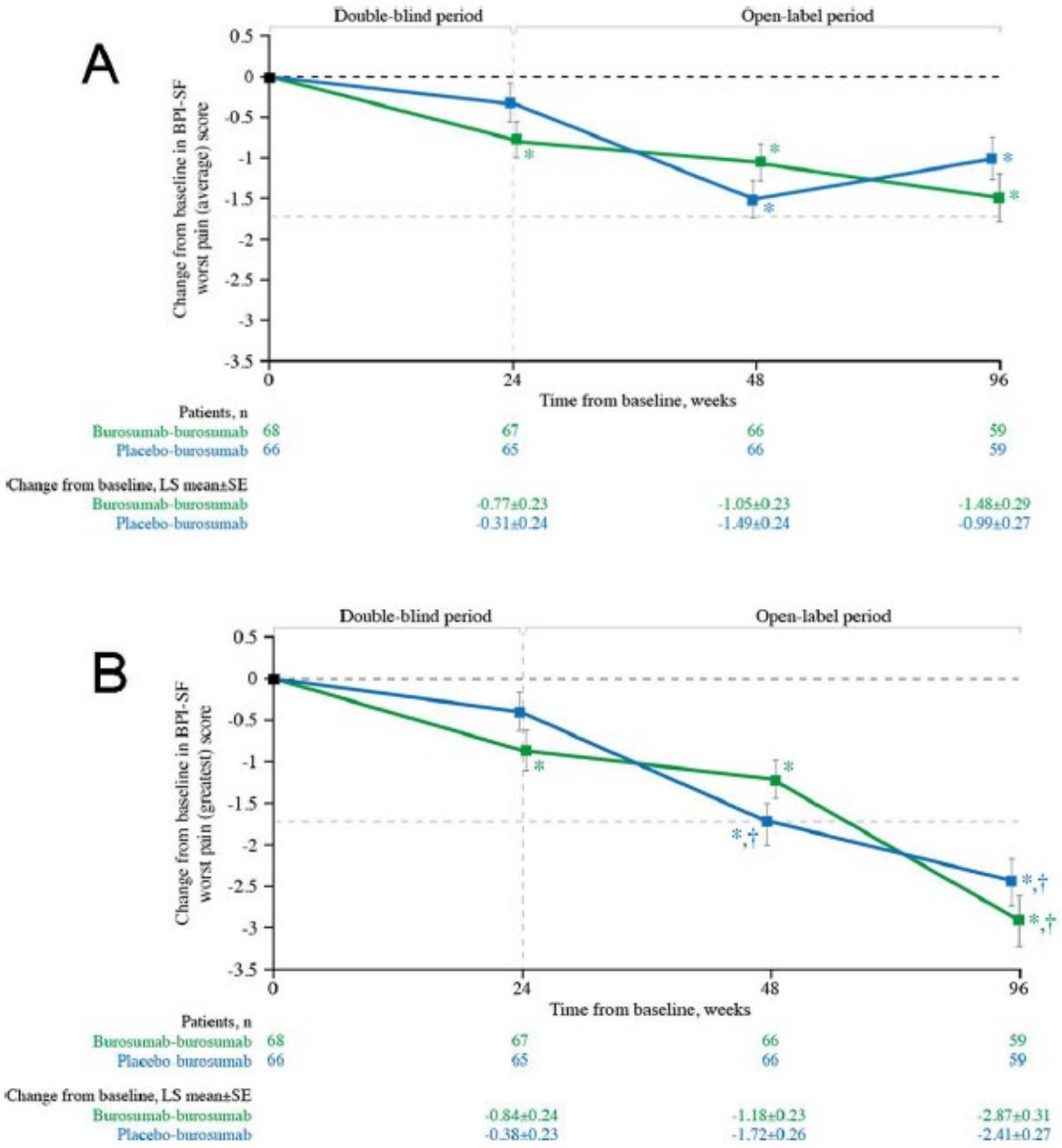
2.6.2.3 Effects of burosumab on pain (measured by BPI)

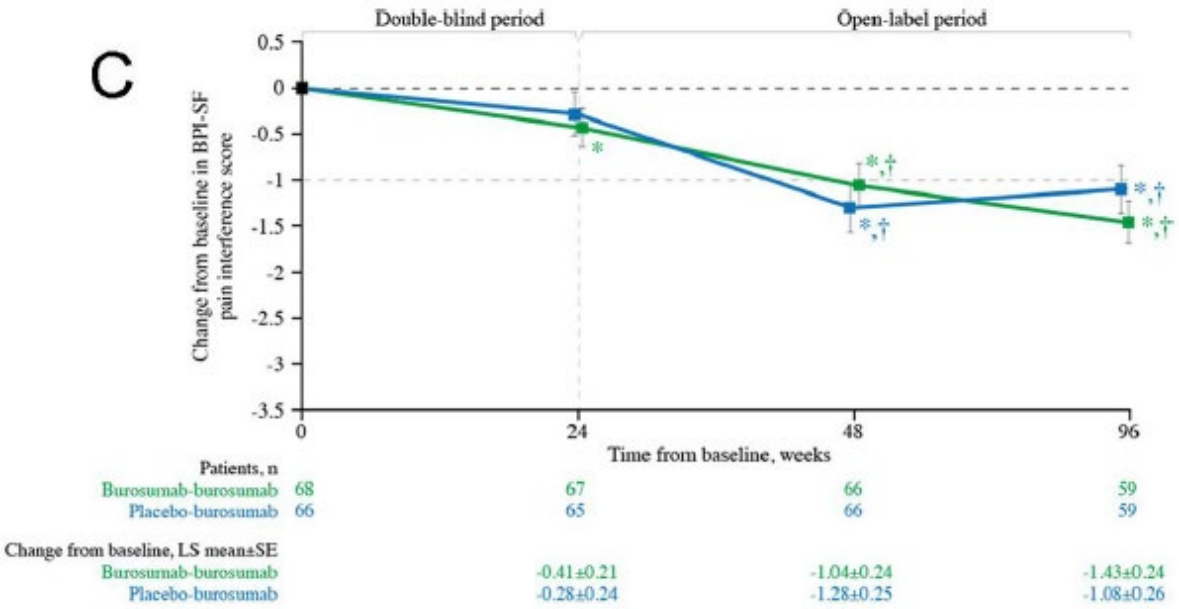
Participants who received burosumab in the double-blind period had statistically significant improvements from baseline in BPI-worst pain (average) (P<0.001), BPI worst pain (greatest) (P<0.001) and BPI pain interference (P=0.05) at Week 24. (Figure 21).[57] At Weeks

48 and 96, improvements from baseline in all BPI-SF scores were significant in both treatment groups (all P<0.001).

Improvements in worst pain (greatest) score met the suggested MCID threshold in the placebo-burosumab group at Week 48 and in both groups at Week 96. For pain interference, the threshold was met at Weeks 48 and 96 in both treatment groups.[57]

Figure 21 Change from baseline in BPI-SF (A) worst pain (average), (B) worst pain (greatest), (C) pain interference scores (CL303)





Data are LS mean (SE) change from baseline; lower scores indicate lower pain severity and less pain interference. *P<0.05 for LS mean change from baseline. †Clinically meaningful changes from baseline; the MCID value is indicated by the pale grey horizontal dashed line.
BPI-SF, Brief Pain Inventory-Short Form; LS, least squares; SE, standard error.
Source: Briot et al. (2021)[57]

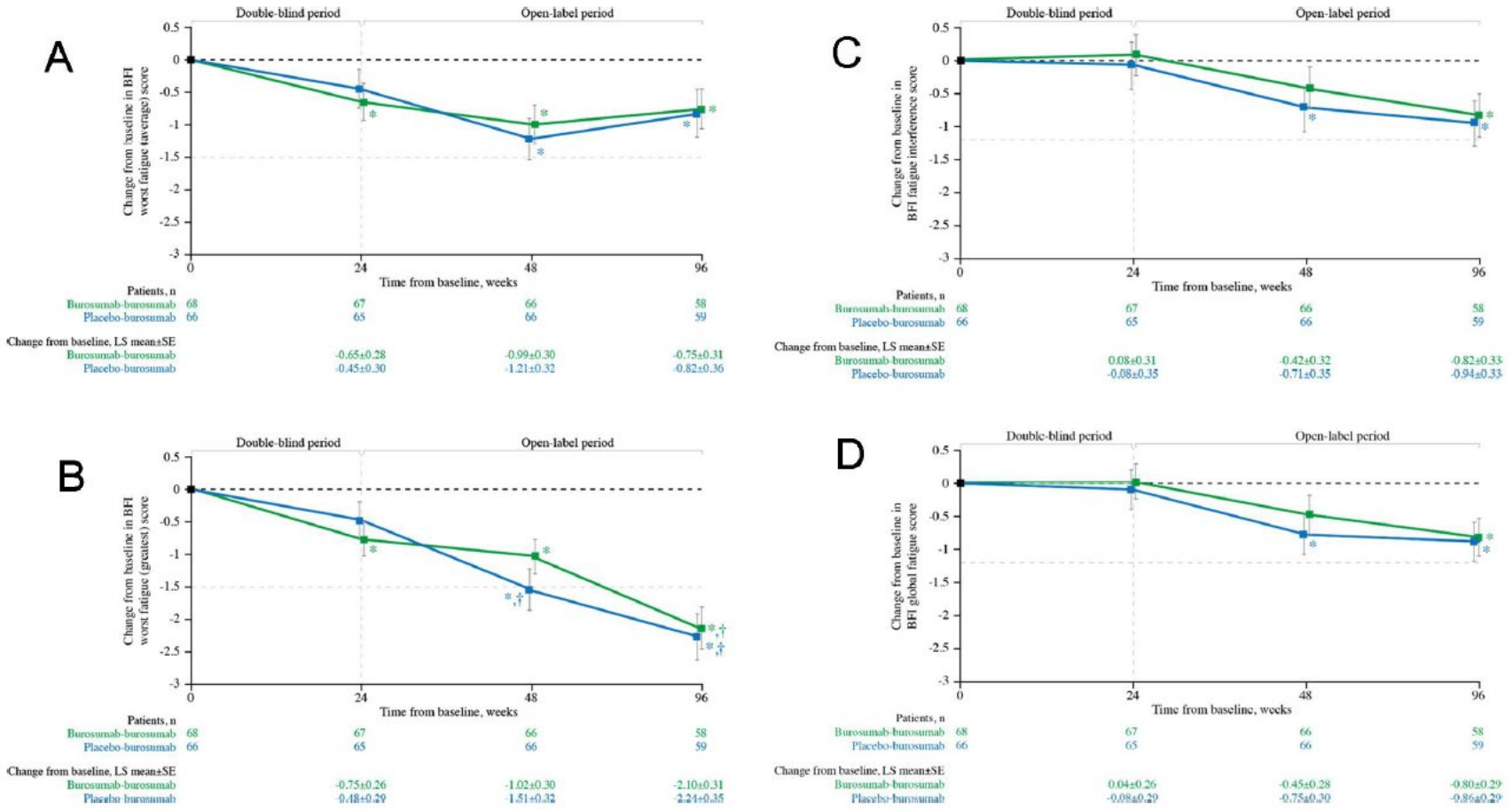
Improvements in pain scores were also seen in the BUR02 study. Improvements in BPI-SF average worst pain scores met the MCID threshold (≥1.72-point decrease) at Week 96a of Study CL303 and Weeks 36b and 48b of Study BUR02. For BPI-SF pain interference, improvement met the MCID threshold (≥1.00-point decrease) at all timepoints except Week 24a in Study CL303. BFI fatigue severity scores decreased from baseline at Week 12a in Study CL303 and were improved at all timepoints through to the end of Study BUR02.[59]

Real-world evidence shows a reduction in opioid use in adults treated with burosumab (see Section 2.6.6.1), which supports the findings of improvement in pain seen in the trial.

2.6.2.4 Effects of burosumab on fatigue

Burosumab also improved fatigue scores.

- Participants who received burosumab in the double-blind period had statistically significant improvements from baseline in BFI worst fatigue (average) (P=0.020) and BFI worst fatigue (greatest) (P=0.004) at Week 24.[57]
- At Week 48 there were significant improvements from baseline in worst fatigue (average and greatest; both P<0.001) in both groups, and in fatigue interference and global fatigue in the placebo-burosumab group (all P<0.05).



Data show LS mean (±SE); lower scores indicate lower fatigue severity and less fatigue interference. *p<0.05 for LS mean change from baseline. †Indicates the minimal clinically important difference from baseline, shown by the pale grey horizontal line. Source: Briot 2021[57]

Figure 22 Change from baseline in BFI (A) worst fatigue (average), (B) worst fatigue (greatest), (C) global fatigue and (D) fatigue interference scores (N=134).

- At Week 96, all fatigue parameters were significantly improved from baseline in both treatment groups (all P<0.05).
- The MCID threshold for BFI worst fatigue (greatest) was met at Week 48 in the placebo-burosumab group and at Week 96 in both groups.[57]

2.6.3 Fracture/pseudofracture healing

Study CL303: Healing of active fractures and pseudofractures was an exploratory endpoint in CL303. Burosumab was associated with significantly greater fracture healing than placebo.

- At Week 24, 43.1% of baseline active fractures/pseudofractures were healed in the burosumab group, compared with 7.7% in the placebo group. The odds of full healing at Week 24 were 16.8-fold higher in the burosumab group than in the placebo group (P<0.001).[7]
- The effect of burosumab on fracture healing continued over time. At Week 48, 63.1% of baseline fractures were fully healed in the burosumab-burosumab group. Importantly, the percentage of baseline fractures that were fully healed in the placebo-burosumab group at Week 48 (35.2%) was similar to that of the burosumab group at Week 24.[62]
- Analysis of partial fracture healing showed that, in both study periods, partial healing predominated during the first 12 weeks of burosumab treatment, followed by progressively greater rates of fully healed fractures/pseudofractures with continued burosumab treatment.[61]

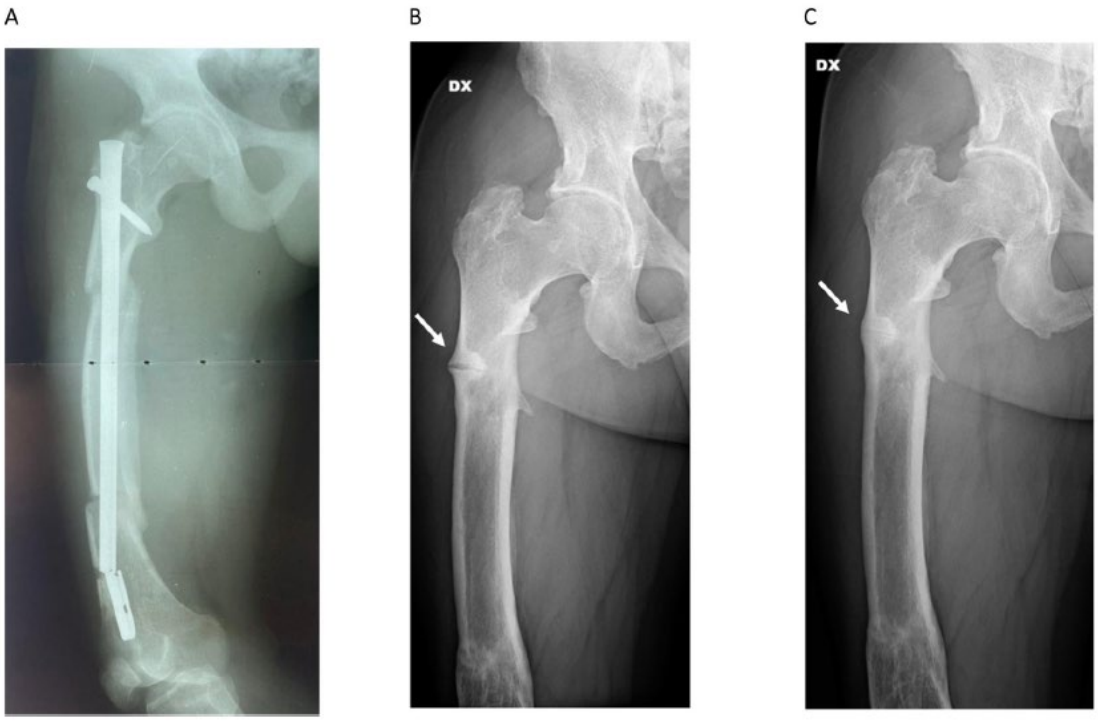
The observed fracture healing was likely mediated though increased mineralisation and bone remodelling in burosumab-treated participants, consistent with the statistically significant increases in P1NP and CTx levels through Week 24 in this group compared with the placebo group.[7]

Study CL304: Four active pseudofractures were identified at baseline. By Week 12, two had fully healed and two had partially healed; by Week 48, one of the partially healed fractures had fully healed (the other was not evaluable because of a missing radiograph).[35]

Study BUR02: This study reported long-term safety data in adults treated with burosumab (N=35).[70] Mean (SD) exposure to burosumab at the most recently published analysis was 116.22 (30.7) weeks. No new fractures or pseudofractures were reported as AEs during this period. While fracture incidence was not a specified efficacy outcome in BUR02, this observation is supportive of the expectation of a beneficial effect for burosumab on incidence of new fractures, as a result of the improvements to bone mineralisation and osteomalacia resulting from treatment (see Section 2.6.5).

Real-world case studies: The effect of burosumab on fracture healing has also been demonstrated in the real-world setting. In a case study from Italy, the authors report that in an adult

male with XLH who had been living with a fracture of his right proximal femur for around 25 years, 10 months of treatment with burosumab led to full healing of the fracture and complete resolution of the associated pain (Figure 23).[71]



Panel A is a radiogram of the right femur after surgical correction of femoral varism in 1996 and shows the proximal surgical fracture.
Panel B is a radiogram taken before the start of burosumab treatment in 2020; the white arrow shows the unhealed femoral fracture.
Panel C is a radiogram taken after 10 months of burosumab treatment; the white arrow shows the healed fracture.
Source: Arcidiacono et al. (2022)[71]

Figure 23: The effect of burosumab treatment on fracture healing in a male adult with XLH

A similar case example is available from Western General Hospital, Scotland, showing before and after one-year of burosumab treatment images for an adult male with XLH (see Figure 24). Post-treatment the radiograph shows disappearance of fracture lines. In the series of 25 patients reported by UCLH with bone scintigraphy at baseline and 1 year, (see Section 2.6.6), one patient demonstrated healing of a fracture and three had partial healing.[4]

Figure 24: Radiographs from adult male XLH patient before/after burosumab treatment (Scotland)

Source: Western General Hospital, Edinburgh

2.6.4 Mobility assessments

The 6-minute walk test (6MWT) and the timed up and go (TUG) test were exploratory outcomes in CL303. In addition, real-world evidence on the effect of burosumab on these and other functional musculoskeletal outcomes is available from UK patients treated under the Early Access Programme (see Section 2.6.6).

2.6.4.1 6MWT

Participants were asked to walk the length of a premeasured course for 6 minutes. The total distance walked was recorded in metres and the percent predicted value for the 6MWT was calculated using normative data based on age, sex and height. At baseline, the mean (SD) actual distance walked was 356.8 (109.5) metres in the burosumab group and 367.4 (103.4) metres in the placebo group.

At Week 24, participants receiving burosumab had statistically significant improvements from baseline in 6MWT distance walked (P=0.018) and percent predicted (P=0.021), compared with slight decreases with placebo (Figure 25).[57] At Weeks 48 and 72, significant improvements from baseline were seen in both the burosumab-burosumab group and the placebo-burosumab group

(all P<0.05). [redacted] [8]

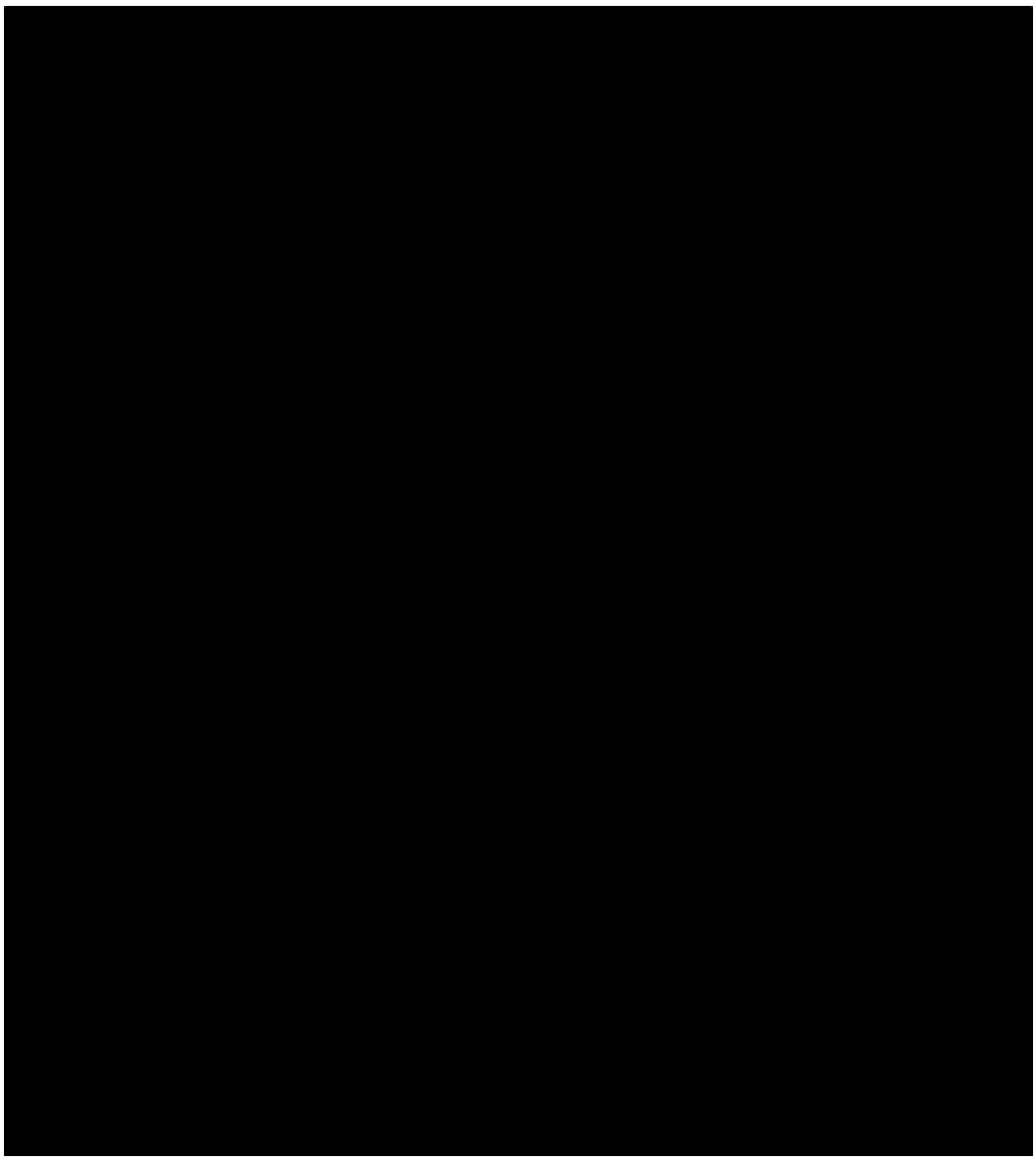


Figure 25: Change from baseline in 6MWT (A) distance walked, (B) percent predicted: Study CL303

Data are LS mean (SE) change from baseline; 6MWT, 6-minute walking test; KRN23, burosumab; SE, standard error.
Source: Study CL303 final clinical study report[8]

2.6.4.2 TUG (timed up and go) test

The TUG test assesses transitions during ambulatory activity, incorporating strength, agility and dynamic balance. The TUG score is reported as the time (in seconds) that the participant takes to rise from a chair, walk 3 metres, turn around, walk back to the chair and sit down. The level of impairment reported for the TUG test in clinical study CL303 was similar to that reported previously for patients with ankylosing spondylitis.[72]

The TUG test was added to the study following a protocol amendment and only a small number of patients completed the first assessment at Week 24 (four in the burosumab group and five in the placebo group).[8] The mean (SD) values for the TUG test at [redacted] in the burosumab group [redacted] in the placebo group. At Week 48, among the nine participants with TUG assessments at both visits, the mean (SE) change from Week 24 to Week 48 was 0.06 (0.43) seconds in the burosumab-burosumab group and -4.2 (2.93) seconds in the placebo-burosumab group, constituting an improvement during their first 24 weeks of burosumab treatment.[8]

2.6.5 Bone remodelling and treatment of osteomalacia

Markers of bone remodelling: In XLH, the poorly mineralised bone prevents osteoclasts from attaching to the bone surface to initiate the bone remodelling process. Therefore, patients with XLH have a low bone remodelling rate that impairs cortical and trabecular bone quality, leading to pseudofractures and atraumatic fractures, delayed fracture healing, and skeletal pain.[35] P1NP (total procollagen type 1 N-terminal propeptide) and CTx (carboxy-terminal collagen crosslinks) are markers of bone formation and bone resorption, respectively. In study CL303:

- Serum P1NP increased by 81% from baseline in the burosumab group at Week 24 in Study CL303, compared with 16% in the placebo group (LS mean [SE] treatment difference 62 [7.5] ng/mL; p<0.001). Serum CTx increased by 38% in the burosumab group at Week 24, compared with 11% in the placebo group (LS mean [SE] treatment difference 190 [41.2] pg/mL; p<0.001).[7] The greater increase in P1NP levels compared with CTx suggests a positive remodelling balance.
- Beyond Week 24, participants in the placebo-burosumab group had increases in both P1NP and CTx following initiation of burosumab treatment. Over time, there were gradual reductions in P1NP and CTx levels in both groups,[62] which likely reflects normalisation of bone homeostasis.
- In Study CL304, there were significant increases in P1NP and CTx between baseline and Week 48 (P<0.0001).[35]

BALP (bone-specific alkaline phosphatase) is an important marker in XLH-related bone disease in children as it is an indicator of rickets. However, it is less indicative of bone disease in adults, and is less sensitive to changes in bone remodelling than P1NP and CTx. [redacted].[8]

Overall, these bone biomarker results suggest that burosumab treatment resulted in a positive bone remodelling balance with a net increase in bone formation.

Osteomalacia: Study CL304 investigated the efficacy of burosumab in improving osteomalacia in adults with XLH who had not been treated for at least 2 years. Data through Week 48 have been published in the Journal of Bone and Mineral Research[35] and are presented below.

Fourteen adults with XLH enrolled in the study, 13 completed 48 weeks of treatment, and 11 had two biopsies. At Week 48, osteomalacia had improved, as shown by a reduction in the amount of osteoid tissue and improved mineralisation (Table 21). The improvements in osteomalacia coincided with increases in serum phosphate and biochemical markers of bone remodelling. The authors noted that "such improvements in phosphorus homeostasis and healing of osteomalacia provide a physiologic basis for the efficacy of burosumab to heal fractures and pseudofractures in patients with XLH, and ameliorate symptoms such as pain and stiffness".

Table 21: Improvements in osteomalacia-related histomorphometric measures from baseline to Week 48: Study CL304

	Mean ±SD			Median (min, max)
	Osteoid volume/bone volume	**Osteoid thickness**	**Osteoid surface/bone surface**	**Mineralisation lag time**
Baseline	26.1% ± 12.4%	17.2 ± 4.1 µm	92% ± 3%	1378 (129, 4090.1) days
Week 48	11.9% ± 6.6%	11.6 ± 3.1 µm	68% ± 14%	233.4 (69.8, 281.9) days
Absolute change from baseline	-15% ± 11%	-	-	-
% change from baseline	-54% ± 20%	-32% ± 12%	-26% ± 15%	-83% (-96%, 54%)
95% CI	-69, -40	-40, -24	-36, -16	-95.1, 51.8
P value	<0.0001	<0.0001	0.0002	0.1094

CI, confidence interval; SD, standard deviation
Source: Insogna et al. (2019) [35]

2.6.6 Real-world evidence for burosumab from UK clinical practice

2.6.6.1 UCLH experience: physical functioning, patient-reported outcomes and opioid use

Data on 40 adults (mean age 42.8 years) receiving burosumab at University College London Hospitals NHS Foundation Trust (UCLH) were analysed.[4] Baseline and one-year measures of EQ-5D-5L, 6-minute walk test (6MWT), and timed up and go (TUG) were recorded, together with serum bone profile and whole-body scintigraphy. Medication use was also examined. Paired parametric or nonparametric descriptive statistics were used for analysis.[4]

- There was a significant improvement in 6MWT (median change 38.2m, P=0.048), and improvements for 9/28 individuals assessed (32%) exceeded the suggested minimally clinically important difference of 80 metres. There was also an improvement in TUG (median change 0.8s), but this did not reach statistical significance (P=0.1).
- There was a significant improvement in HRQoL. The mean EQ-5D visual-analogue scale (VAS) score was 55.9 (on a scale of 0-100, with 0 'the worst health you can imagine and 100 'the best health you can imagine'). After 1 year this increased to 63.9 (P=0.03).
- At baseline, the proportion reporting moderate to severe limitations was 75% for mobility, 32% for self-case, 61% for usual activities, 82% for pain and 46% for anxiety. The proportion reporting improvement, no change or worsening of scores is shown in Figure 26.
- Of the 23 patients with paired scintigraphy, two demonstrated healing of a fracture, three had partial healing and two had suspicious new foci of turnover.
- In addition, 9 of 20 patients (45%) who were using opioids at baseline had stopped opioid use at 1 year (P=0.008) and there was no new opioid use.

The authors concluded that this real-world experience in UK adults with XLH showed significant symptomatic, functional and radiological benefits, replicating the benefits seen in clinical trials and extending the benefit to reducing opioid use.[4]

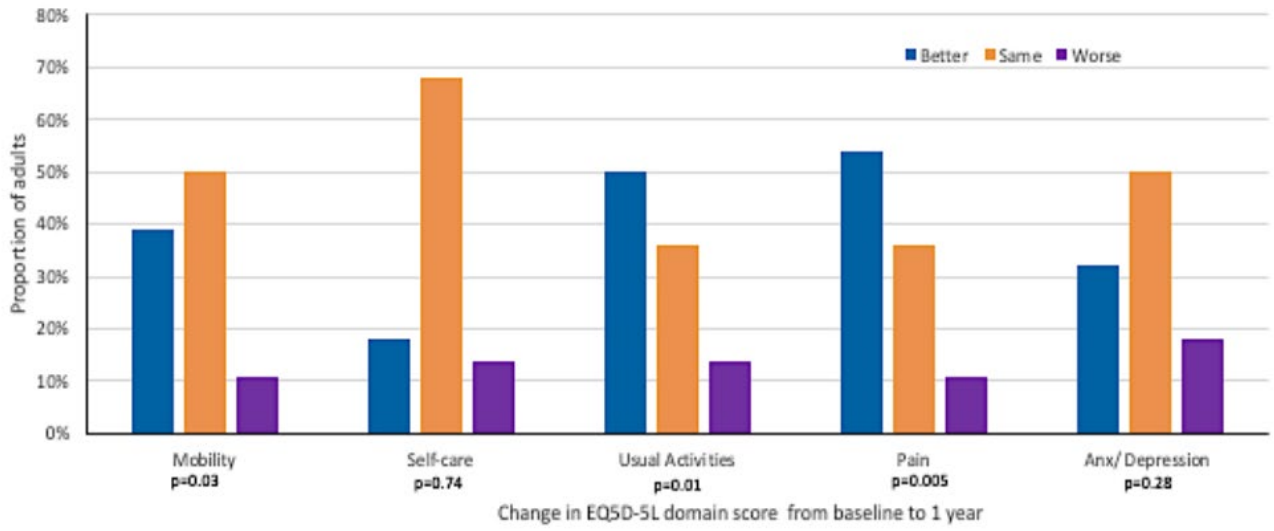


Figure 26 Change in EQ5D domain score from baseline to 1 year in adults initiating burosumab for XLH

Source: Krishna et al. 2023[4]

2.6.6.2 Additional physical function outcomes

UK real-world evidence also shows improvements in multiple aspects of physical functioning with burosumab. Ten adults with XLH (mean age 41.1±15.7y) were recruited from specialist centres in London and Bristol for a study assessing musculoskeletal outcomes with burosumab.[73] Physical function and physical activity assessments were performed during clinical visits for initial burosumab treatment and at six-month and twelve-month follow-up. Lower limb power was

assessed by mechanography via a countermovement jump, mobility by short physical performance battery (SPPB), functional capacity by six-minute walk test (6MWT), upper limb strength by hand grip dynamometry and physical activity via an International Physical Activity Questionnaire (IPAQ).

[redacted]

2.6.6.3 Patients' accounts of burosumab treatment in UK clinical practice

HRQoL data across all UK sites participating in the Early Access Programme for burosumab is not yet available. However, some patients have experienced substantial benefits to their wellbeing. Case histories and testimonies from a small number of individuals who have volunteered to share their experience of burosumab are shown in Appendix N, and in a poster presentation by Day et al.(2023).[74] They describe marked improvements to their mobility, strength, pain and fatigue levels, with concomitant improvements to their mental wellbeing.

2.6.6.4 Accounts from family members of adults treated with burosumab

In the research with family members of adults with XLH in the UK (Section 1.3.5.6 and Appendix S), all but four care recipients received burosumab. Overwhelmingly, participants described positive impacts burosumab has had on the adult they provide support or care for, also noting how their own lives have improved as a result of their partner or family member receiving burosumab. For some participants, this led to a reduction in the amount of support they provide for the individual with XLH, making their life "easier" by easing their "workload". Participants described having to do "less for [them] because… [they're] more able-bodied".

2.7 Subgroup analysis

Pre-specified subgroup analyses of the primary endpoint by baseline BPI Worst Pain (≤ 6.0,> 6.0), actual randomisation stratification factor based on BPI Average Pain (≤ 6.0, > 6.0), geographic region (North America/EU, Japan, South Korea), sex, and race (white, non-white) produced results similar to the analysis for the overall population.[61] The overall consistency of the results of these subgroup analyses demonstrates the robustness of the results for the primary endpoint. Subgroup results are provided in Appendix E.

In addition, Brandi et al. published a post hoc subgroup analysis of the 24-week data from CL303 to assess whether the benefits of burosumab were evident in 14 clinically relevant subgroups

defined by baseline demographic and functional criteria.[75] This was undertaken because of the variability in baseline characteristics among trial participants. The subgroups considered were sex, Brief Pain Inventory-short form (BPI-SF) Average And Worst Pain, region, race, WOMAC Stiffness, Physical Function and Pain domains and total score, use of opioid/other pain medication, active fractures/pseudo-fractures, and 6-minute walk test distance. They found that burosumab was similarly effective across subgroups defined by symptoms, impairment, and fractures. Burosumab was largely superior to placebo in the primary, key secondary, and additional efficacy endpoints in the 14 subgroup variables. (Results for Asian region favoured placebo for some outcomes, which may reflect cultural differences in patient-reported outcome responses; there were only 18 participants in this region, so patient numbers were small.)

2.8 Meta-analysis

No meta-analysis has been performed, because randomised, blinded data comparing burosumab with standard care are only available from one study (CL303).

2.9 Indirect and mixed treatment comparisons

Not applicable: no indirect or mixed treatment comparison was performed, because data on burosumab versus standard care are available from a head-to-head RCT (CL303).

2.10 Adverse reactions

Key points

- The overall incidence, nature, and severity of adverse events were comparable in the burosumab and placebo treatment groups in the pivotal trial (CL303). Most AEs were mild or moderate in severity.[7]
- There were no deaths, discontinuations due to adverse events or dose-limiting toxicities; a small number of patients required dose reductions for hyperphosphataemia.[7]
- The incidence of injection site reactions was similar in the two groups, and no participant developed neutralising anti-burosumab antibodies during treatment.[7]
- No new safety signals were seen during long-term follow-up of patients treated with burosumab.[56]

2.10.1 Overview

The most common adverse reactions reported in adults treated with burosumab during clinical trials, as reported in the SmPC, were: back pain (23%), headache (21%), tooth infection (19%), vitamin D decreased (15%), restless legs syndrome (13%), muscle spasms (12%) and dizziness (11%).[1] An overview of adverse events observed during clinical trials of burosumab in adults with XLH is shown in **Table 22**. No additional safety concerns have been identified. In the most recently published Periodic Safety Update Report (PSUR 8, dated April 2022), most reported AEs were expected with burosumab use and/or the underlying conditions being treated.[76] Tables from the EPAR[61] summarising treatment-emergent adverse events in all burosumab studies are provided in Appendix F.

Table 22: Burosumab adverse reactions reported in adults with XLH (n = 176)

MEdDRA system organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Tooth infection[a]
Nervous system disorders	Very common	Headache[b]
	Very common	Dizziness
	Very common	Restless legs syndrome
Gastrointestinal disorders	Common	Constipation
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Very common	Muscle spasms
Investigations	Very common	Vitamin D decreased[c]
	Common	Blood phosphate increased[d]

[a]Tooth infection includes tooth abscess and tooth infection. [b]Headache includes headache and head discomfort. [c]Vitamin D decreased includes vitamin D deficiency, blood 25-hydroxycholecalciferol decreased and vitamin D decreased. [d]Blood phosphate increased includes blood phosphate increased and hyperphosphataemia. XLH, X-linked hypophosphataemia
Source: Burosumab SmPC[1]

Anti-drug antibodies: The incidence of people who tested positive for ADAs to burosumab in adult clinical studies, based on data from completed long term clinical studies, was 16%. None of these developed neutralising ADAs. No adverse events, loss of efficacy, or changes in the pharmacokinetic profile of burosumab were associated with these findings.[1]

2.10.2 Adverse reactions in Study CL303

The overall incidence, nature, and severity of adverse events were comparable in the burosumab and placebo treatment groups in CL303. Most AEs were mild or moderate in severity. A summary of treatment-emergent adverse events during the placebo-controlled treatment period is shown in Table 23.

Table 23 Summary of Treatment-Emergent Adverse Events - Placebo-controlled treatment period (Safety Analysis Set), CL303

Category	Placebo (N=66) n(%)	Burosumab (N=68) n (%)
Any TEAE	61 (92.4)	64 (94.1)
Related[a] TEAE	27 (40.9)	30 (44.1)
Serious TEAE	1 (1.5)	2 (2.9)
Related[a] serious TEAE	0	0
Grade 3 or 4 TEAE	8 (12.1)	8 (11.8)
TEAE leading to study discontinuation	0	0
TEAE leading to treatment discontinuation	0	0
TEAE leading to death	0	0

TEAE = treatment-emergent adverse event. [a] TEAEs classified by the Investigator as possibly related, probably related, or definitely related. Source: Clinical study report[8] and EPAR[61]

For the adverse events of interest in the study, injection site reactions (i.e. injection site reaction, erythema, rash, bruising, pain, pruritis and haematoma) occurred in 12% of participants in both groups.[1] These reactions were generally mild, occurred within 1 day of study drug administration, lasted approximately 1 to 3 days and required no treatment. Potential hypersensitivity reactions (including injection site rash, rash, urticaria, facial swelling and dermatitis) were reported by 6% of participants in both groups.[1] All events were mild or moderate in severity.

Nine participants (13%) in the burosumab group had at least one high serum phosphate measurement, of whom five required protocol-specified dose reduction(s).[1] During the open-label treatment extension period, eight participants (12%) in the placebo-burosumab group had high serum phosphate levels. Four required a protocol-specified dose reduction and one required a second dose reduction for continued hyperphosphataemia.[61]

Approximately 12% of participants in the burosumab group and 8% in the placebo group had worsening of baseline restless legs syndrome or onset of new restless legs syndrome during the placebo-controlled treatment period of Study CL303.[1] All of these events were mild to moderate in severity.

2.10.3 Long-term safety data

In the BUR02 long-term extension study, after a mean exposure to burosumab of 116.22 (SD 30.7) weeks in 35 patients, safety data were in line with previous findings. [redacted]

[redacted][70] A publication by Weber et al 2022[56] contained data on 20 patients from UX023-CL203 (NCT02312687), a Phase 2b, open-label, single-arm, long-term extension study of adult subjects with XLH who participated in KRN23-INT-001 or KRN23-INT-002 studies. Data were available to 184 weeks. The safety profile of burosumab was similar to that observed in the prior studies in adults with XLH, with no new safety findings emerging.

2.11 Ongoing studies

2.11.1 Study BUR03 (BurGER)

BUR03 (BurGER; NCT04695860) is an investigator-sponsored, Phase 3b, open-label, single-arm study to confirm the safety and efficacy of burosumab in adults with XLH. It was carried out at a single centre in Germany.[77] It enrolled 34 patients, who received burosumab 1 mg/kg body weight every 4 weeks for 48 weeks. The study is now completed and an analysis that will include data up to Week 50 (i.e. two weeks after the last dose of study medication) is expected in second half 2023. Endpoints include mean serum phosphate concentrations, functional assessments (including the chair rise test, 6MWT and the timed up and down stairs test) and HRQoL. Due to the single-arm design, it will not provide comparative data.

2.11.2 UK Real World Experience via Early Access Programme

The burosumab Early Access Programme (EAP) in England currently includes [redacted] (as of April 2023) who have received burosumab via this free of charge route. Data from all participants enrolled in the EAP will be considered for inclusion in a multicentre, single-arm retrospective real-world data collection capturing deidentified data from adults with XLH being treated with burosumab in routine clinical practice.[78] This will constitute high-quality real-world evidence. Data are not expected to be available within the timeframe of the submission.

2.11.3 Study CL401: disease monitoring programme

Study CL401 (NCT03651505) is a Phase 4, long-term, prospective, observational outcomes study in adults and children with XLH that is currently underway in the US, Canada and South America.[79] It aims to characterise the presentation and progression of XLH, as well as assess the long-term efficacy and safety of burosumab. It is planned to enrol approximately 800 people; they can enter the study regardless of how their XLH is being treated, provided they have a life expectancy of at least 1 year and are not taking part in an Ultragenyx-sponsored clinical trial. The study will collect demographic, biochemical, physiologic, disease severity and progression data over 10 years. The expected completion date is July 2028. Congress presentations are planned for 2023 covering patient-reported outcomes, safety and efficacy, work and productivity, and the patient journey. A manuscript describing nephrocalcinosis and renal function is in development; further manuscripts

are planned covering topics such as long-term efficacy and safety, and outcomes according to serum phosphate levels.

2.11.4 International XLH registry

This prospective, non-interventional, observational registry (NCT03193476) aims to characterise the treatment, progression and long-term outcomes of XLH in adults and children.[80] Clinics across Europe and in Israel are currently taking part. Data will be collected over a 10-year period, with an expected completion date of July 2029. A subset of the data collected in the XLH registry will be used to fulfil a Post-Authorisation Safety Study (PASS); centres taking part in the PASS will record information on adverse events. The first interim analysis (data cut off 29 March 2021) has been carried out and a publication is available detailing demographic and clinical characteristics.[81] No outcomes data are yet available, with analyses for future congress submissions and manuscripts planned throughout 2023 and beyond.

2.12 Interpretation of clinical effectiveness and safety evidence

The pivotal study of burosumab in adults with XLH was CL303, a randomised, double-blind, placebo-controlled, Phase 3 study. A total of 134 participants were enrolled, with 68 randomised to burosumab and 66 to placebo.[7,8,57,62] Additional evidence is available from a single-arm Phase 3 study on the effects of burosumab on osteomalacia (CL304),[35] and a Phase 3b single-arm follow-on study (BUR02).[60] Some real-world evidence from Early Access use of burosumab in the UK is also available.[4]

2.12.1 Unmet need in highly symptomatic adults with XLH

In the absence of burosumab, highly symptomatic adults with XLH whose needs are not met by conventional therapy currently have no treatment options for XLH beyond symptomatic and supportive treatment (e.g. analgesia, surgery etc). XLH has profound effects on these patients' physical and mental wellbeing, their capacity for daily activities, their family life and their HRQoL.[2,16,20,21] There is a clear need for a well-tolerated therapy that corrects the underlying cause of disease and restores phosphate homeostasis, thereby normalising serum phosphate levels and improving symptoms, physical functioning and HRQoL.

2.12.2 Summary of the clinical evidence for burosumab

The clinical evidence available consistently shows that burosumab is highly effective at normalising serum phosphate levels in adults with XLH.[7,60] Hypophosphataemia (low serum phosphate) has a multisystem impact[3,14,31] and is the primary driver of the ongoing manifestations of XLH in adulthood.[14,31] By normalising phosphate levels, treatment with burosumab is shown to result in significant improvements to pain, stiffness and physical functioning, and to promote fracture healing.[7,35,57,60] Osteomalacia (soft bone, a hallmark of XLH in adulthood) and other markers of bone quality are also improved by burosumab.[7,35] These effects in turn result in significant,

clinically meaningful improvements to patients' utility (see Section 3.4.3 and 3.9.1). Thus, although serum phosphate level is a biochemical outcome, the clinical consequences of normalised serum phosphate levels are clearly demonstrated in the clinical evidence, confirming that it is directly related to patient-relevant benefits.

- Burosumab normalises serum phosphate levels in the great majority of patients: after 24 weeks, 94.1% of those receiving burosumab had achieved a mean serum phosphate level above the LLN across the midpoints of the dose intervals (the primary study endpoint), compared with 7.6% of those on placebo.[7]
- Phosphate normalisation is maintained over time (with evidence out to 3.5 years).[8,56,60]
- Burosumab was associated with a steady and consistent improvement in patient-reported outcomes relating to stiffness, pain, physical functioning and fatigue (WOMAC, BPI and BFI scores) in the CL303 study.[7,57]
- At Week 24, participants receiving burosumab also had significant improvements from baseline in 6MWT distance walked (P=0.018) and percent predicted (P=0.021), whereas those in the placebo group had slight decreases.[57]
- The odds of full fracture healing at Week 24 in CL303 were 16.8-fold higher with burosumab than with placebo (P<0.001).[7] Over half of patients had active fractures or pseudofractures at baseline. In study CL304, two of the four active fractures present at baseline had fully healed by Week 12 and two had partially healed.[35]
- Changes in bone biomarkers in burosumab-treated patients in the pivotal trial were consistent with a positive bone remodelling balance and a net increase in bone formation, compared with placebo. Burosumab improved bone mineralisation and osteomalacia-related measures of bone quality (48 weeks of treatment) in study CL304.[35]
- Real-world clinical experience in the UK suggests that burosumab is associated with a reduction in opioid use: five of the 13 (38.5%) opioid users at baseline had discontinued opioids by one year (p=0.006).[4]
- Burosumab is well tolerated: the overall incidence, nature, and severity of adverse events were comparable in the burosumab and placebo treatment groups in the pivotal trial (CL303). Most AEs were mild or moderate in severity and there were no discontinuations due to AEs.[7] No new safety signals have been detected during long-term follow-up, and no development of neutralising antibodies has been observed.[8,56,60]

2.12.3 Discussion of findings

The clinical evidence clearly shows that burosumab treatment results in important benefits for adults with XLH via the mechanism of serum phosphate normalisation (and possibly also negation of the direct physical effects of excess FGF23). When mapped to EQ-5D, the change in WOMAC scores translated to a lifetime incremental discounted QALY gain of [redacted] out of the total [redacted]

discounted QALY gains (the remainder being [redacted] QALY gains due to impact on morbidities, and [redacted] incremental QALYs due to impact on carers and family members)."

XLH-specific minimal clinically important difference (MCID) thresholds for WOMAC, BPI and BFI scores have been suggested.[57] While all improvements in PROs are meaningful, MCIDs may provide an additional aid to interpretation of changes. The magnitude of improvements in PROs with burosumab generally increased over time. In patients randomised to burosumab in the initial 24-week treatment period, the suggested MCID thresholds for WOMAC stiffness and physical function scores and BPI worst pain (greatest) and pain interference scores and BFI worst fatigue (greatest) had been met by week 48. At week 96 the threshold was met for WOMAC pain and WOMAC total score. Improvements in patients who crossed over from placebo to burosumab at week 24 met these MCID thresholds at week 96, and for some measures at week 48.[57]

It is noteworthy that changes in pain scores in a condition such as XLH may not be as large as expected, for two reasons. Firstly, adults with XLH have pain from a variety of causes, not all of which are modifiable by phosphate normalisation in adulthood (e.g. dental pain is largely due to tooth architecture created in childhood, and pain due to skeletal misalignment and existing osteoarthritis would not be expected to be modified). Secondly, a reduction in pain may enable patients to increase their activity levels, which in turn may aggravate pain. Patients may choose to increase their activity levels at the expense of pain reduction, up to the level of pain they feel able to tolerate. Even so, burosumab was associated with significant improvements in pain scores.

Burosumab was associated with a reduction in opioid use in the first (and so far only) published real-world experience from a UK centre (accepted for conference poster presentation). Krishna et al. concluded that: “The real-world experience of burosumab in adults with XLH replicates the benefits seen in clinical trials and extends the benefit to reducing opioid use.”[4] This is likely to be beneficial for patients, as chronic opioid use for pain relief is associated with adverse effects including fractures, breathing problems during sleep, hyperalgesia, immunosuppression, chronic constipation, bowel obstruction and myocardial infarction,[46] and increased risk of mortality (Odds ratio = 1.5 [95% CI 1.1, 1.9] at 3 years according to one study).[47]

2.12.4 Strengths and limitations of the evidence base

The evidence base has several strengths. The availability of RCT data from 134 patients (study CL303) represents a strength in a very rare disease such as XLH. This was a well-designed, good quality study providing robust comparative data versus placebo up to 24 weeks. The endpoints measured captured the modification of the underlying mechanism of disease via the action of burosumab, and the range of patient-relevant outcomes that could be expected to result from this (changes in stiffness, pain, physical functioning, fatigue and fracture healing).

The evidence base is generalisable to adult patients with XLH treated in the NHS in England. Study CL303 was carried out in the US, UK, Japan, France, South Korea, Ireland and Italy. More than 80% of participants were from Europe or North America; 35 European participants subsequently took part in Study BUR02. According to clinical expert opinion, the patients recruited into the pivotal study (CL303) are reasonably representative of the English patient population that would receive burosumab (see Appendices P and Q for clinical validation reports). Most patients (90.3%) had received prior therapy with both oral phosphate and active vitamin D metabolites or analogues, and almost all of the remainder had been treated with one or the other (3.0% had received only phosphate and 4.5% only vitamin D metabolites or analogues). In total, 82.8% had received conventional therapy after the age of 18 years.[8] Thirty-six patients were on conventional therapy at screening and underwent a washout period as per the study protocol; however, a post hoc analysis showed that these patients had mean serum phosphate below LLN at the screening visit prior to washout, indicating that they were not being adequately treated.[68]

After 24 weeks, patients randomised to placebo crossed over to burosumab. Another important strength is the availability of long-term (single-arm) follow-up of burosumab-treated patients, extending to 96 weeks from the CL303/BUR02 studies and to 168 weeks in the CL203 study, showing that normalisation of phosphate levels is maintained and that clinical and patient-reported benefits increase over time.[56,57,60] An additional study (study CL304) provides more evidence on the effects of burosumab on bone quality, showing that osteomalacia (the hallmark of XLH in adults) is improved. The absence of comparative data with conventional therapy is not a limitation in the population under consideration, i.e. patients for whom conventional therapy is not suitable due to ineligibility, intolerance or inadequate efficacy.

A limitation of the evidence base is that neither generic measures of HRQoL or preference-based utility were captured in the RCT (study CL303). Patient-reported outcomes were captured by the WOMAC, BPI and BFI instruments, which comprehensively cover the physical aspects of a bone disease such as XLH. WOMAC can be mapped to EQ-5D, and this was undertaken for the economic modelling. However, effects on mental health and emotional wellbeing are not captured. Given that patient surveys and testimonies consistently cite the heavy mental and emotional burden of living with XLH, this is a limitation. The improvements in pain and physical functioning seen with burosumab could be expected to have a positive effect on mental health, as discussed in Section 3.12 (benefits not captured in the QALY).

The effects of the condition on the HRQoL of family members of people with XLH have been documented (see Section 1.3.5). Improvements in HRQoL for adults treated with burosumab are expected to ‘spill over’ to family members However, no data on the effects of burosumab treatment in adults with XLH on HRQoL of family members is available.

The trial was too short to ascertain any effect of burosumab on mortality. It is anticipated that by addressing the root cause of XLH (i.e. normalising phosphate homeostasis) and thus mitigating the ongoing, multi-system effects of hypophosphataemia that may drive increased mortality, treatment with burosumab will extend life expectancy. Plausible potential mechanisms for this are detailed in Section 1.3.4. Data to confirm this will require longer-term follow-up, and any effect on mortality will take a long time to emerge in this small patient population.

Conclusion: the clinical evidence shows that treatment with burosumab normalises phosphate homeostasis and vitamin D metabolism, which in turn leads to improved bone quality, improved fracture healing, reductions in patient-reported stiffness, pain and fatigue, and improvements in physical functioning scores and mobility (compared with placebo). This in turn leads to marked improvements in health-related quality of life, as measured by the mapping of WOMAC scores to EQ-5D. Burosumab is well tolerated, with low rates of treatment discontinuation. Burosumab addresses a high unmet need in highly symptomatic adults with XLH for whom conventional treatment is not suitable.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

No published cost-effectiveness studies for burosumab or best supportive care in adults with XLH were identified. Please refer to Appendix G for details on the search strategies and results of the literature review to identify cost-effectiveness studies.

3.2 Economic analysis

The only previous NICE appraisal of burosumab in XLH was HST 8,[13] which covered children and adolescents aged 1-17 years. Burosumab has shown sustained efficacy and safety in children, with improved phosphate homeostasis and improvement to rickets reported for up to 160 weeks.[82] Burosumab was recommended by NICE, within its marketing authorisation, for treating "X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children aged 1 year and over, and in young people with growing bones". The clinical manifestations of XLH are different in children and adults. Among other manifestations, XLH has a severe effect on growing bones that typically leads to skeletal deformities such as hypophosphataemic rickets. As bone growth ceases after puberty, the benefits to skeletal maturation seen with burosumab in children are not applicable in adults. Thus, although outcomes such as phosphate levels were measured in both populations, the benefits derived and the primary functional outcomes measured in adults are very different from those in children. The key outcomes in the paediatric trials and the paediatric model focused on bone deformity (Rickets Severity Score [RSS] and Radiographic Global Impression of Change [RGIC], whereas these were not relevant in the adult trials, which focused on phosphate levels and patient-reported outcomes (pain, stiffness, fatigue, physical functioning). This means that the parallels between the two appraisals are limited, and uncertainties and assumptions associated with the appraisal in children are not necessarily relevant to the adult appraisal (and vice versa). Because of these considerable differences, a de novo model was developed for the appraisal in adults.

3.2.1 Patient population

The patient population covered by the submission is adults (aged ≥18 years) with a confirmed diagnosis of XLH who have chronic hypophosphataemia, symptoms that include a Brief Pain Inventory (BPI) score of ≥4 (upper limit of mild pain), and for whom conventional therapy is unsuitable due to ineligibility (e.g. patients with contraindications, such as presence of toxicities developed on conventional treatment such as renal or parathyroid toxicity), or intolerance or insufficient efficacy (i.e. failure to normalise phosphate levels, or persistence of symptoms despite treatment). The rationale for this choice is explained in Section 1.1.

Based on clinical expert opinion of clinicians participating in the EAP, the patient population who participated in the CL303 study is similar to the population who are currently receiving treatment with burosumab through the programme and is generalisable to the adult XLH population who would be treated with burosumab (see Appendix Q for clinical validation report). The generalisability of the CL303 study to English clinical practice is discussed in Section 2.12.4; there are no significant problems with generalisability.

3.2.2 Model structure

A cost utility model was developed to examine the cost-effectiveness of burosumab for the treatment of adults (≥18 years of age) with a diagnosis of X-linked hypophosphataemia (XLH). The model is implemented as a cohort model. In order to account for the distribution of ages at which patients may start treatment, the model is run discretely for a range of starting ages. The age-specific results are then aggregated according to the proportion of the adult population with XLH in each age category to obtain estimates of total population costs and effects.

The model captured costs and quality-adjusted life years (QALYs) and calculated an incremental cost-effectiveness ratio (ICER) between burosumab and usual care. The model, built in Microsoft Excel, has annual cycles and tracks patients' treatment status (whether receiving burosumab or standard of care) and mortality. The impact of burosumab treatment is captured in three different ways:

- Reducing the excess mortality due to XLH, estimated by applying a hazard ratio to the general public life tables in the UK,[83] representing the increased risk of death amongst XLH patients.
- Improvement in quality of life due to reduction in fatigue, pain, stiffness and improvement in physical functioning as captured by changes in WOMAC scores. A mapping algorithm from WOMAC scores to a preference weighted instrument (EQ-5D) is available, enabling the use of trial evidence to derive the utility benefit associated with the observed symptomatic benefit.
- The effect of burosumab treatment on the probability of increasing serum phosphate above the lower limit of normal (LLN) compared to patients randomised to placebo, and thereby reducing the incidence of fractures (modelled in the base case) and potentially other XLH-related morbidities (dental problems, spinal stenosis and hearing loss; modelled in a scenario analysis).

The model is a state transition model tracking survival and treatment status, while at the same time tracking proportions of patients with morbidities within the "Alive" health states (see **Figure 27**).

3.2.2.1 Survival Model

The survival model calculated the survival of SoC patients over a lifetime and provided the proportion of the XLH population that is female in each age band based on treatment and model start age. This provided input data for the other interlinked models for each age band. The age bands and the distribution in each band are taken from the CL303 pivotal trial. The proportion of female patients at age 18 (65%) was also taken from the trial (CL303) for consistency and reflects the X-linked, inherited nature of this genetic disease leading to more females being affected than males.

Table 24: Patient age distribution (From CL303)

Age range	Number of patients	Distribution of population
18-23	16	13%
24-28	17	13%
29-33	14	11%
34-38	12	9%
39-43	21	17%
44-48	17	13%
49-53	11	9%
54-58	8	6%
59-63	9	7%
64+	2	2%

Excess mortality due to XLH was calculated by using a hazard ratio derived from Hawley et al. (2020).[19] This was then applied to the age and sex specific general population hazard of death based on general population life tables in the UK.[84]

The analysis by Hawley et al. used data from the UK Clinical Practice Research Datalink (CPRD) database and reported overall survival (OS) in individuals identified using an algorithm that graded subjects based on their likelihood of having XLH; the grading included: “highly likely”, “likely”, “possible”, “unlikely” or “unable to determine”. Of the 522 initially identified potential cases, 122 were used in the Hawley main analyses: these comprised 27 highly likely, 37 likely and 58 possible cases which were compared to matched patients from the Clinical Practice Research Datalink (CPRD) GOLD database. XLH cases were matched by age, gender, and practice to up to four controls. The hazard ratio for OS between the “likely” or “highly likely” XLH population and the matched cohort was 6.65 (95% CI 1.44 to 30.72). The corresponding hazard ratio between all at least “possible” XLH patients and the matched cohort was 2.93 (95% CI 2.8 to 8.1) [19]. These values are tested in a scenario analysis (see Section 3.10.3).

The study also included a 'sensitivity' analysis that did not censor patients at the time they transferred from their index GP practice but continued to follow them until the end of follow-up (given that XLH is a lifelong condition). This analyses greatly reduced uncertainty around the estimates since it increases the number of death events from the original 3 and 4 to 15 and 8 in the control and XLH arms respectively. The hazard ratio reported was 2.88 (95% CI, 1.18 to 7.00).

Additionally, Kyowa Kirin conducted a confirmatory study which aimed to extend Hawley's work by applying the same XLH grading algorithm and investigating life expectancy of adult XLH patients using real-world data from both CPRD GOLD and CPRD AURUM, a larger UK data source, linked to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) mortality data. This study presented a larger, more robust and independent validation of the findings made by Hawley et al. and reported a hazard ratio of 2.33 (95% CI, 1.16-4.67) in a predominantly independent sample (study methodology and results are reported in Appendix R). After consultation with clinical experts, it was decided that the model should use the HR from the Hawley analysis that used censoring at the end of follow-up rather than at transfer out of practice (HR=2.88), as this analysis is likely to provide more precise estimates and its findings were confirmed by the independent study relying on a largely independent sample, as reported in Appendix R.

There is a lack of published evidence on causes of death in people with XLH or the mechanisms which might lead to increased mortality. However, a range of factors that affect adults with XLH are known or hypothesised to be associated with reduced life expectancy, as explored in Section B.1.3.4 and shown in Figure 5. It is plausible that this constellation of risk factors would result in increased mortality, as observed in both the Hawley analysis and Kyowa Kirin's study (see Appendix R). The impact of burosumab treatment is included as a reduction in this increased mortality (see Section 3.3.1.3 below).

3.2.2.2 Modelling of treatment status

Treatment status was tracked for patients on the burosumab arm as they move through the following states:

- Alive (on treatment)
- Alive (off treatment)
- Dead.

All patients started in the Alive (on treatment) state and transitioned to the Alive (off treatment) state based on annual discontinuation rates and initial response to treatment. According to the proposed stopping rules for treatment, only patients achieving a clinically relevant benefit from burosumab remain on long-term treatment. Thus, continuation of treatment after year 1 in the model is based on a requirement of reaching serum phosphate levels above LLN after 24 weeks of

treatment and an improvement in WOMAC total score at 12 months after starting treatment. As mentioned in Section B.2.6.1, 92.3% of participants in CL303 reached LLN after 24 weeks of treatment and 83.1% of participants in CL303 also saw an improvement in WOMAC score at 48 weeks, which was the closest study visit to one year where these data were recorded. As such the model allows for (100%-92.3%=) 7.7% of patients to discontinue treatment after 24 weeks, and a total of (100%-83.1%=) 16.9% of patients to discontinue treatment in year 1. Clinical opinion gathered during the elicitation exercise (see Section 2.3.7, and Appendices P and Q) suggested that while serum phosphate assessments are routinely carried out to assess response and the need for dose modifications, WOMAC score may not be commonly used in clinical practice to evaluate whether a patient should have access to treatment. However, clinicians agreed that WOMAC scores are a good proxy for reflecting the criteria for continuation of treatment that might be used as it captures improvement in pain, stiffness and fatigue.

Discontinuation in years 2 and beyond (a 3% discontinuation rate) is based on assumptions sourced from expert elicitation from three England-based clinical experts, who have experience of managing adults with XLH in the UK (see Appendix Q). This assumption is also supported by the observed annual discontinuation rates from the EAP (see Table 25**)** It should be noted that the EAP does not include the proposed stopping rule, therefore it cannot be used to validate the first year discontinuation rate, but provides a real-life indication of what proportion of patients are expected to stop due to other reasons over time.

Table 25: Annual discontinuation rate from EAP

Year	Starting population	Discontinued (n)	Annual discontinuation rate
2020	[redacted]	5	3%
2021	[redacted]	5	3%
2022*	[redacted]	6	4%

* 1 patient discontinued in 2023 before the time of the NICE submission

Table 26: Discontinuation rates for burosumab in the model

Year	Discontinuation rate
Year 1	16.9%
Year 2+	3%

Source: CL303 and clinical opinion

3.2.2.3 Modelling of morbidities

A series of models predict the incidence of individual morbidities. The probabilities of patients experiencing incident morbidities were estimated as a function of age and treatment status. For patients in the burosumab arm the probability of experiencing an incident morbidity was reduced

whilst the patient was on treatment. The improvement was only applied to the incremental proportion of patients versus SoC who had also achieved serum phosphate levels above the LLN.

The selection of morbidities for inclusion was validated by three England-based clinical experts who have experience of treating adults with XLH in the UK (see Appendix P). The clinicians were asked to consider four different criteria:

1. Is the morbidity causally linked with excess circulating FGF23 and hypophosphataemia and/or caused by musculoskeletal systems deformities developed in childhood and/or associated with treatment with conventional treatment for XLH?
2. If the patient did not have the morbidity, would use of burosumab prevent future occurrence of that morbidity?
3. If that morbidity is present and in its early stages would use of burosumab either lead to resolution of the morbidity or cause the morbidity to remain in the early stage?
4. If the morbidity is present and past the early stages, would use of burosumab lead to stabilisation or, if the morbidity is reversible, would use of burosumab lead to a reversal or resolution?

Based on this consultation, the model only includes morbidities where treatment with burosumab is likely to reduce the incidence of future events or lead to the resolution of the events. Therefore, fractures including upper limb, vertebrae/spinal, foot, tibia/fibula, femur/pelvis, and other fractures were included in the model base case, where reduction of the incidence of future events was captured directly through the use of lower fracture rates for burosumab-treated patients, while resolution of existing fractures was captured through the observed quality of life improvements. Sensitivity analyses were performed which also included dental abscesses, spinal stenosis (and subsequent surgical treatment), and tinnitus/hearing loss.

The base case also includes the effect of treatment on stiffness, pain and fatigue (the impact of the resolution of baseline morbidities), as recorded via WOMAC scores from CL303 and BUR02.

3.2.2.4 Combining treatment status, impact on morbidities and survival

All three of these overarching models are connected such that being on treatment influences the occurrence of morbidities and mortality risk. Costs and impact on utilities of each morbidity are accounted for separately. Figure 27 outlines the logic of the economic model, while Figure 28 below shows how each of the models interconnect with each other.

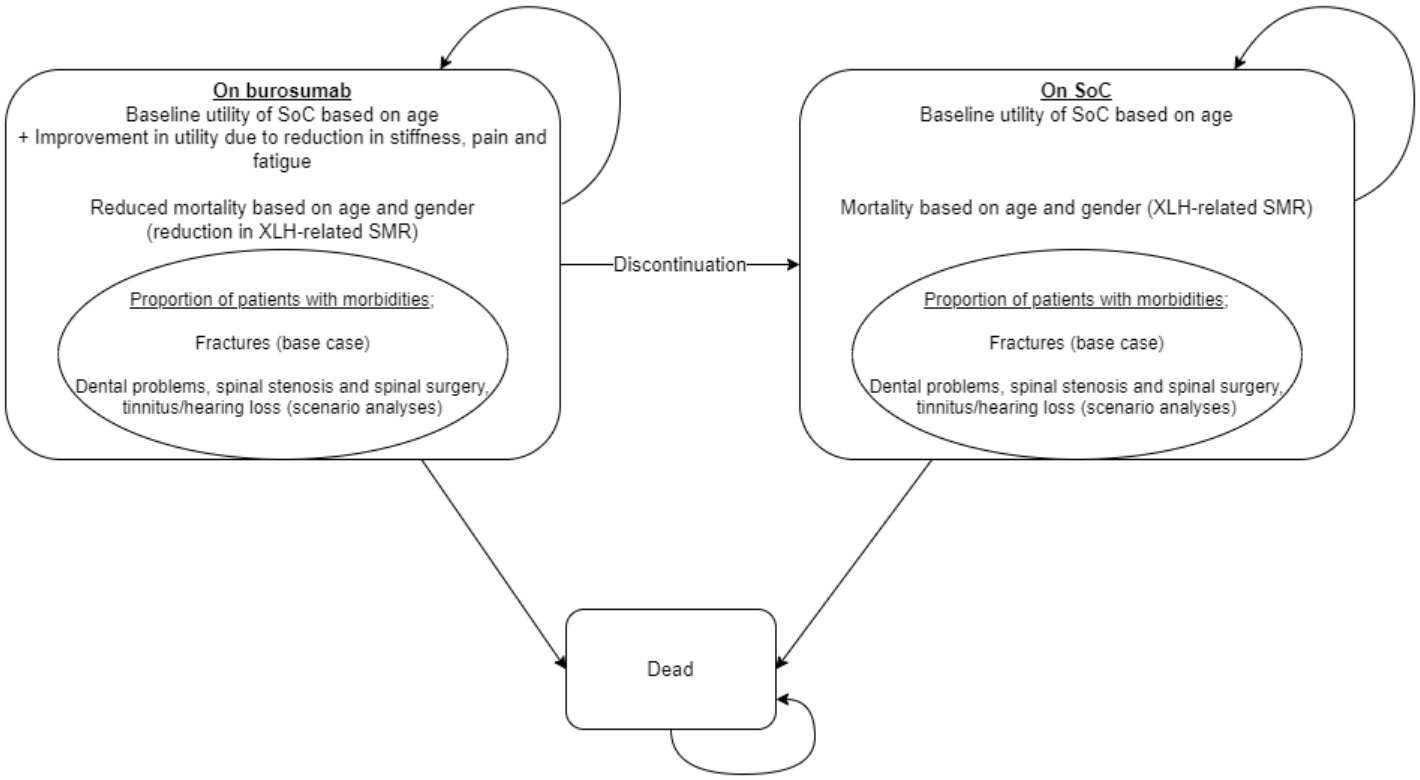
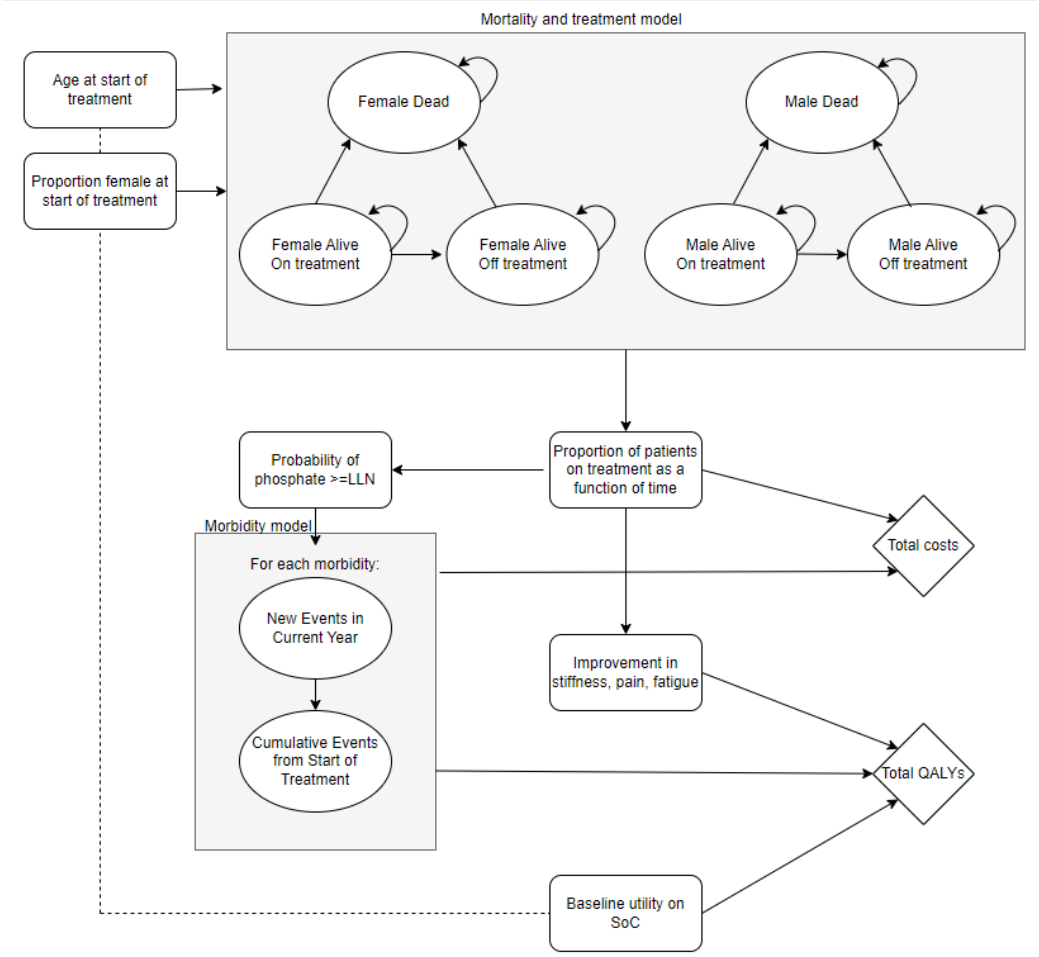


Figure 27: Model logic



LLN – lower limit of normal range; SoC – standard of care, QALY – quality adjusted life year

Figure 28: Cost-effectiveness model structure

3.2.3 Summary of features of the analysis

Summary features of the analysis are shown in Table 27. The 'previous evaluation' column of the template table is not applicable, as there have been no previous evaluations of burosumab or best supportive care in adults.

Perspective: The perspective adopted is that of National Health Service (NHS) and Personal Social Services (PSS), in line with NICE guidance. Thus, all relevant healthcare utilisation costs are considered in the decision model including inpatient care, primary care visitations, and medication costs.

Time horizon: The model utilised a lifetime time horizon, as XLH is a genetic, lifelong condition.

Discount rate: An annual discount rate of 3.5% is applied to costs and benefits. Rates of 0% - 6% were tested in scenario analyses.

Table 27 Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (up to age 100)	Genetic condition
Treatment waning effect?	Tapering of magnitude of treatment effect on morbidities, utility and mortality both at start and after treatment stop. However, no treatment waning effect whilst on treatment	Mineralisation and demineralisation of bones and muscles takes time, therefore all impacts are delayed. No waning of effect whilst on treatment was observed on trial and no obvious physiological mechanisms for treatment waning whilst on treatment (e.g. no ongoing mutations, or neutralising antibodies)
Source of utilities	Pivotal trial (CL303)[7,57] and follow-on study (BUR02)[60] as base case; natural history study (CL001)[18] as scenario analysis	Utilities were taken from the clinical trials (via mapping)
Source of costs	NHS reference costs 2020-2021[85] and PSSRU 2021[86]	As per NICE reference case

3.2.4 Comparison with NICE reference case

The model complies with all aspects of the NICE reference case.

3.2.5 Intervention technology and comparators

3.2.5.1 Intervention

Burosumab is implemented in the model as per its marketing authorisation. The recommended starting dose in adults is 1.0 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, given by intravenous injection every 4 weeks.[1]

3.2.5.2 Comparator

The comparator is best supportive care (BSC). As described in Section 1.3.6, treatment options for adults with XLH are limited. For the population in this assessment, i.e. symptomatic adults for whom conventional therapy is not suitable due to ineligibility, intolerance or inadequate efficacy, there is no other active treatment option in the absence of burosumab. Therefore, only symptomatic treatment of morbidities, i.e. BSC, is offered. As

such, BSC represents usual care for this population, and is hereafter referred to as standard of care (SoC).

3.2.5.3 Continuation rule

As discussed in Section 3.2.2.2 above, continuation of treatment in the model is based on a requirement of reaching serum phosphate levels above LLN after 24 weeks of treatment and an improvement in WOMAC score at 12 months after starting treatment. As described in the draft UK clinical recommendations, monitoring costs applied in the model incorporate additional serum phosphate tests in the first year of treatment to allow assessment of reaching LLN, as well as monitoring visits to assess patients' pain, stiffness and muscle function included in WOMAC scores.[6]

3.3 Clinical parameters and variables

3.3.1 Incorporation of treatment effect

Treatment (with burosumab or SoC) is assumed to influence the proportions of patients with normalised serum phosphate levels and through that the proportions of patients developing morbidities linked to hypophosphatemia and osteomalacia, and patients' risk of mortality. In addition, improvements in pain, stiffness and energy levels are captured through increases in utilities (see Section 3.4.3).

3.3.1.1 Phosphate normalisation

The probability of serum phosphate normalisation was taken from the CL303 trial based on the observed values at the end of the blinded, placebo-controlled study period (Week 24),[7] while everyone in the burosumab arm was assumed to reach LLN, as the treatment stopping rules require serum phosphate normalisation after 24 weeks of treatment for continuation of therapy

Table 28: Serum phosphate normalisation probability by treatment (week 24)

	Probability of serum phosphate normalisation
Burosumab (after application of stopping rule)	100%
SoC (from CL303)	7.58%
Incremental	92.42%

Effectiveness data for SoC patients were sourced from the CL303 trial. This is the appropriate main source of data to reflect 'no treatment' since the comparator in CL303 was

placebo. The comparator arm in CL303 received matching placebo, not conventional therapy, which was not allowed in order to ensure blinding within the trial (concurrent administration of phosphate supplements with burosumab is not permitted in the SmPC). The serum phosphate level check at the initial screening visit (SIV1) of the CL303 trial (before washout of any conventional therapy) found that 94% of patients (including both those receiving and not receiving phosphate supplements previously) were below LLN.[68] The model uses the observation at week 24 in the trial (where 7.6% of patients were > LLN in the placebo arm) to represent the proportion with normal phosphate levels in the SoC.

The model assumes that patients in the burosumab arm experience a reduction in morbidities due to the incremental difference in serum phosphate normalisation rates (i.e. serum phosphate >LLN) between the two arms

3.3.1.2 Fracture incidence

Fracture incidence rates were assumed to be affected by treatment. Bone is an active tissue that undergoes continuous remodelling. In patients with XLH this is impaired due to poor bone mineralisation caused by hypophosphataemia, increasing the risk of fractures associated with osteomalacia (termed ‘pseudofractures’; see Section 1.3.2). These differ from fractures due to trauma experienced by non-affected individuals or fractures due to osteoporosis usually experienced by the elderly.

Patients with normalised serum phosphate levels are assumed to experience fracture incidence rates similar to the general population. This reflects the improvements to a range of markers of bone health seen in the CL303 and 304 studies and described in Section B.2.6.5. According to clinical expert feedback this is a conservative estimate of the expected effect of burosumab on fracture incidence rates, as XLH patients treated with burosumab are likely to have stronger bones than the general population after bone remineralisation (refer to Appendix Q). This is because bones of adults with XLH are usually broader but softer than normal bones, therefore after receiving burosumab treatment, their bones may actually become stronger compared to the general population. It is worth noting that despite the high proportion of patients having active fractures and pseudofractures at baseline in CL303 (32 subjects in the burosumab group had a total of 65 active fractures and/or pseudofractures), no new fractures were identified during the skeletal surveys in either the double-blinded or the open-label or long-term extension periods of the trial.[70]

The effect on fracture incidence was applied to the burosumab arm according to the incremental probability of serum phosphate normalisation compared to the placebo arm. The incremental effect is used here under the assumption that the rate of serum normalisation

reflects a regression to the mean effect. It should be noted that this impact was applied to development of new fractures after the start of treatment. The effect of healing active fractures seen in CL303 was captured through improvements in mobility and pain as captured by WOMAC and included in the economic model as an impact on utilities (see Section 3.4.3).

The calculation of event rates for fractures and other morbidities in the general population is described in Section 3.3.1.5.

3.3.1.3 Mortality

As noted above and in Section B.1.3.4, there are multiple inter-related mechanisms (hypophosphataemia and excess FGF, multimorbidity, physical inactivity, impaired mental wellbeing, opioid use, socioeconomic deprivation) that may drive excess mortality in adults with XLH.

Burosumab works by binding to FGF23 and blocking its action,[1] thereby restoring normal phosphate and vitamin D homeostasis. Treating adults with burosumab has been shown in study CL303 to normalise serum phosphate levels; improve physical functioning, stiffness, pain and HRQoL; and promote fracture healing.[7,35] Real-world evidence also shows a reduction in opioid use (not an outcome examined in the trial due to the requirement for stable analgesic use during the placebo-controlled period). These benefits directly address many of the likely drivers of increased mortality discussed above. In addition, the improvements in physical functioning and pain are likely to promote increased physical activity and improved mental wellbeing, and potentially improve socio-economic status through increased capacity for employment. It is highly plausible that this constellation of benefits will, over time, result in a reduction in the excess mortality associated with XLH, although the exact mechanisms and magnitudes remain unclear.

Clinical experts have noted that treatment with burosumab in adulthood is likely to have an impact of variable magnitude on many of these drivers (see Section 3.10). For example, some comorbidities will be resolved (e.g. through addressing pain and fracture, leading to increased physical activity), but some of the features of XLH that originate in childhood (particularly skeletal deformity) cannot be altered. There were no deaths reported in CL303 during the placebo-controlled period,[7] therefore it was not possible to estimate the impact of burosumab on mortality from the trial.

The HR for mortality in people with XLH versus the general population, published by Hawley et al. (2020),[19] is described in Section 3.2.2.1. Our base case assumption in the cost-

effectiveness model is that the use of burosumab in symptomatic adults addresses approximately 50% of the ***excess*** mortality risk for people with XLH; in other words burosumab treatment provides a 50% reduction in the mortality HR of the SoC arm versus the general population (i.e. the burosumab population has a mortality HR of 1.94 versus the general population (Table 29). This assumption was validated with clinical experts, with one of the clinical experts also providing estimates of uncertainty around the reduction in excess mortality through a structured expert elicitation exercise (see Appendix Q). The reduction in mortality is applied to patients in the burosumab arm whilst they are receiving burosumab. The degree of reduction in mortality is tested in a scenario analysis (refer to Section 3.10.3). As a consequence of the above application methods, death was conditional on sex, age and treatment in the calculations.

Table 29: Mortality hazard ratio showing assumed reduction in XLH-related excess mortality with burosumab

	Mean (SE) excess mortality HR vs. general population
SoC	2.88 (0.45)
Burosumab	50% reduction = 1.94 in base case 95% CI: 19%-75% reduction

Source: Clinical expert input, Hawley et al. 2020[19]

3.3.1.4 Tapering (build-up and waning) of treatment effects

The effect of serum phosphate normalisation on the incidence of morbidities may not be immediate, and differing tapering assumptions can be tested for both the time it takes for the effect to be fully developed and the time it takes for the effect to wear off. Table 30 below shows the assumed rates of treatment effect tapering on fractures and other morbidities in the scenario analysis based on clinical expert opinion (Appendix Q). Since no new fractures were observed in the trial, the impact on fractures rates was assumed to be effectively immediate (i.e. effect took place before new fracture events were likely to occur). Similarly, after discontinuation, the effect is assumed to be lost relatively quickly, as analysis of patients with a gap between treatment received as part of CL303 and BUR02 showed that WOMAC scores returned to baseline during the treatment interval between the two studies (mean 9 months, range 6-16 months).

A tapering effect also applies to the effect of burosumab on mortality. Table **31** shows the assumed rates of treatment effect tapering on mortality. As shown in Section 3.3.1.3 above, impact of burosumab on mortality is more indirect and build-up of effect in terms of impact on physical activities, BMI, and/or social deprivation may take a longer time compared to impact

on fractures and utilities. Alternative tapering assumptions are explored as a scenario (Section 3.10.3.)

Table 30: Treatment effect build up and waning on morbidities

Time period	Treatment effect assumption
Year 1 on treatment	100%
Year 2 on treatment	100%
Year ≤3 on treatment	100%
1 year after end of treatment	50%
2 years after end of treatment	0%

Table 31: Treatment effect build up and waning on mortality

Time period	Treatment effect assumption
Year 1 on treatment	75%
Year 2 on treatment	100%
Year ≤3 on treatment	100%
1 year after end of treatment	75%
2 years after end of treatment	50%

3.3.1.5 Morbidity event rates

3.3.1.5.1 Fracture events for SoC

Estimates of annual fracture rates in adults with XLH receiving SoC were informed by the CL303 trial scan data, as this source provided complete bone scan radiograph data, which provided information on repeat fractures (i.e. the total number of fractures at each location, rather than the proportion of patients who had sustained at least one fracture) and was not self-reported. Complete bone scan radiographs taken at the trial baseline were able to detect multiple fractures in the same bone.

Figure 29 shows the shows the distribution of the observed total number of fracture events for all patients (n = 134) at trial baseline (mean age of 40 years), while Figure 30 shows the mean crude estimated annual fracture rate (total number of fractures divided by age) by fracture site. Fractures in the lower limbs, particularly in the tibia/fibula, are common, most likely due to the weight-bearing nature of these bones coupled to the fact that they are most likely to be deformed from childhood. The estimated mean number of (all active and non-active) fractures across the 134 patients over a mean period of 40 years is 2.38. The mean number of fractures by fracture site is shown in Figure 30.

Figure 29: Distribution of the observed total number of fractures at trial baseline by fracture site

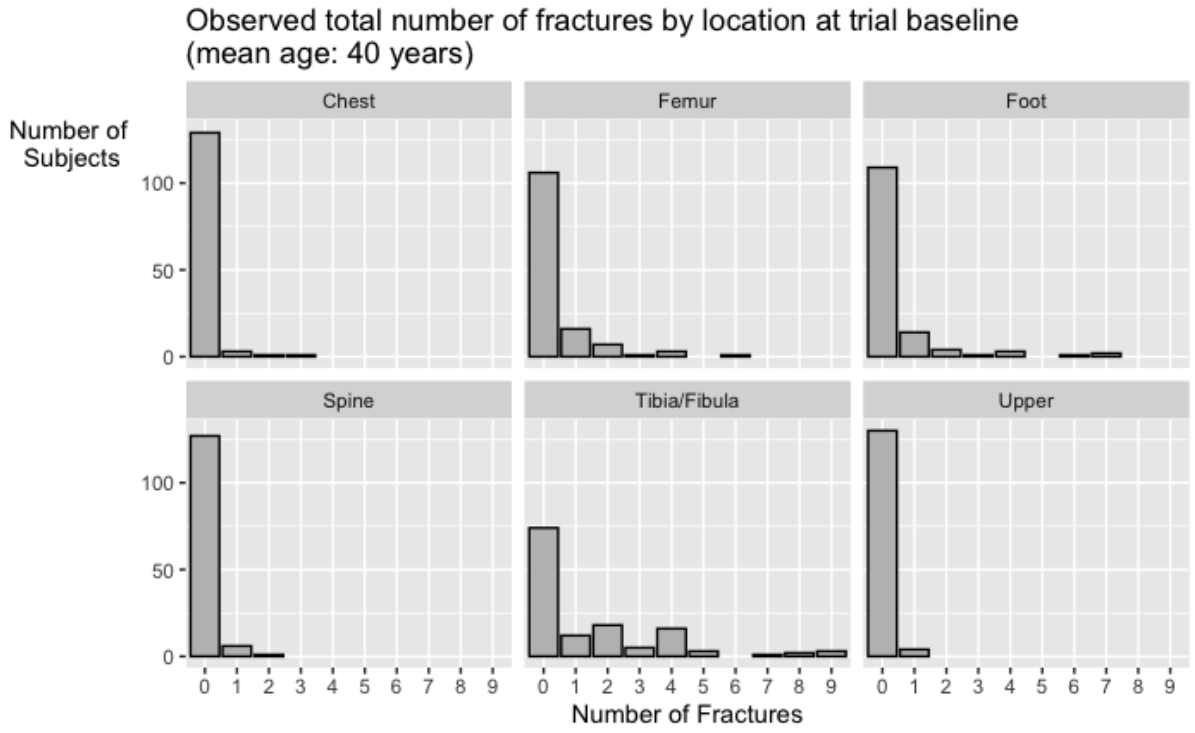


Figure 30: Mean observed total number of fractures by site) (n=104) at CL303 baseline visit

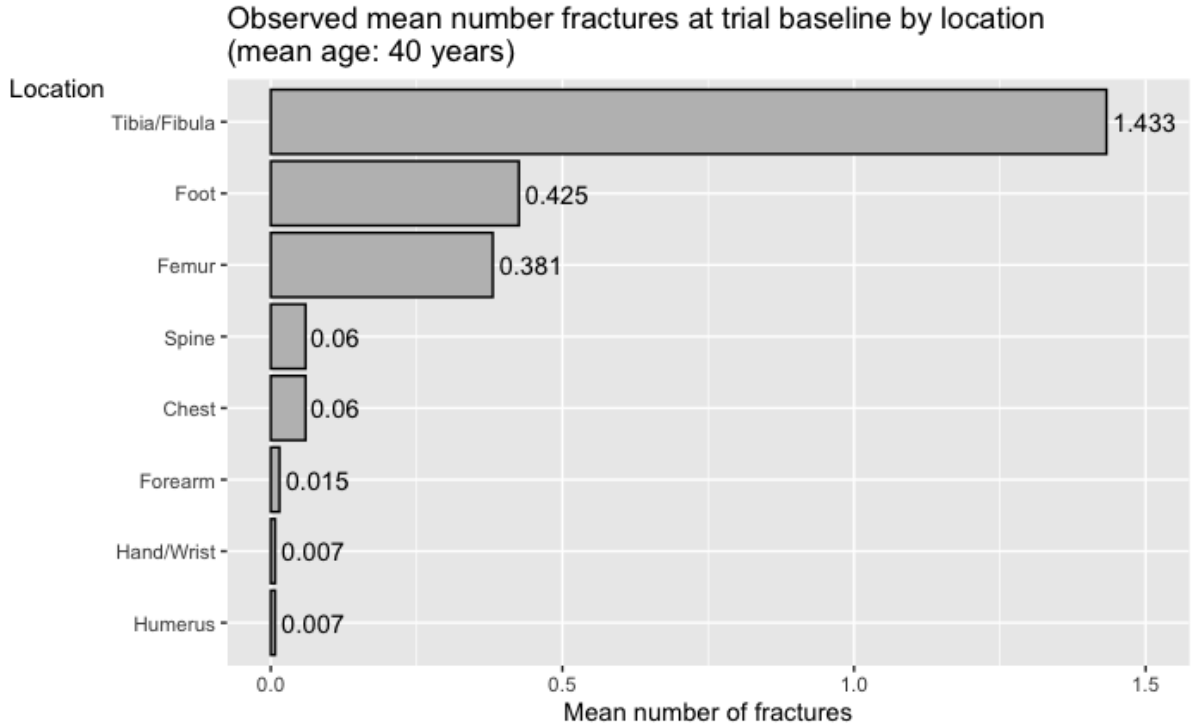
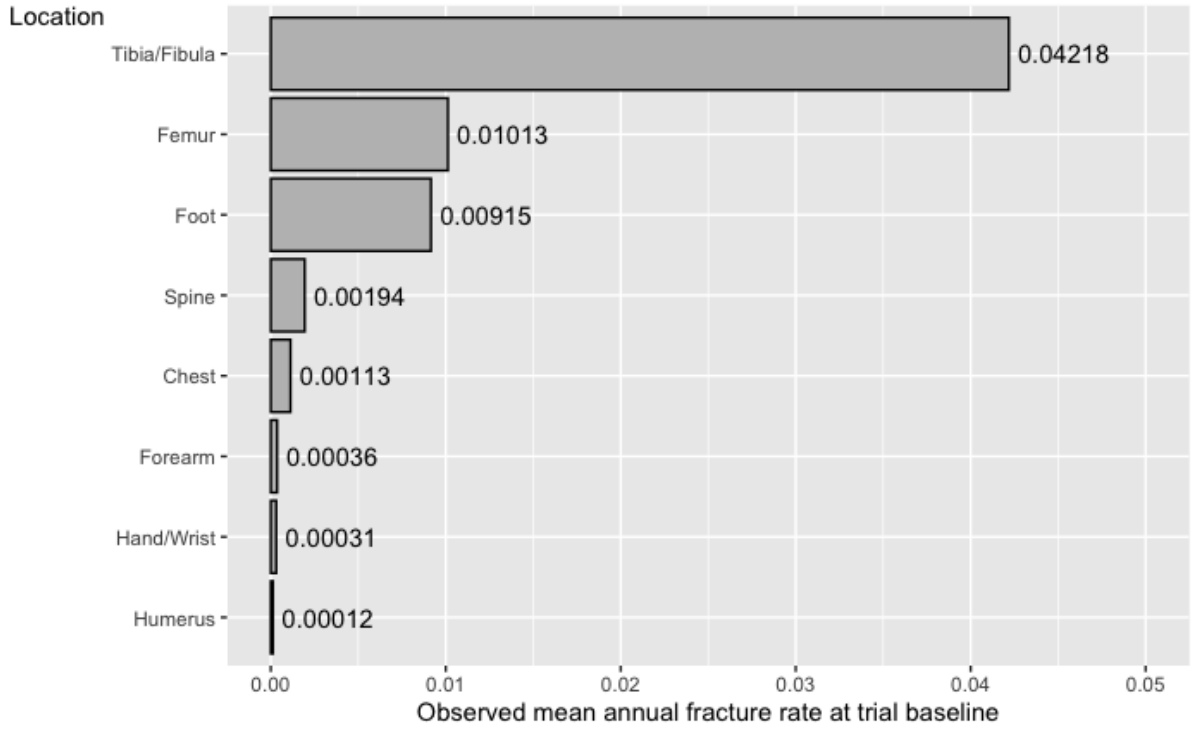


Figure 31: Mean observed annual fracture rate (number of fractures divided by age) by fracture site for adults (n=104) at CL303 baseline visit



All fractures were modelled as repeat events. A test of the null hypothesis of equidispersion in Poisson GLMs against the alternative of overdispersion and/or underdispersion indicates overdispersion for number of fracture sites, as shown in Table 32 .

Due to evidence of overdispersion, the fit of Poisson, Negative Binomial, and Zero-inflated Poisson models were compared based on AIC statistics, see Table 33. The comparisons suggests that the negative binomial model was a better fit for 'Other' fractures, Femur and Pelvis Fractures, Foot fractures, and Tibia/Fibula fractures. The Poisson model was a better fit for Upper limb fractures (humerus, hand/wrist, forearm) and the Zero-Inflated Poisson model was a better fit for vertebral/spinal fractures.

Fracture events were modelled assuming a constant rate over time using a negative binomial model, except for upper limb fractures, where a Poisson model was used. The negative binomial model was also used for vertebral spinal fractures for convenience. Given the low rates for these fractures this had little impact on estimates. Log age was included as an 'offset' controlled for age for all fracture locations. Note, the coefficient for the offset is constrained to be 1 so it is not reported in table 10. The estimated model coefficients are shown in Table 34. The estimated predicted annual rates from the fracture rate models reported here are similar to the observed annual rates shown in Figure 31 .

Table 32: Repeat fracture models dispersion statistics

Fracture location	Z*	P
Other fractures	1.332	0.0914
Femur/Pelvis fracture	2.514	0.006
Foot fracture	2.403	0.0081
Upper limb fractures	-1.004	0.8423
Vertebrae/spinal fractures	0.833	0.2024
Tibia/Fibula fracture	5.191	0

*Tests the null hypothesis of equidispersion (VAR[*y*]=*μ*) in Poisson GLMs against the alternative of overdispersion and/or underdispersion.

Table 33: AIC score by model type

Fracture location	Poisson	Negative Binomial	Zero-inflated Poisson
Other fractures	63	55	57
Femur/Pelvis fracture	249	212	215
Foot fracture	269	203	221
Upper limb fractures	**38**	40	40
Vertebrae/spinal fractures	67	67	**65**
Tibia/Fibula fracture	602	**443**	605

Best fitting model by AIC in bold.

Table 34: Negative binomial coefficients by fracture site

Fracture location	Model	Model Co-efficients		
		Intercept	SE	Predicted annual rate
Other fractures	Negative Binomial	-6.62	0.51	0.001
Femur/Pelvis fracture	Negative Binomial	-4.62	0.22	0.01
Foot fracture	Negative Binomial	-4.63	0.24	0.01
Upper limb fractures	Poisson	-7.20	0.25	0.001
Vertebrae/spinal fractures	Negative Binomial	-6.45	0.40	0.002
Tibia/Fibula fracture	Negative Binomial	-3.20	0.16	0.04

3.3.1.5.2 All other morbidities and surgery for SoC – for scenario analysis

Event rates for spinal stenosis, spinal surgery, dental problems, and tinnitus/hearing loss were informed by cross-sectional prevalence data from CL303 for the base case and CL001 as scenario analysis. As the data were cross-sectional, rather than longitudinal, it was possible for the estimated cumulative incidence of events to decrease with increasing age for particular morbidities and age comparisons due to random variation or cohort effects. However, this occurred infrequently. The observed cumulative incidence of morbidities from CL001, CL001 (BPI>4 subgroup), and CL-303 studies are shown in Figure 32.

For each non-fracture morbidity, a generalised linear model was developed which predicted the cumulative incidence of the morbidity as a function of age using a binomial distribution and a logit link. This form of modelling was used for the non-fracture events as we did not have data regarding repeated events in individuals. This model constrained the cumulative probability to vary monotonically with age. The estimated logit parameters are shown in Table 35. Within the model, age specific annual incidence rates were calculated by comparing predicted estimates of cumulative incidence at different ages.

Figure 32 Observed cumulative incidence of morbidities from CL001, CL001 (BPI>4 subgroup), and CL303 studies.

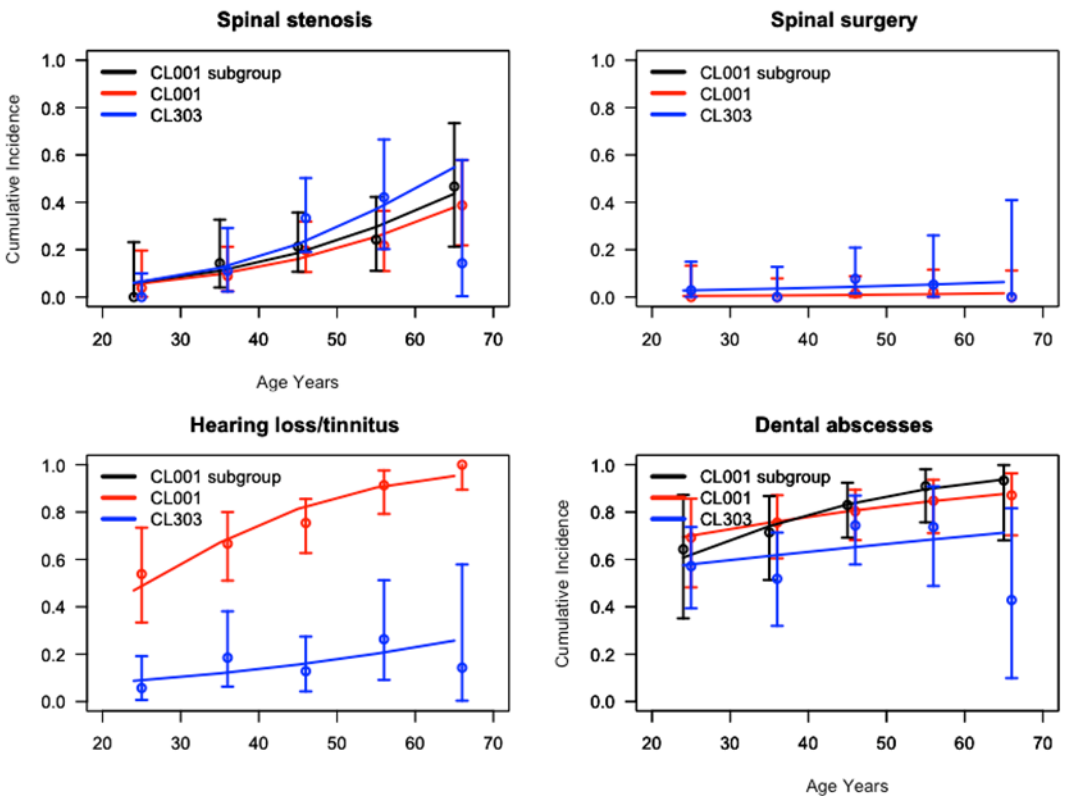


Table 35 Estimated logit model parameters for the cumulative incidence of morbidities as a function of age.

Event	Model	CL-303		CL-001		CL-001 BPI>4 subgroup	
		Est.	SE	Est.	SE	Est.	SE
Spinal Stenosis	Intercept	-4.48	0.979	-4.26	0.838	-4.216	1.051
	Age (Years) Co-efficient	0.072	0.021	0.058	0.016	0.061	0.021
Spinal Surgery	Intercept	-4.063	1.633	-6.096	3.046		

	Age (Years) Co-efficient	0.021	0.037	0.031	0.059		
Hearing Loss / Tinnitus	Intercept	-3.098	0.934	-1.95	0.655		
	Age (Years) Co-efficient	0.031	0.021	0.076	0.016		
Dental Abscesses	Intercept	-0.047	0.619	0.157	0.627	-0.891	0.874
	Age (Years) Co-efficient	0.015	0.015	0.028	0.014	0.055	0.021

3.3.1.5.3 Fracture rates for burosumab treated cohort

Sources for fracture rates in the general population (Table 36) were identified in the literature using targeted searches. When performing these searches, priority was given to studies with a large sample size, and which reported the incidence of a condition by age group. UK population sources were also preferred.

The degree to which excess fracture incidence rates are reduced is modifiable and the degree of reduction is explored in sensitivity analysis. This approach of estimating independent rates for burosumab treated and untreated patients allows the increase in risk to vary over time rather than fixing it be constant. This follows the clinical presentation of XLH as effectively an acceleration in ageing.

Table 36 General population fracture rate sources

Morbidity	General population source	Clinical justification for incidence being reduced to that of the general population	Justification for general population source
Tibia/fibula fracture	Curtis 2016[87], incidence of tibia/fibula fractures for people aged 18-49 and 50+	In CL303 and BUR02, no fractures were reported in patients receiving burosumab. There is also evidence of fracture healing due to improved bone remodelling: 43.1% of baseline active fractures in adults randomised to burosumab in CL303 were fully healed by week 24, compared to 7.7% in those randomised to	Based on UK population (using CPRD) Large study Reports fracture by location (radius/ulna, femur/hip, spine), sex and age group
Femur/pelvis fracture	Curtis 2016[87], femur/hip fracture incidence reported for 15 age brackets†		
Foot fracture	Curtis 2016[87], combined incidence of foot and ankle fractures for people aged 18-49 and 50+		
Upper limb fracture	Curtis 2016[87], radius/ulna fracture		

	incidence reported for 15 age brackets†	placebo[88]. By week 48, 63.1% of baseline fractures were fully healed in the burosumab → burosumab arm[89]	
Vertebrae/spinal fractures	Curtis 2016[87], spine fracture incidence reported for 15 age brackets†		
Other fractures	Curtis 2016[87], combined incidence of ribs, skull, pelvis and patella fractures for people aged 18-49 and 50+		
Spinal stenosis	None identified*, rate set to 0	Included in model in sensitivity analysis only. In the expert elicitation, some clinicians indicated that these morbidities may also be caused by chronic hypophosphataemia which, if corrected, would prevent incident cases of these morbidities.	Not applicable
Spinal surgery	None identified, rate set to 0		Not applicable
Dental abscesses	Adult Dental Health Survey 2009[90]		Based on UK population Large study Reports incidence by age group
Hearing loss/tinnitus	Martinez 2015[91]		Based on UK population Large study Reports incidence by age group
*Sources for spinal stenosis were identified (e.g. Framingham Heart Study, Kalichman 2013) but it was not clear that the definition of spinal stenosis matched that used in the life course analysis † Age brackets reported: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 80-84, 85-89, 90+			

For certain ages, estimated morbidity incidence rates derived from the XLH cohorts were lower than those of the general population. In these cases, incidence rates for patients in the SoC arm were set to those of those of the general population.

3.3.2 Expert validation

Seven international expert physicians (including one dental expert, and two clinical experts from the UK) were consulted in order to explore causal links between XLH pathophysiology and clinical sequelae. This clinical expert input was sought to elicit the expected impact of burosumab on the development of morbidities, given the CL303 clinical trial results and based on clinical experience; which provided a basis for how to best extrapolate the

intermediate trial results into clinically meaningful long-term outcomes in the model (See Appendix P). [92]

Expert opinion interview was further undertaken with UK-only clinical experts with experience in treating and managing adults with XLH – this comprised the engagement of three England-based clinicians in order to validate the model structure, resource utilisation and to inform model assumptions (see Appendix P and Q). A summary of the expert opinion sought is provided in Table 37. The experts broadly agreed with the model structure, resource use, and assumptions. A summary of the findings is provided in Appendix D and Appendix G.

Table 37: Summary of expert opinion sought

Aspect	Experts involved	Date conducted	Appendix
Global expert elicitation that supports morbidities in the model	Seven global experts with XLH expertise: UK: metabolic medicine specialist UK: rheumatology and metabolic bone disease specialist Canada: endocrinologist France: rheumatologist Chile: adult endocrinologist USA: orthopaedics expert Germany: orthopaedics expert France: Dental specialist	July – November 2020	Appendix P, Section 1
England expert validation model structure, resource utilisation and to inform model assumptions	Three England-based clinical experts with XLH expertise, including: Metabolic medicine Rheumatology and metabolic bone disease Orthopaedic surgeon [Additionally, a health economics expert provided input into model development]	2021, 2022 and 2023	Appendix P, Sections 2 & 3 Appendix Q

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

Within the model ‘baseline' utility values for patients are estimated as a function of age based on data from CL303. An incremental treatment effect was then applied to estimate utilities for patients on the treatment arm whilst they receive burosumab. This was estimated from data combining both CL303 and BUR02. This was estimated from data combining both CL303 and BUR02 (open-label follow-up study of patients from CL303).

Utilities produced by preference-based instruments are generally preferred within cost-utility analysis. Preference-based utilities were not collected in CL303 or any other study. CL303 assessed patient-reported outcomes relating to pain, stiffness and physical function using the WOMAC instrument (see Section 2.3.1.3). Therefore, utilities were estimated by mapping WOMAC data to EQ-5D using a published utility mapping algorithm described below. The CL001 natural history study[18] (see Section 2.3.4) collected SF-36 and WOMAC scores, and these were used for validation. Values obtained by mapping from CL303 were used in the base case because the trial population is most closely aligned with the modelled population.

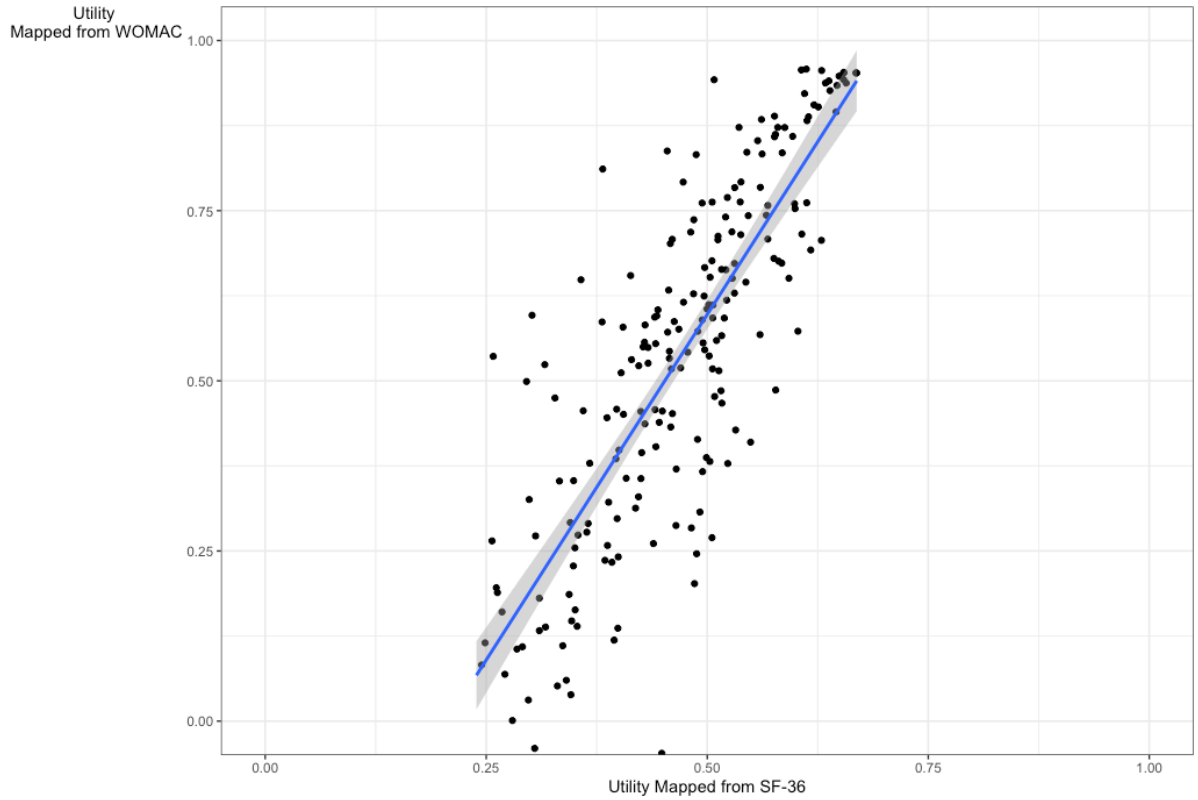
3.4.2 Mapping

A number of algorithms mapping WOMAC pain, stiffness and physical function scores to EQ-5D were identified in the literature: Xie et al. 2010;[93] Wailoo et al. 2014;[94] Barton et al. 2008;[95] and Bilbao et al. 2020.[96] The algorithm developed by Wailoo et al. was selected, as it was considered to be the most methodologically robust, being based on mixture models in order to capture the typical multi-modality in EQ-5D utility data. A study conducted by Kiadaliri et al. 2014[97] compared the mapping algorithms developed by Xie, Barton and Wailoo and concluded that “The mixture model [Wailoo 2014] outperformed the OLS models at the extremes of the EQ-5D-3L distribution and more accurately captured the characteristics of the distribution.” It was noted that all the models were associated with bias overpredicting utility for severe health states and underprediction utility for mild health states. This may lead to an under-estimation of treatment effects on utility. The mixture model was associated with the lowest bias in this respect.

To further validate the approach, we compared EQ-5D utility values mapped from WOMAC scores collected in CL001 with EQ-5D utility values mapped from SF-36 scores collected in the same study, using an algorithm published by Rowen et al. 2019.[98] This algorithm was used as all co-efficients are in the public domain. The Pearson correlation coefficient is 0.82, indicating a strong correlation between the two mapping algorithms. The mapping based on

the WOMAC showed greater variation between patients suggesting that the WOMAC based mapping is more sensitive to XLH effects (See Figure 33). All analyses were conducted in R.

Figure 33: Comparison of EQ-5D utility mapped from WOMAC vs. EQ-5D utility mapped from SF-36 (CL001)



3.4.2.1 Standard of Care (SoC) arm utilities

Linear regression models were fitted to predict baseline (pre-treatment) utility as a function of age for both CL001 and CL303 (Figure 34 and Figure 35). Regression parameters of these models are provided in Table 38.

Figure 34: EQ-5D utility mapped from WOMAC vs. EQ-5D utility as a function of age (CL001)

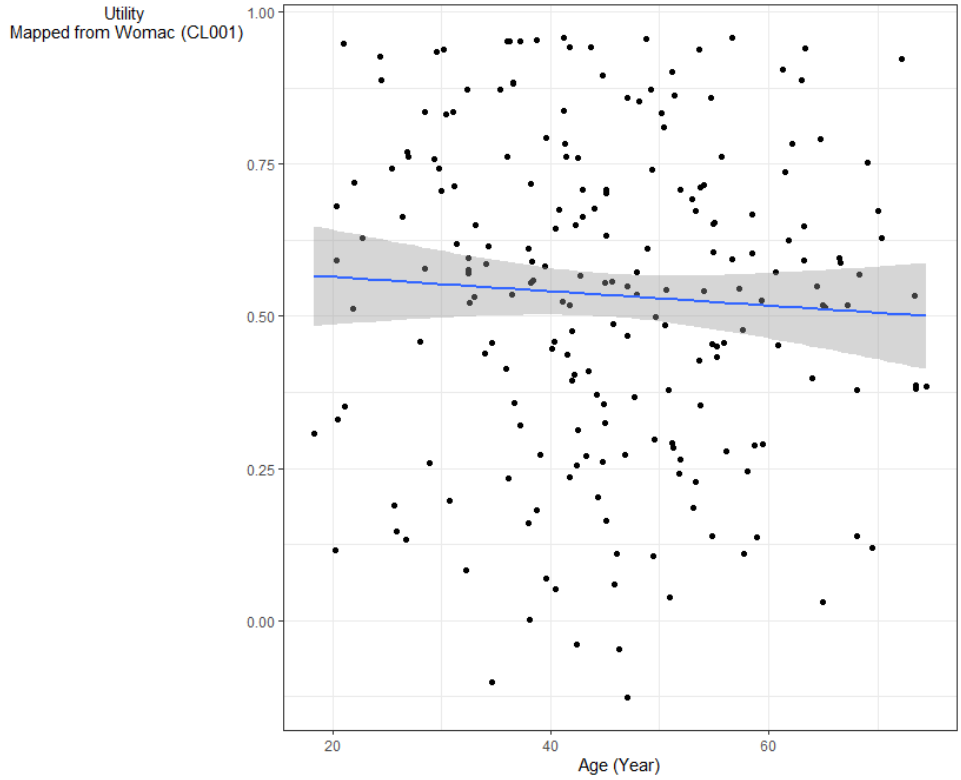
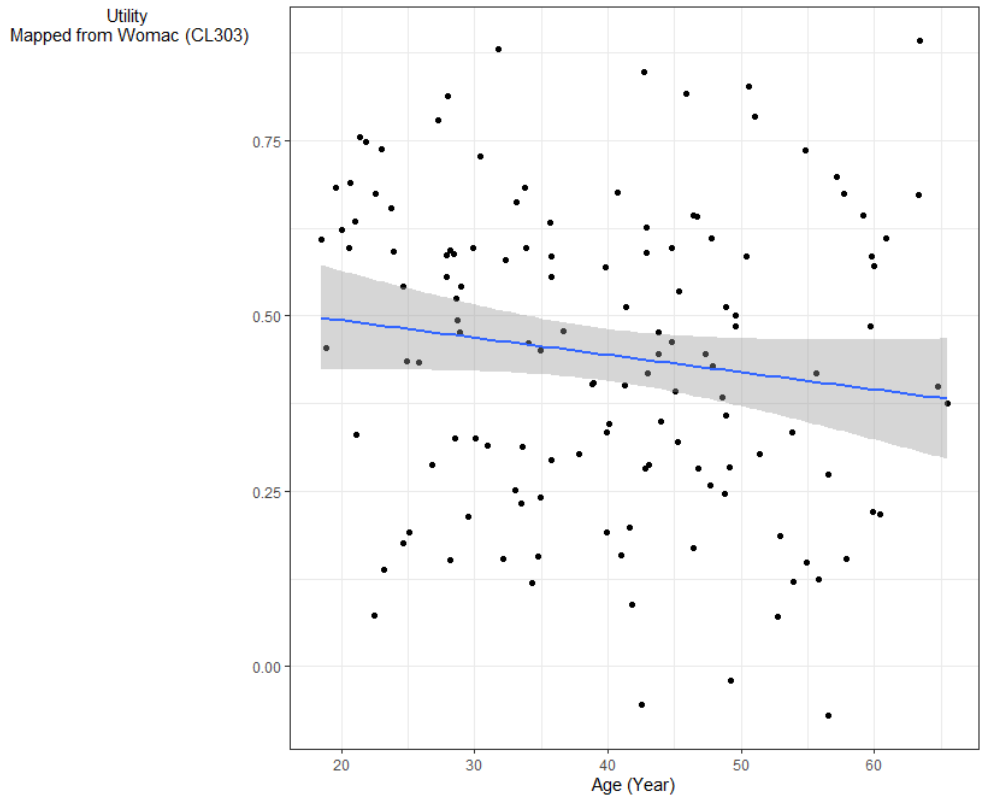


Figure 35: EQ-5D utility mapped from WOMAC vs. EQ-5D utility as a function of age (CL303CL303)



It is notable that in both studies average utilities are low and show a modest, not statistically significant (p>0.05) reduction with age. There is also considerable variation between individuals.

Table 38: SoC utility linear regression model values

Source		Coefficient	SE	95% CI
CL303, pooled burosumab and placebo arm pre-treatment baseline	Intercept	0.5428	0.0639	0.416 to 0.669
	Age	-0.0025	0.0015	-0.005 to 0.001
CL001	Intercept	0.5880	0.0657	0.458 to 0.718
	Age	-0.0012	0.0014	-0.004 to 0.002

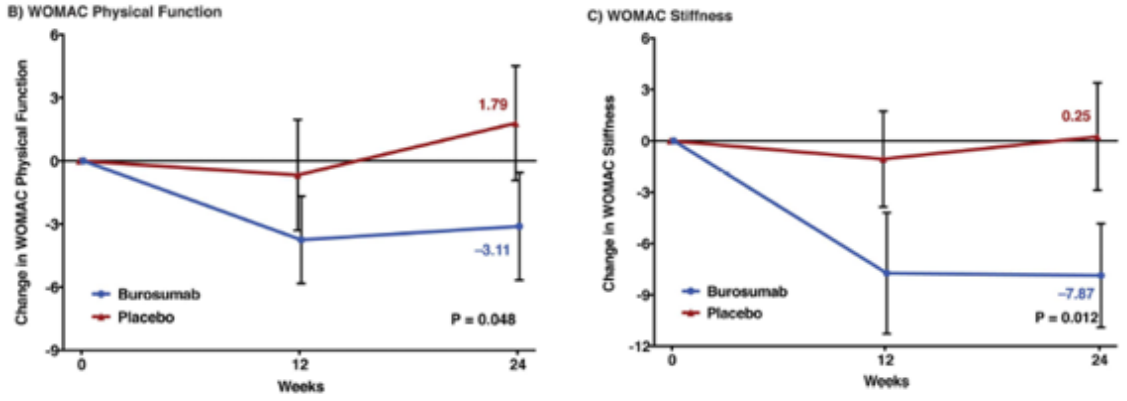
The low utilities observed for those in the SoC arm are consistent with longitudinal analysis performed in other cohorts of patients with XLH. Cole et al. (2020) [99] analysed adult XLH data from RUDY, a cohort of individuals with rare diseases in the UK, reporting an EQ-5D (5L version cross-walked to 3L) at baseline of 0.552 (SD=0.303, SE=0.044) among adults with XLH (n=47). We note that the expected trend of decreasing utility with age is not

obvious in this case the baseline utility is already low reflecting the 'premature' ageing seem in this population. Although the age co-efficient from the XLH studies is not significant we have included it in the model as, a priori, a residual age effect on utility is expected.

3.4.3 Effect of burosumab treatment on utility

Functional improvement in PROs and HRQoL is reported within the 24-week double blind randomised period of the CL303 trial for patients randomised to treatment with burosumab (see Section 2.6.2). There are statistically significant (unadjusted for multiple testing) improvements in the physical function and stiffness WOMAC subscales (Figure 36).

Figure 36: CL303 reported statistically significant improvements in physical function and a reduction in stiffness



	Burosumab at week 24 relative to placebo LS mean (± standard error difference)
Improvement in physical function as measured by WOMAC (scale: 0-100)	-4.9 (±2.48)
Reduction in stiffness as measured by WOMAC (scale: 0-100)	-8.1 (±3.24)

After week 48 of CL303, participants continued burosumab for a further 48 weeks (open-label treatment extension period I); week 96 was the final study visit at European centres. Participants in the USA continued for up to 53 weeks further. Further open-label follow-up data beyond 96 weeks for European patients were available from the phase 3b open-label extension study, BUR02. Resulting patient numbers at each time point are shown in Table 39.

WOMAC scores for both arms of the trial were mapped to EQ-5D values using the Wailoo 2014[100] mapping algorithm; resulting EQ-5D scores over time are shown in Figure 37. These outcomes show how improvements in WOMAC scores translate into improvements in

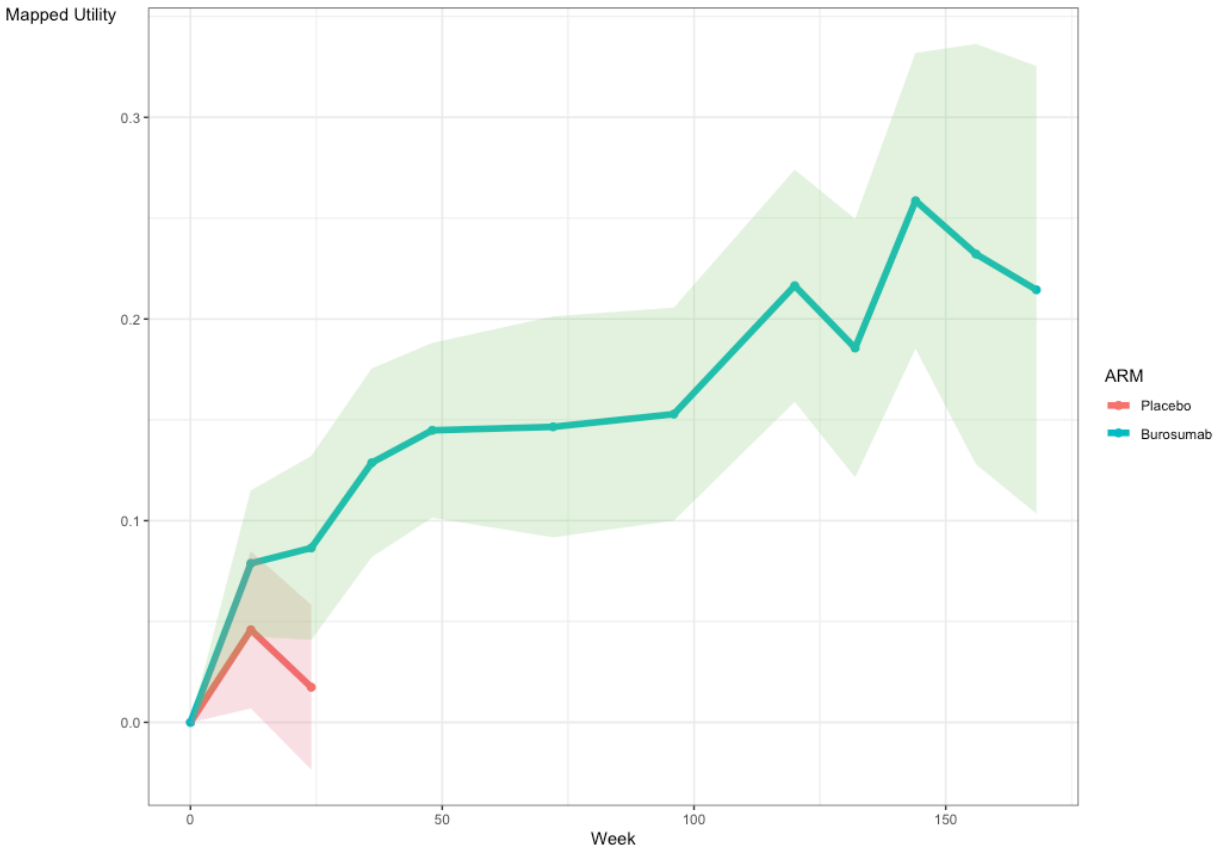
HRQoL. These reflect improvements in the patients physical functioning, pain and stiffness due to healing of pseudofractures and improvements in muscle strength. Note it cannot directly reflect improvements in mental health as this is not captured in the WOMAC. These will only be captured insofar as they are mediated by the WOMAC dimensions and were present in the datasets used for mapping. Resulting mapped changes in utility from baseline for the CL303 subjects are shown in Figure 37.

To provide additional data, WOMAC outcomes from CL303 were combined with WOMAC outcomes from the phase 3b open-label extension study, BUR02. Resulting patient numbers at each time point are shown in Table 39. Resulting mapped changes in EQ-5D from baseline for the combined CL303 trials are shown in Figure 37.

Table 39: Number of adults randomised with WOMAC data at each follow-up time

Timepoint	Source of patient population	N Burosumab	N Placebo
CL303 Baseline	CL303	66	65
Week 12		66	65
Week 24		66	65
Week 36		64	0
Week 48		66	0
Week 72		60	0
Week 96		59	0
Week 120	US patients from CL303 only	46	0
Week 132†	BUR02	11	0
Week 144†	BUR02 and US patients from CL303	24	0
Week 156†	BUR02	10	0
Week 168†	BUR02	10	0

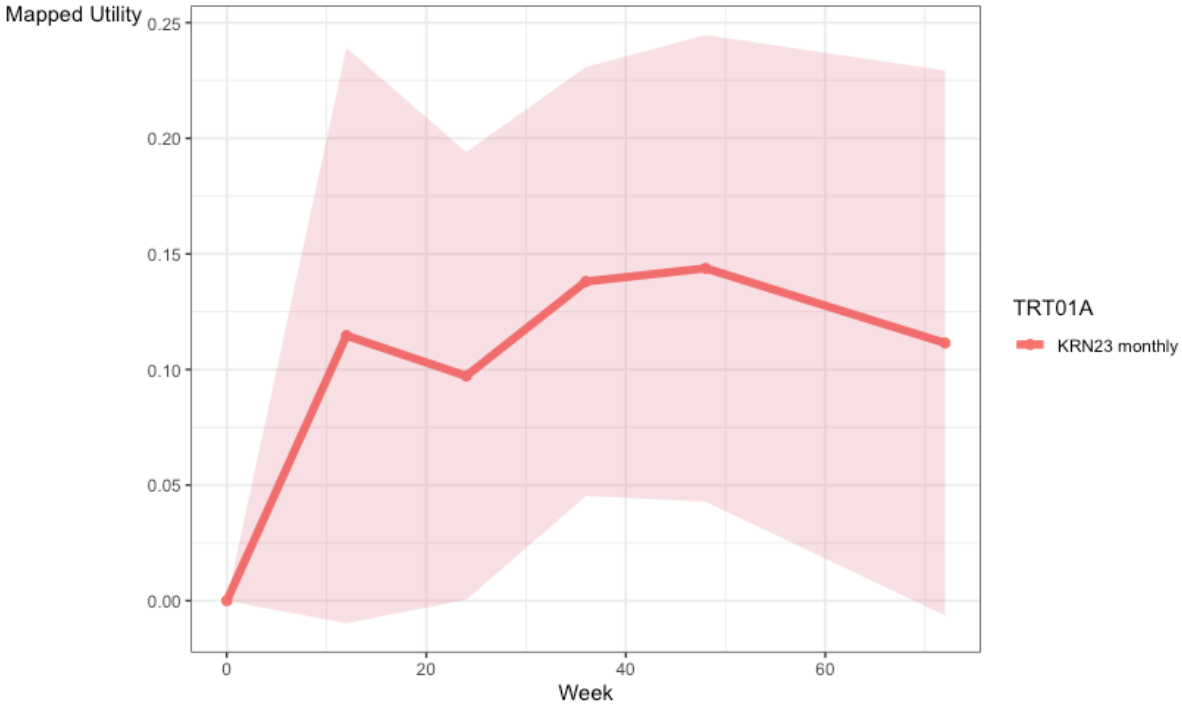
Figure 37: Change from baseline Utility mapped from WOMAC in CL303 Subjects (data from CL303 and CL303 patients enrolled in BUR02 open-label follow-up)



Weeks	0	12	24	36	48	72	96	120	132	144	156	168
Tx Obs	66	66	66	64	66	60	59	46	11	24	10	10
Placebo Obs	65	65	65	0	0	0	0	0	0	0	0	0

Similar responses were seen in the CL203 trial, a long-term, phase 2b open-label extension study of adults with XLH who had previously participated in Phase 1/2 repeat-dose study KRN23-001 or the long-term Phase 1/2 extension study KRN23-002, but who did not receive burosumab treatment for at least 1 year between the last dose in the previous studies and the first dose in this study.[101] Mean baseline utility for these patients was 0.55 (standard deviation: 0.22). Figure 38 shows that utility increases again once treatment with burosumab resumes, demonstrating the requirement for burosumab treatment to be taken on an ongoing bases for the long-term utility benefit to be maintained. Twenty participants are included in this data at baseline, with little drop out N=19 at week 48, N= 18 at week 72).

Figure 38: Mapped change from baseline in utilities mapped from WOMAC for patients in CL203



Weeks	0	12	24	36	48	72
Obs	20	20	20	20	19	18

We observed an initial marked response to treatment over the course of the first year. The estimates become increasingly uncertain in the later periods due to censoring.

3.4.4 Health-related quality-of-life studies

In appendix H describe how systematic searches for relevant health-related quality-of-life data were done.

There were three studies which reported the humanistic burden of XLH in adults using the EQ-5D-5L (Table 40). Luis Yanes 2019/2022 and Monzo 2019 were conducted in Spain and reported EQ-5D-5L index values of 0.562 (0.15) and 0.6375 (0.2286) respectively. All were observational studies. Compared to the general Spanish population (0.914 [0.15]), XLH patients reported more moderate and severe problems across all domains. Luis Yanes 2019

also reported a caregiver utility of 0.821 (0.15).[102] Since both studies are based on Spanish population the utility data was not considered generalisable for the UK population.

Forestier-Zhang 2016 reported an EQ-5D-5L index value of 0.648 (0.29) for patients in the UK.[104] Jandhyala 2022 reported that EQ-5D-5L reduced by -2.7 in a XLH population followed for 12 months in the UK.[105] A study by Cole et al (2023),[106] published after the SLR search date but included in the table below, reported EQ-5D-5L values for 48 adults with XLH in the UK as part of the RUDY prospective cohort study. The overall value reported was 0.651.

Table 40: Results from SLR search for utility values in adults with XLH

Study	Instrument/ valuation method	Population	N	Index score (SD)
Base case utilities used in the model (baseline)		XLH	131 (at baseline)	0.54
Jandhyala 2022[105] *UK*	SEIQoL-DW (Schedule for the Evaluation of Individual Quality of Life -Direct Weighting)	XLH	10	-2.7 after 12 months
Luis Yanes 2019[102] *Spain*	EQ-5D-3L, EQ-5D-5L	XLH	29	0.562 (0.15)
		General Spanish population	20587	0.914 (0.15)
		Caregiver	Not reported	0.821 (0.157)
Monzo 2019[103] *Spain*	EQ-5D-5L	XLH	19	0.6375 (0.2286)
Forestier-Zhang 2016[104] *UK*	EQ-5D-5L	XLH	24	0.648 (0.29)
Cole 2023[106] UK (published after search cut-off date)	EQ-5D-5L	XLH	48	0.651 (0.270)

3.4.5 Adverse reactions

Disutilities for adverse reactions were not modelled, because the overall incidence, nature, and severity of adverse events were comparable in the burosumab and placebo treatment groups in the pivotal trial (CL303) (see Section B.2.10). Most AEs were mild or moderate in severity.[7] Additionally, utilities were modelled as a function of treatment (baseline utility for

SoC and additional impact of burosumab treatment), therefore impact of any AEs would already be captured in the estimated utilities.

3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

To quantify the HRQoL benefit of burosumab in the CEM, asymptotic models were fitted to mapped EQ-5D change from baseline outcomes from CL303 and BUR02 for burosumab and the CL303 trial 24-week randomised data for placebo. Linear and polynomial models were also explored, but these predicted clinically implausible results when extrapolated beyond the observed period, for example a continuing increase in utilities or a progressive decrease in utility beyond the observed period (note these values are for patients continuing to receive treatment). See Appendix T for comparison of the alternative functional forms. An alternative approach would have been to assume a constant utility benefit after a give timepoint. However, the use of an asymptotic model also avoids selection of an arbitrary time point for such an extrapolation, this is a particular advantage where there is increasing uncertainty in estimates at later timepoints. The asymptotic model fit is shown in Figure 39.

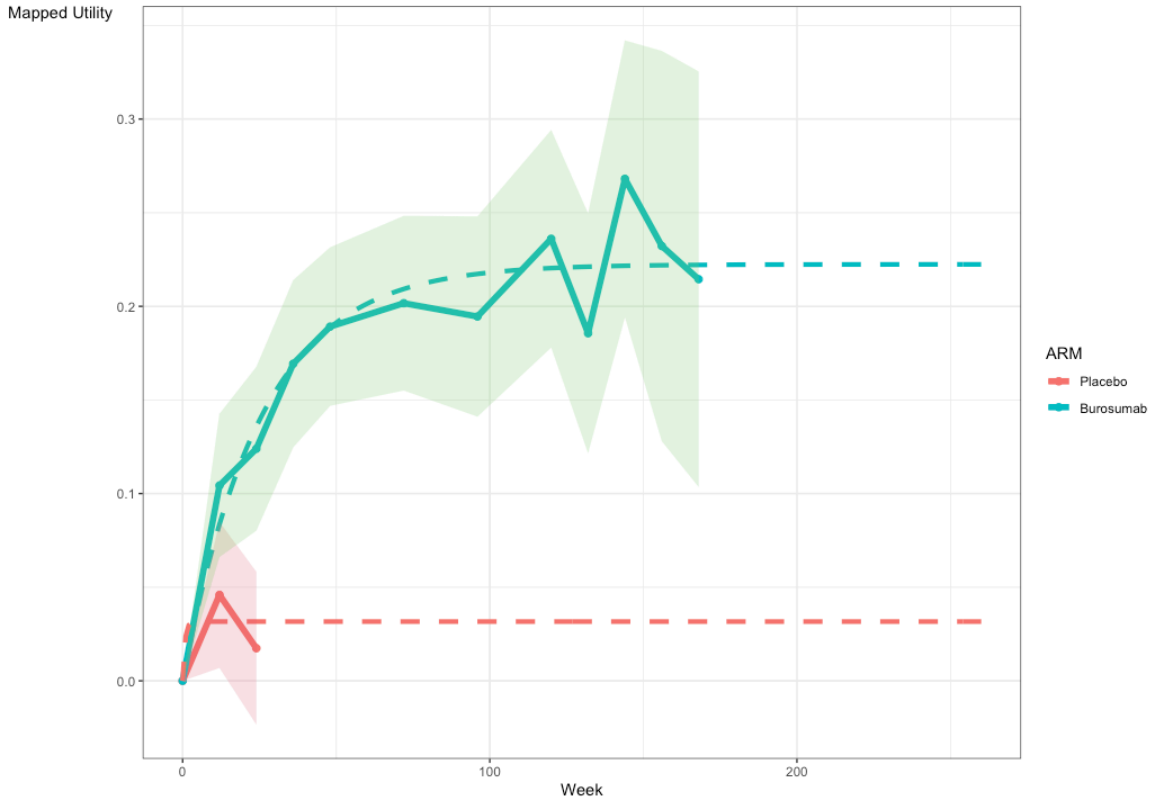
This was performed in R, using the package 'drc' and the function drm(), which fits a non-linear model to predict utility as a function of time. The selected functional form was AR.2 (Asymptotic regression with initial value 0):

$$f(t) = d.(1 - \exp\left(\frac{-t}{e}\right))$$

The parameter d represents the upper limit and e determines the steepness of the increase as a function of t. The initial value of 0 was used as these were change from baseline values that, by definition, start from 0. The standard errors were estimated using bootstrapping stratified by patient to account for correlation between repeated measurements within individuals.

This model was fitted to each arm independently to allow both the trajectories and the equilibrium levels to vary between treatment arms.

Figure 39: Asymptotic models fit to CL303CL303 and BUR02 WOMAC mapped utility change from baseline patients on treatment)



Weeks	0	12	24	36	48	72	96	120	132	144	156	168
Tx Obs	55	55	55	54	55	50	49	42	11	23	10	10
Placebo Obs	65	65	65	0	0	0	0	0	0	0	0	0

The utility benefit of treatment with burosumab in the CEM was estimated both as the estimated change from baseline values for the burosumab arm (non-placebo adjusted results) and as the estimated change from baseline values for the burosumab arm minus corresponding values for the placebo arm (placebo adjusted results). Kamenicky et al (2023)[60] studied the impact of breaks in burosumab treatment on clinical laboratory tests of efficacy, patient-reported outcomes (PROs) and ambulatory function in adults with X-linked hypophosphatemia who continued from CL303 into BUR02 (a 48-week open-label extension). The study reports that QoL measures returned to baseline during the 6 - 16 month treatment gap. There was no evidence of a persistent regression to the mean effect in this study. Following this the model used the non-placebo adjusted values (Table 41) as the base case.

After three years, incremental utility is assumed to remain constant, since asymptotic models show little change after this time point.

Table 41: Non placebo-adjusted predicted mean utilities mapped from WOMAC whilst receiving treatment with burosumab

	Burosumab (all patients continue) Mean (SE)	**Burosumab (stopping rule applied)** Mean (SE)
Year 1 on treatment	0.147 (0.011)	0.147 (0.011)
Year 2 on treatment	0.193 (0.011)	0.211 (0.015)
Year 3+ on treatment	0.207 (0.018)	0.215 (0.018)

Table 42: Placebo-adjusted predicted mean utilities mapped from WOMAC whilst receiving treatment with burosumab

	Burosumab (all patients continue) Mean (SE)	**Burosumab (stopping rule applied) Mean (SE)**
Year 1 on treatment	0.115 (0.016)	
Year 2 on treatment	0.161 (0.016)	
Year 3+ on treatment	0.176 (0.022)	

Additionally, asymptotic models were fitted to mapped EQ-5D scores for the burosumab arm, applying the stopping rule that only patients who achieve an improvement in WOMAC at 48 weeks continue treatment and had serum phosphate above the lower level of normal at 24 weeks were included. A total of 54 out of 65 patients in the burosumab arm experienced an improvement in WOMAC at week 48. This model was used to calculate the utility effects for burosumab at year 2 and 3; the utility benefit under the assumption that all patients continue was used for year 1. Resulting values are shown in Table 42.

Tapering of the impact of burosumab at the start of treatment was captured through differing estimates for the first two years of treatment. When treatment with burosumab is discontinued, patients are assumed to revert to the SoC utility. This impact may also be tapered over 2 years. In the base case, in the first year post-discontinuation 50% of the utility benefit from burosumab is received, while from the second year post-discontinuation onwards all discontinued patients return to the SoC baseline utilities, in line with findings in the Kamenicky et al (2023)[60,107] study on how patient-reported outcomes (PROs) and ambulatory function in adults with X-linked hypophosphatemia changed in the time period where treatment stopped between CL303 and BUR02.

3.4.6.1 Morbidity disutilities

The previously calculated utilities for the SoC arm already include the impact of morbidities on HRQoL. Therefore, to avoid double counting, only the net improvement in utility associated with the reduction of morbidities is applied to the burosumab arm. This requires an estimate of how each morbidity impacts HRQoL in order to calculate the improvement proportionate to the reduction in morbidities predicted for the treatment arm.

Each individual morbidity was assumed to proportionally reduce the age- and treatment-specific utilities calculated above (i.e. each morbidity is independently associated with a utility multiplier). The disutility of living a year with the given morbidity was then calculated as the difference between the age- and treatment-specific utility with and without the multiplier. Any treatment effect on morbidities is assumed not to be captured in reported WOMAC scores because they did not occur over the 96-week time horizon of the CL303 trial.

The impacts of morbidities on utilities were categorised as either acute or chronic. Acute disutilities are applied in the year in which the event happens, while chronic disutilities are applied over the remainder of the patient's lifetime if there was clinical evidence suggesting such long-term impact. Some multipliers were sourced directly from the literature, while others were calculated. For calculated values, the observed utility value reported in the literature was divided by an estimate representing the UK general population (0.855). For these values an assumption had to be made that relative values for the general population are consistent with an XLH population. This is likely a conservative assumption, as managing certain aspects of XLH patient care, such as fractures, is known to be more difficult in XLH patients.

Fractures were assumed to have both an acute and chronic impact on HRQoL, as the bone would not be the same post-fracture as it was pre-fracture; this was validated by clinical opinion.

NICE TA204[108] (Denosumab for the prevention of osteoporotic fractures in postmenopausal women) identified through a targeted literature review for fracture rates in the UK general population provided several sources of literature used in the model. Lower limb/hip fracture multipliers were taken from a beta analysis by Peasgood et al. (2009),[109] which was used in NICE TA204 for osteoporotic hip fracture. The population for the technology appraisal (TA) was postmenopausal women with osteoporosis, and as such it was assumed that the HRQoL loss post-fracture would continue over a patient's entire lifetime.[108] The TA204 evidence review group noted that, while suitable utility multipliers were used, many of them were derived from observational time-series studies without independent control groups, and

therefore did not control for all potential confounding factors.[108] The NICE committee accepted the multipliers in their final decision.[108]

The acute multiplier for vertebrae/spinal fractures were sourced from Oleksik et al. (2000), which was also used in TA204. The estimate was based on prevalent morphometric fracture populations, rather than clinical fracture populations, meaning that the multiplier may be underestimated.[110] The estimate in Cockerill et al. (2004), as used in TA204, is also based on prevalent morphometric fracture populations, meaning that it may be similarly underestimated.[111]

Borgström et al. (2006) and Ström et al. (2008) reported values for wrist fractures, which was used for upper limb fractures and other fractures in the model.[112,113] It was assumed that quality of life values would return to baseline after the first year post-fracture.

Table 43: Multipliers applied to reference utility (Fracture)

Morbidity	Mean	SE	SE calculation	Application: Chronic or acute	Source
All lower limb/hip fractures first year*	0.70	0.01	Using CI	Acute**	Peasgood et al. (2009) [109]
All lower limb/hip fractures subsequent years*	0.80	0.01	Using CI	Chronic	Peasgood et al. (2009) [109]
Vertebrae/spinal fractures first year	0.91	0.01	Using CI	Acute	Cockerill et al. (2004) [111]
Vertebrae/spinal fractures subsequent years	0.99	0.01	Using CI	Chronic	Cockerill et al. (2004) [111]
Upper limb fractures first year	0.93	0.01	Using CI	Acute	Borgström et al. (2006); Strom et al. (2008) [112,113]
Upper limb fractures subsequent years	1.00	0.01	Using CI	Chronic	Borgström et al. (2006); Strom et al. (2008) [112,113]
Other fractures first year	0.93	0.01	Using CI	Acute	Borgström et al. (2006); Strom et al. (2008) [112,113]
Other fractures subsequent years	1.00	0.01	Using CI	Chronic	Borgström et al. (2006); Strom et al. (2008) [112,113]

*Tibia/fibula, femur/pelvis and foot; ** all 'acute' impacts are assumed to be applied for 1 cycle (1 year)

Multipliers used for morbidities included in scenario analysis (spinal stenosis/surgery, dental abscess and hearing loss/tinnitus) are outlined in Appendix U.

3.4.7 Impact of burosumab treatment on caregivers and family members

The disutility associated with a patient's health state can be understood as "spilling over" to impact the quality of life of caregivers and other household members. There are two interconnected but distinct elements to this: the caregiver effect (associated with informal care of the patient) and the family effect (associated with non-caregiving effects that lead to a reduction in the quality of life of family members).[114]

Patient advocates have described the impact of XLH on the family unit as "catastrophic" (see Appendix M). The burden was confirmed by a study which interviewed families of adults with XLH in the UK about their experiences, described in Section B.1.3.5.6 and Appendix S. It is therefore relevant to include the impact of effective treatment of an adult with XLH on the HRQoL of other family members within the economic evaluation.

A targeted literature review exploring the burden and spillover effects in carers and family members of adults with musculoskeletal conditions found conflicting results.[50] Quantitative research studies indicated minimal spillover effects on caregiving and non-caregiving family members. At the same time qualitative studies revealed significant impacts, with caregivers reporting notable impacts to their physical health, work and finances, daily activities as well as emotional and social well-being. The study conducted by Kyowa Kirin on the impact on caregivers and family members (see Section 1.3.5.6 above and Appendix S for details) found that the mean difference in observed versus expected EQ-5D utilities for family members of XLH patients was -0.184 (95% CI: -0.339 – -0.029), when compared with age-linked UK general population utility data. To remain conservative, the utility improvement on family members and caregivers is calculated as 20% of the utility benefit of burosumab treatment experienced by the patient. This assumption ensured that the magnitude of benefit for family members and caregivers assumed to be achievable as a consequence of burosumab treatment (0.043 improvement in the long term, as reported in **Table 44**) remained well below the overall impact of caring for an adult with XLH. Nonetheless, excluding the impact on caregivers and family members was tested in a scenario analysis. A recent study in the UK by Canaway et al. investigated how many people are close to patients near their end of life in order to determine who should be included when estimating spillover effects.[115] The study found that close-person networks at end of life contained eight individuals, three of whom were rated as being the closest. No similar study was identified for musculoskeletal conditions, therefore, again to be conservative, the spillover was applied

to only two family members. As the impact on the patient is assumed to be gradually increasing, the impact on family members was assumed to follow the same pattern. This assumption was validated by XLH patient and clinical experts.

Table 44: Utility improvements for family members if patient receives burosumab

Year	Mean per family member	Mean in model (2 family members)
Year 1 on treatment	0.029	0.059
Year 2 on treatment	0.042	0.084
Year ≥3 on treatment	0.043	0.086

3.4.8 Summary of utility values used

Table 45: Summary of utility values for cost-effectiveness analysis

	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Coefficients for development of age dependent utilities*				
Intercept (base case)	0.5428		Section 3.4.2.1	CL303, pooled burosumab and placebo at trial baseline
Age (base case)	-0.0025		Section 3.4.2.1	CL303, pooled burosumab and placebo at trial baseline
Intercept (scenario)	0.5880		Section 3.4.2.1	CL001 natural history study (considered most representative of the population in clinical practice)
Age (scenario)	-0.0012		Section 3.4.2.1	CL001 natural history study
On treatment utility (Mean change in utility)				
Year 1	0.1468 (0.011)		Section 3.4.6	CL303
Year 2	0.2112 (0.015)		Section 3.4.6	CL303
Year ≥3	0.2150 (0.018)		Section 3.4.6	CL303
Utility multipliers for morbidity related disutilities (only applied to burosumab arm)				
All lower limb/hip fractures first year**	0.700 (0.010)	0.57-0.53	Section 3.4.5.1	Morbidity-related disutilities were taken from the literature as they were not available from the clinical trials; reasons for selection are described in the relevant sections
All lower limb/hip fractures subsequent years**	0.800 (0.013)	0.89-0.84	Section 3.4.5.1	

Vertebrae/spinal fractures first year	0.910 (0.013)	0.7-0.65	Section 3.4.5.1	
Vertebrae/spinal fractures subsequent years	0.990 (0.005)	0.87-0.85	Section 3.4.5.1	
Upper limb fractures first year	0.934 (0.011)	0.956-0.911	Section 3.4.5.1	
Upper limb fractures subsequent years	1.000 (0.008)	1.00-0.97	Section 3.4.5.1	
Other fractures first year	0.934 (0.011)	0.956-0.911	Section 3.4.5.1	
Other fractures subsequent years	1.000 (0.008)	1.00-0.97	Section 3.4.5.1	
Utility spillover benefit for 2 family members				
Year 1	0.059		Section 3.4.5.2	20% of the benefit experienced by the patient. Plausibility validated with patients and clinical experts.
Year 2	0.084		Section 3.4.5.2	
Year ≥3	0.086		Section 3.4.5.2	

*From regression analysis, *Tibia/fibula, femur/pelvis and foot

3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic literature review was undertaken to identify published costs and healthcare resource use for XLH; no relevant studies were identified (Appendix I).

Details of costs used in the model are provided below.

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Burosumab arm

The model includes drug acquisition and administration costs, treatment monitoring costs, and various costs associated with morbidities. A systematic literature review was conducted to find any existing economic studies conducted in the treatment of adults with XLH, and no existing economic studies were found.

Most costs for non-drug resources were sourced from the National Schedule of Reference Costs 2020-2021[85] and the Personal Social Services Research Unit (PSSRU) 2021 report.[86] Costs were inflated to 2020/2021 using the Health Services Index obtained from the PSSRU report, if necessary.[86]

3.5.1.2 Burosumab drug costs

The recommended dose for burosumab in adults is 1 mg/kg of body weight, rounded to the nearest 10 mg, with a maximum dose of 90 mg[116]. Burosumab is administered subcutaneously every 28 days, and since the rounding to the nearest 10 mg dose is specified in the summary of product characteristics and the smallest available vial is 10 mg, there is no vial wastage. Pricing is linear, and as such all vials cost the same per mg.

The mean patient weight, which is used to calculate costs, is derived using weights recorded in the clinical trial CL303. Weights were split into 10 kg bands and the distribution of patients in each band was used for the mean weight calculation. The model base case uses EU patients from the analysis (N=47), as there were substantial weight differences between patients in different regions. The distribution in each age range is presented in Table 46.

Table 46: Burosumab dosing and proportion of population by weight band

Weight band (kg)	Dose (mg)	Proportion (EU population from CL303)
25-34	30	0%
35-44	40	6%
45-54	50	15%
55-64	60	23%
65-74	70	28%
75-84	80	11%
85-94	90	13%
95-104	90	2%
105-115	90	2%

Dose reductions are recommended in the SmPC if serum phosphate is above the upper limit of normal range, and a total of 9 (13.2%) cases of dose reduction due to an increase in serum phosphate concentration above the target range were observed in the pivotal CL303 clinical trial. Of these, five (3.5%) were in the burosumab arm in the placebo-controlled treatment period and four (6%) were in the placebo-burosumab group of the open-label treatment extension period. One of these participants subsequently received burosumab at the original dose of 1 mg/kg, while all others continued at the reduced dose, therefore the model applies a dose reduction for 5.97% (8 out of 134) of patients. Dose in the trial was and in clinical practice is expected to be reduced by 50% to 0.5 mg/kg in the case of hyperphosphataemia, which is applied as a permanent reduction in dose.[1]Based on the proportions of patients falling into each weight category requiring doses from 30mg up to

90mg, as well as the dose reductions, the average calculated dose per cycle is 65.23 mg. Considering a 28-day cycle and 365.25 days in a year this meant an average dose of 851 mg per year, which represents 42.54 20 mg vials. The model predictions are aligned with data reported from the EAP. [redacted].

[redacted] We would welcome that the NICE Committee has this information for their decision making.

Table 47: Price of burosumab

Size per unit	Pack size	List price per pack	Discount	Price per pack	Price per mg
20mg	1 vial	£5,984.00	[redacted]	[redacted]	[redacted]

The list price of a 20mg/1ml solution of burosumab is £5,984.00. The effective cost for a 20 mg/1 ml solution injection vial of burosumab when the HST8 PAS price is applied is [redacted]. Thus, the average burosumab drug acquisition cost per patient per year in the model is estimated as [redacted]

3.5.1.3 Administration costs

Based on initial discussions with sites participating in the EAP, it is anticipated that the majority of patients receiving burosumab will be suitable to move across to self-administration. This will involve a nurse-led training, but the training is a KK funded service. The model assumes 95% of patients self-administer, which is a conservative estimate

compared to rates reported from the EAP. For the patients that do not move to self-administration the model assumes that burosumab is administered by a hospital nurse and requires 20 minutes. Given the 28-day administration cycles, patients receive burosumab 13 times a year.

Table 48: Drug administration costs with burosumab

Resource	Cost per year	Source
13x 20 min hospital nurse administration per year	£199.33	PSSRU 2021[86] cost (2/6 of hourly (20 mins) nurse cost x 13 times a year as 4-weekly injections)

As discussed above, no XLH-specific treatment is used in the SoC arm, only monitoring and symptomatic management of morbidities.

3.5.1.4 Treatment management

Treatment management costs were calculated based on draft clinical practice recommendations for the UK,[6] and validated with clinical experts who have experience of diagnosing and managing XLH in the UK (see Appendix Q). Healthcare resource use (HRU) total costs vary by whether the patient is on treatment with burosumab (stratified by first year on treatment vs. subsequent years on treatment) or on SoC. As discussed above, cost of pain management is not included in the model as the trial protocol required maintenance of analgesic regimen. Therefore, the model conservatively assumes pain management costs are the same across treatment arms.

Table 49: Treatment management resource utilisation

Resource	Annual usage: burosumab	Annual usage: SoC
Base case HRU		
Multidisciplinary team or clinic with accompanying biochemistry	1.00	1.00
Lab measurement of serum phosphate (first year)	6.00	2.00
Lab measurement of serum phosphate (subsequent years)	2.00	2.00
Kidney ultrasonography	0.50	0.50
Practice nurse (10 minutes to take blood sample for serum phosphate measurement) in the first year	6.00	2.00
Practice nurse (10 minutes to take blood sample for serum phosphate measurement) in subsequent years	2.00	2.00

Source: Clinical opinion[1,6]

Table 50: Treatment management unit costs

Resource	Cost	Source
Multidisciplinary team or clinic with accompanying biochemistry	£230.27	NHS reference costs 2020/21, Multi-professional Non-Admitted Face-to-Face Attendance, Follow-up (Rheumatology). WF02A, CL.
Lab measurement of serum phosphate	£3.63	NHS reference costs 2020/21, DAPS05 Haematology
Kidney ultrasonography	£69.63	NHS reference costs: Weighted direct and outpatient: Ultrasound Scan with duration of less than 20 minutes, without Contrast, RD40Z
Hospital nurse	£46.00	PSSRU 2021: Hospital-based nurses cost. Cost per working hour. Average cost of Band 5 and Band 6 nurse.
Practice nurse	£42.00	PSSRU 2021: Nurse (GP practice)

Source: NHS Reference costs 2020/21[85]; PSSRU 2021[86]

Based on the costs and resources above, the calculated base case treatment management costs for burosumab were £333.85 for the first year and £286.35 in subsequent years, while for the SoC arm the cost was estimated to be £286.35 per annum.

3.5.1.5 Fracture costs

NICE TA204 (Denosumab for Fracture Prevention in Postmenopausal Osteoporosis)[108] was used as the basis for the proportion of patients who have their fractures treated in different care settings and which required surgery. That submission was informed by Bouee et al. (2006), which reported the results of two prospective, randomised, double-blind clinical trials of postmenopausal women, SOTI and TROPOS.[117] A total of 533 patients across Belgium, Spain, Italy, the UK, and France were examined in the study,[117] and the results were validated by clinical experts with experience treating XLH patients (see Appendix P). These experts reported whether they would expect the values to be higher or lower than those sourced from Bouee et al. (2006).

Table 51: Fracture site management proportions

Fracture site	% managed by a GP	% treated as hospital day case	% hospital admission no procedure	% with admission surgical procedure
Tibia/fibula fractures†	0%	44%	42%	14%
Femur/pelvis fractures‡*	0%	44%	42%	14%
Foot fracture†	0%	44%	42%	14%
Vertebrae/spinal fractures‡	80%	6%	14%	0%
Upper limb fractures‡	0%	44%	44%	12%
Other fractures	0%	48%	40%	12%

Source: Bouee et al. (2006)[117]

†Validated by Consultant orthopaedic and trauma surgeon; ‡validated by Consultant rheumatologist; * Orthopaedic surgeon did not want to provide values, but said the proportion receiving surgery should be higher than the tibia/fibula proportions. Therefore, as a conservative approach, the proportions suggested by the rheumatologist for general 'lower limb fractures' were used.

The proportion of patients requiring longer and shorter stays was also taken from Bouee et al. (2006).[117] It was divided into two categories, non-elective short stay (NES), which represented a 1-day length of stay, and non-elective long stay (NEL), which represented a 2+ day length of stay. These results were also validated by clinical experts, who noted whether proportions should be higher or lower (see Appendix Q).

Table 52: Proportion of fractures treated NES/NEL, by site

Fracture site	Proportion NES	Proportion NEL
Hospital admission, no procedure (all fractures) †φ	36%	64%
Hospital admission, procedure for lower tibia/fibula fractures*†	16%	84%
Hospital admission, procedure for femur/pelvis fractures**†	2%	98%
Hospital admission, procedure for foot fractures†	25%	75%
Hospital admission, when procedure is required for upper limb fractures‡	60%	40%
Hospital admission, when procedure is required for other fractures‡	52%	48%

Source: Bouee et al. (2006) [117]

†Validated by Consultant orthopaedic and trauma surgeon; ‡validated by Consultant rheumatologist; φ Orthopaedic surgeon indicated that the proportion in long stay for all fractures should be higher, but would not provide a value; *Assumed same as 'knee fracture' in the NHS reference costs; **Assumed same as 'hip fracture' in NHS reference costs

It was assumed that, for patients managed by a general practitioner (GP), an hour would be required to treat a fracture. The associated PSSRU unit cost used was 'General practitioner – unit costs per hour of patient contact, with qualification costs', which was £255.[86] All other fracture costs were sourced from 2020-2021 NHS reference costs.[85] In order to best identify which costs should be used, the consultant orthopaedic and trauma surgeon used to validate other elements of resource utilisation was consulted. They indicated that fractures in the model could be classified as pathological, and that NHS reference costs with lower complexity and comorbidity (CC) scores could be excluded, in part because the smaller, typically fragile and deformed skeletons of these patients are very complex to treat or operate on and slow to heal. Therefore, for the SoC arm, weighted average costs were calculated excluding lowest CC category from the calculations. As discussed above, remineralised bones of burosumab treated patients are expected to be thicker and stronger and according to the results of CL303 and reports from the EAP heal similarly to the general population, therefore for burosumab the weighted average cost included all CC categories. The cost of pathological fractures by CC score can be found in Appendix U.

After weighting costs by CC score, the final average cost per patient treated as a day case was £445.05, and the final average cost per patient fracture admitted but with no procedure, which was further weighted using the data from NHS finished consultant episode (FCE) counts, was £3,524.94 for SoC arm (excluding the lowest CC category), and £437.72 and

£3,488.66, respectively, for the burosumab arm. Fractures requiring admission and surgical procedures were weighted by fracture site, as taken from Bouee et al. 2006,[117] and are presented in Table 53.

Table 53: Pathological fractures requiring admission and surgical procedure costs, by fracture site

Fracture site	Cost excluding lowest CC category	Cost including all CC categories
Foot fracture	£3,976.90	£3,937.22
Tibia/Fibula fracture	£4,347.51	£4,304.22
Femur/Pelvis fracture	£4,924.02	£4,875.12
Vertebrae/spinal fractures	£0.00	£0.00
Upper limb fractures	£2,535.65	£2,509.98
Other fractures	£2,865.08	£2,836.20

Expert elicitation suggested that follow-up visits, analgesics, and physiotherapy costs should be captured as well (see Appendix P). NICE guidance on hip fractures recommends paracetamol, or additional opioids if paracetamol alone does not provide relief, before and after surgery. It was assumed that treatment for other fractures would be similar, and, considering the low cost of paracetamol and other analgesics, these costs have thus not been included in the model.

The total resource utilisation for physiotherapy and follow-up visits were assumptions based on clinical elicitation and costs were taken from PSSRU 2021.[86]

Table 54: Additional fracture costs and resource utilisation

Resource	Cost	Number required after hospitalisation and procedure	Number required after hospitalisation and no procedure
Physiotherapy	£67.00	6.00	4.00
Follow-up visit with GP	£39.00	2.00	1.00

Source: Expert opinion; PSSRU 2021[86]

Table 55: Total weighted cost per fracture

Fracture site	Total weighted cost per patient SoC	Total weighted cost per patient burosumab
Foot fracture	£2,427.65	£2,514.40
Tibia/Fibula fracture	£3,631.66	£3,185.64
Femur/Pelvis fracture	£3,551.47	£3,280.71
Vertebrae/spinal fractures	£767.03	£761.66
Upper limb fractures	£2,386.82	£2,379.62
Other fractures	£2,153.15	£2,131.99
Total fracture costs	£14,917.77	£14,254.01

Cost and resource use for morbidities included in scenario analysis (spinal stenosis/surgery, dental abscess and hearing loss/tinnitus) are outlined in Appendix U.

3.5.2 Summary of unit costs and resource use

Costs used in the model are summarised in Table 56.

Table 56: Summary of costs used in the cost effectiveness model

Items	Value (£)	Reference in submission
Burosumab drug cost per mg (PAS price)*	[redacted]	Section 3.5.1.1
Burosumab drug cost per year	[redacted]	Section 3.5.1.1
Disease monitoring costs per year		Section 3.5.1.3
Burosumab, first year	£333.85	Section 3.5.1.3
Burosumab, subsequent years	£286.35	Section 3.5.1.3
SoC	£286.35	Section 3.5.1.3
Morbidity costs per year (average)		
SoC		
Foot fracture	£2,427.65	Section 3.5.1.4
Tibia/Fibula fracture	£3,631.66	Section 3.5.1.4
Femur/Pelvis fracture	£3,551.47	Section 3.5.1.4
Vertebrae/spinal fractures	£767.03	Section 3.5.1.4
Upper limb fractures	£2,386.82	Section 3.5.1.4
Other fractures	£2,153.15	Section 3.5.1.4
Burosumab		
Foot fracture	£2,514.40	Section 3.5.1.4
Tibia/Fibula fracture	£3,185.64	Section 3.5.1.4
Femur/Pelvis fracture	£3,280.71	Section 3.5.1.4
Vertebrae/spinal fractures	£761.66	Section 3.5.1.4
Upper limb fractures	£2,379.62	Section 3.5.1.4
Other fractures	£2,131.99	Section 3.5.1.4
* [redacted]		

3.5.3 Adverse reaction unit costs and resource use

As reported in Section B.2.10, the overall incidence, nature, and severity of adverse events were comparable in the burosumab and placebo treatment groups in the pivotal trial (CL303).[7] Most AEs were mild or moderate in severity, and there were no deaths, discontinuations due to adverse events or dose-limiting toxicities. The small number of dose reductions required for hyperphosphataemia were taken into account in the calculation of the required doses of burosumab per year. Due to the comparability with the placebo arm, no additional adverse events were accounted for in the model.

3.5.4 Miscellaneous unit costs and resource use

The model does not take into account any additional costs and resource use apart from those stated above.

3.6 Severity

XLH is a lifelong genetic disease which considerably shortens life expectancy and has significant detriment to quality of life. When QALYs are not discounted, XLH patients meet the absolute shortfall criteria for a 1.7 severity weighting. Even with discounting, patients reaching adulthood may meet the criteria for a 1.2 severity weighting depending on the data source used to estimate general population utilities. Therefore, we believe, severity of XLH should be taken into account. However, base case results are presented with no QALY weighting to adhere to the reference case.

Section 3.4 provides details on EQ-5D mapping and utilities used in the cost effectiveness analysis for the SoC arm. For the comparison with the general population, ONS National Life Tables for 2017-19[83] were used to estimate mortality, while general population utilities were based on the model provided by Ara & Brazier 2010.[118] Shortfall was also calculated using the web-based QALY shortfall calculator provided by Schneider et al., 2021 using the Reference case settings[119]. QALY shortfall was calculated and is presented below for age 18 (as XLH is a genetic disease all patients are diagnosed in childhood; however patients have to be 18 or over to be eligible for burosumab in its current indication) and age 40 (which was the mean age of patients in the pivotal trial (CL303). Gender distribution of 65% females is also taken from CL303 for consistency. The higher proportion of females corresponds to the X-linked nature of the disease.

3.6.1 Undiscounted QALY shortfall

When QALYs are not discounted XLH patients meet the absolute shortfall criteria for a 1.7 severity weighting. The absolute QALY shortfall when burosumab treatment is started at 18 years is 31.42, which meets the criteria for the 1.7 severity weighting (See Table 57). When treatment is started at age 40 the absolute QALY shortfall is 21.69, which still meets the severity criteria as per NICE guidelines. Of note, in NICE HST 6, the determination of whether or not to weight QALYs was based on undiscounted QALY gains.[120] HST 6 appraised the use of asfotase alfa for treating paediatric-onset hypophosphatasia.

Table 57: Summary of QALY shortfall analysis without discounting

Starting age	Expected total QALYs for the general population	Total QALYs patients with XLH	Absolute QALY shortfall	Proportional QALY shortfall	NICE Severity Weighting
18	54.59	23.17	**31.42**	0.58	**x1.7**
40	35.02	13.33	**21.69**	0.62	**x1.7**

3.6.2 Discounted QALY shortfall

When discounting is applied, XLH patients aged 18 almost meet the shortfall criteria for a 1.2 multiplier as the absolute QALY shortfall is 11.93 QALYs using the reference case. A multiplier of 1.2 would apply if the absolute QALY shortfall were above 12 QALYs. Note that the absolute shortfall would be 12.76 if the general population utilities reported by Ara & Brazier 2010 are used.[118] At the average age enrolled in the clinical trial (age 40) it falls below the specified threshold for meeting shortfall criteria for severity weighting (see Table 58).

Table 58: Summary of QALY shortfall analysis with discounting

Start age	Calcul-ation	Expected total QALYs for the general population	Total QALYs patients with XLH	Absolute QALY shortfall	Proport-ional QALY shortfall	NICE Severity Weighting
18	Alava et al., 2022	22.92	10.99	11.93	0.52	x1.0
	Ara&Brazier 2010	23.47	11.02	**12.46**	0.53	**x1.2**
40	Alava et al., 2022	18.63	7.94	10.70	0.57	x1.0
	Ara&Brazier 2010	19.28	7.98	11.31	059	x1.0

Note: All QALYs are discounted at 3.5%

Table 59: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution	65% female (from CL303)	Section 3.2.1
Starting age	18 and 40 (from CL303)	Section 3.2.1
Discount Rate	3.5% (as per NICE guidelines)	Section 3.2.3
XLH mortality hazard ratio	2.88 (Hawley 2020)	Section 3.2.2

3.7 Uncertainty

XLH is a very rare disease, estimated to affect approximately 300 adults in England, of whom fewer than 200 will be eligible for treatment with burosumab.[30] This rarity affects the ability to generate high-quality evidence in a number of ways:

- The number of patients available to be recruited into RCTs is limited
- Data on natural history, outcomes under standard treatment and life expectancy under standard treatment are all sparse, and sample sizes are low
- Comparative data only available from CL303 up to 24 weeks.

The life-long nature of XLH, involving the progressive accumulation and worsening of XLH-related morbidities over the adult life course, means that the duration of RCTs is insufficiently long to capture the effect of treatment on long-term outcomes. However, burosumab's mechanism of action restores normal phosphate homeostasis by inhibiting the root cause of morbidity, i.e. hypophosphataemia caused by excessive levels of FGF-23.[1] This results in normalisation of phosphate levels for the great majority of patients, which is maintained throughout treatment. It is therefore reasonable to assume that the incidence of morbidities that result from FGF-23 over-expression and hypophosphataemia in adulthood will revert to general population levels whilst on treatment. In the base case fractures are the only morbidity modelled, with other morbidities explored in scenario analyses.

Study CL401 (Phase 4, US, Canada and South America disease monitoring programme) and the International XLH Registry (see Section 2.11) will provide additional long-term data on XLH including the use of burosumab for up to 10 years. These evidence sources will look to provide longer-term data and clarity across a multitude of outcomes, including incidence of new fractures, normalisation of serum phosphate, physical functioning, development/avoidance of morbidities, and QoL impact. However, data on outcomes are not yet available.

3.8 Summary of base-case analysis inputs and assumptions

3.8.1 Summary of base-case analysis inputs

A summary of the model base case inputs can be found in Table 60.

Table 60: Data sources for clinical parameters and population characteristics in the model base case

Variable	Value or source if multiple values (source)

Time horizon	Lifetime
Morbidities included in model	Fractures (spinal stenosis, dental abscesses and hearing loss and tinnitus included in scenario analysis)
Discount rates	
Discount rate for costs	3.50% (as per NICE Guidance)
Discount rate for health benefits	3.50% (as per NICE Guidance)
Patient characteristics	
Age distribution of patients	CL303 values
Gender distribution	65% female (CL303)
Weight distribution	CL303 EU population
Treatment continuation rules	Serum phosphate normalisation after 24 weeks of treatment and improvement in WOMAC after one year
Serum phosphate normalisation	
On treatment with burosumab	100.0% (based on continuation rule)
SoC	7.58% (CL303)
Treatment discontinuation	
Year 1	16.9%
Year 2+	3%
Morbidity event rates	
SoC (all morbidities)	CL303
When treated with burosumab (fracture)	Curtis 2016[121]
Impact of burosumab on morbidity	
Year 1 onwards on treatment morbidity reduction	100%
1 year after end of treatment morbidity reduction	50%
2 years after end of treatment morbidity reduction	0%
Excess mortality	
HR applied to general population life tables for SoC	2.88 (Hawley 2020)
Degree of reduction in excess mortality on burosumab treatment	
Year 1 on treatment	75%
Year 2 on treatment	100%
Year ≤3 on treatment	100%
1 year after end of treatment	75%
2 years after end of treatment	50%

Utilities and disutilities	
Baseline utility mean	Age dependent value estimated from CL001
Utility change in first year on burosumab treatment*	0.147 (CL303 and BUR02 for subsequent years)
Utility change in second year on burosumab treatment*	0.211 (CL303 and BUR02 for subsequent years)
Utility in all subsequent years on burosumab treatment*	0.215 (CL303 and BUR02 for subsequent years)
Tapering of utility value in first year after stopping treatment with burosumab	50% (assumption)
Tapering of utility value in second year after stopping treatment with burosumab	0% (assumption)
All lower limb/hip fractures first year	0.70 (Peasgood et al. 2009)
All lower limb/hip fractures subsequent years	0.80 (Peasgood et al. 2009)
Vertebrae/spinal fractures first year	0.91 (Cockerill et al. 2004)
Vertebrae/spinal fractures subsequent years	0.99 (Cockerill et al. 2004)
Upper limb fractures first year	0.93 (Borgström et al. 2006; Strom et al. 2008)
Upper limb fractures subsequent years	1.00 (Borgström et al. 2006; Strom et al. 2008)
Other fractures first year	0.93 (Borgström et al. 2006; Strom et al. 2008)
Other fractures subsequent years	1.00 (Borgström et al. 2006; Strom et al. 2008)
Spillover disutility as % patient benefit (if phosphate abnormal)	20% applied to 2 family members (assumption)
Treatment-related costs and resource use	
Burosumab cost per mg as per HST8 PAS ^	[redacted]
Burosumab administration cost (annual)	£199.33
Treatment monitoring cost (annual): burosumab	First year: £333.85; Subsequent years: £286.35
Treatment monitoring cost (annual): SoC	£286.35
Morbidity-related cost and resource use	

SoC	
Foot fracture	£2,427.65
Tibia/Fibula fracture	£3,631.66
Femur/Pelvis fracture	£3,551.47
Vertebrae/spinal fractures	£767.03
Upper limb fractures	£2,386.82
Other fractures	£2,153.15
Burosumab	
Foot fracture	£2,514.40
Tibia/Fibula fracture	£3,185.64
Femur/Pelvis fracture	£3,280.71
Vertebrae/spinal fractures	£761.66
Upper limb fractures	£2,379.62
Other fractures	£2,131.99

*If treatment continuation rules are applied

^ Refer to [redacted]

Legend: HR – hazard ratio

3.8.2 Assumptions

The key model assumptions are summarised in Table 61 below. All assumptions were validated with clinical experts as part of the model development process. See Table 37 for a summary of the expert opinion sought.

Table 61: Summary of key model assumptions

Parameter	Assumption	Supportive evidence
Utilities	Mean change in utility at year 1, year 2 and year >=3 is based on extrapolation of CL303 and BUR02 trial data after mapping WOMAC to EQ-5D	Utilities aligned with utilities mapped from SF-36 data (see Figure 33) as well as magnitude of change from real-world evidence[4] (see Section 2.6.6) Validated with clinical experts (Appendix Q)
Mortality – excess mortality in XLH patients	The mortality risk is higher for XLH patients than the general population (HR = 2.88, [Hawley 2020]).[19]	Hawley 2020 hazard ratio Validated by clinical experts (Appendix P, Q) Validated by additional independent analysis (Appendix R)
Mortality – risk reduction on burosumab treatment	Adults with XLH have an increased risk of mortality relative to the general population. Treatment with burosumab and subsequent serum	Hawley 2020 Mechanism of action of burosumab (restoring phosphate homeostasis[7];

	phosphate normalisation reduces this risk. The model assumed that burosumab has no impact on skeletal malformations when given to adults, but may improve physical activity, pain, opioid use, mental well-being and social deprivation over time. All these are hypothesised to contribute to the excess mortality seen in XLH (see Section 1.3.4) and thus assumed a 50% mortality risk reduction in the base case.	see Section 1.3.4 for details.) Evidence on improvements in physical functioning and pain comes from the clinical trial (CL303 and extension [BUR02])[7,57,60] Reduction in opioid use is supported UK by real-world evidence[4] Validated by clinical experts (Appendix Q)
Utility impact on family and caregivers	The model applied 20% of the additional patient benefit on treatment to 2 family members	Patient survey (see Section 1.3.5.6 and Appendix S) Validated by clinical XLH expert (Appendix Q)
Treatment continuation rule and discontinuation	The model includes the proposed stopping rules: only those achieving serum phosphate normalisation after 24 weeks of treatment and an improvement in WOMAC after 1 year should continue treatment	Validated by clinical experts (Appendix Q)
Equal morbidity rates to the general population	Burosumab patients who have achieved serum phosphate normalisation are assumed to experience morbidity rates equal to the general population	Validated by clinical experts (Appendix P)
Tapering: the impact of burosumab on morbidity, mortality and utility is tapered over 2 years	The model assumes that patients in the burosumab arm experience a reduction in morbidities due to the incremental difference in serum phosphate normalisation rates (i.e. serum phosphate >LLN) between the two arms. The effect of serum phosphate normalisation on the incidence of morbidities/mortality and utilities is not immediate, and tapering is applied both to the time it takes for the effect to be fully developed and the time it takes for the effect to wear off	Validated by clinical experts, based on time needed for bone and muscle de/mineralisation for morbidities, and impact on WOMAC scores for utilities (Appendix Q) Supporting evidence from Kamenicky 2023[60]
Subsequent utility loss due to fractures, tinnitus/ hearing loss, spinal surgery	Patients who experience fractures, tinnitus/hearing loss, spinal surgery have a loss in utility for all subsequent years after the initial incident/diagnosis/surgery	Validated by clinical experts (Appendix P)
Serum phosphate normalisation rate for	Serum phosphate normalisation rate (7.58%) for adults not treated	Validated by clinical experts (Appendix Q)

adults not treated with burosumab	with burosumab is equivalent to the placebo arm in CL303[7] (who were not allowed conventional therapy)	

3.9 Base-case results

3.9.1 Base-case incremental cost-effectiveness analysis results

The results that follow are based on the current confidential patient access scheme (HST8 PAS) price for burosumab in the treatment of children with XLH [redacted] We would welcome the NICE Committee has this information for their decision making.

When treatment with burosumab is compared to treatment with the current standard of care the model estimates a final discounted incremental lifetime per patient cost of [redacted] and [redacted] incremental discounted QALYs, which leads to an ICER of [redacted].

A full breakdown of discounted costs and health can be found in **Table 62**.

Table 62: Discounted base-case results with HST8 PAS price (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Increment-al costs (£)	Increment-al LYG	Increment-al QALYs	ICER incremental (£/QALY)
SoC	£9,489	18.90	7.83				
Burosumab	[redacted]	19.42	[redacted]	[redacted]	0.52	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 63: Net health benefit with HST8 PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Soc	£9,489	7.83				
Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

Disaggregated results are presented in Appendix J.

3.10 Exploring uncertainty

The main aspects of uncertainty relate to the long-term effects of burosumab on morbidities and mortality. An analysis by Hawley et al. has suggested that adults with XLH have increased mortality compared with the general population, but data on life expectancy and mortality rates in this group are sparse.[19] By normalising phosphate levels, treatment with burosumab is assumed to reduce mortality risk by reducing the cumulative impact of XLH-related manifestations and co-morbidities; a validation exercise carried out with expert clinicians practising in England (see Appendix Q) confirmed that in their opinion, multiple related mechanisms are plausible drivers of shortened survival in XLH. However, a survival benefit is not captured in the trial data due to insufficient length of follow-up. Data are lacking on the relationship between phosphate levels and mortality in adults with XLH, and would require many years to collect. Similarly, robust data on any effect of burosumab will not be available for some time owing to small patient numbers. Thus, some uncertainty will remain around the modelling of survival and mortality in this very rare disease.

In addition, long-term comparative evidence on fracture rates and fracture healing between burosumab and best supportive care is not available, although exploratory evidence was collected in the 24-week placebo-controlled period of study CL303.

There is also uncertainty over the magnitude of the HRQoL benefit that would be experienced by caregivers or close family members of adults treated with burosumab.

Uncertainty was explored using probabilistic and deterministic sensitivity analyses, and different scenarios were also modelled. These explorations are described below.

3.10.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), uncertainties in the parameter values were estimated by randomly drawing a parameter value from predefined distributions and averaging model cost and QALY predictions over 2,500 iterations. Please refer to Appendix U for estimates of cumulative incremental costs, QALYs and ICER which show the expected probabilistic ICER remains stable after approximately 800-1,000 simulations, therefore the use of 2,500 iterations was enough to capture parameter uncertainty.

Results are presented as cost effectiveness acceptability curves as well as on a cost effectiveness plane. The mean probabilistic results are presented in Table 64 and align with the deterministic results.

Table 64: Probabilistic sensitivity analysis results with HST8 PAS price

Technol-ogies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SoC	£9,514	18.92	7.83				
Burosumab	[redacted]	19.40	[redacted]	[redacted]	0.48	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 65: Net health benefit probabilistic results with HST8 PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Soc	£9,514	7.83				
Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

Figure 40 shows the results on cost-effectiveness plane. All of the 2,500 simulations were in the upper right-hand quadrant, indicating that burosumab is more effective although a more costly treatment option compared to SoC.

Figure 40: Cost effectiveness plane

At the £20,000 to £30,000 threshold the probability of burosumab being cost effective compared to SoC is 0% with the current HST8 PAS price approved for children. [redacted]

3.10.2 Deterministic sensitivity analysis

All major model variables in the base case for which values were uncertain were tested in a one-way deterministic sensitivity analysis to identify model drivers and examine key areas of uncertainty. Where possible, confidence intervals or published ranges were used as alternative values. In the absence of confidence intervals or published ranges, upper and lower bounds tested in the one-way sensitivity analysis were calculated assuming a standard error of 0.1. Please see Appendix U for ranges applied. Results of the deterministic sensitivity analysis are presented as a tornado diagram (Figure 42).

The deterministic sensitivity analysis shows that the ICER is most sensitive to the utility gain associated with burosumab treatment in the long run (after year 3), the age dependent utilities and the mortality ratio of SoC vs. general population. However, none of the scenarios increased the ICER to above [redacted].

Table 66: Top 20 parameters influencing the ICER with HST8 PAS price

Parameter	Upper ICER	Lower ICER	Difference
Utility whilst on burosumab Year ≥3 on treatment	[redacted]	[redacted]	[redacted]
Age dependent utilities	[redacted]	[redacted]	[redacted]
SOC mortality ratio vs. general population	[redacted]	[redacted]	[redacted]
Utility multiplier all Lower limb/hip fractures subsequent years	[redacted]	[redacted]	[redacted]
Probability of serum phosphate normalisation on SOC	[redacted]	[redacted]	[redacted]
Degree of reduction in mortality on treatment vs. SoC	[redacted]	[redacted]	[redacted]
Utility whilst on burosumab Year 2 on treatment	[redacted]	[redacted]	[redacted]
Utility whilst on burosumab Year 1 on treatment	[redacted]	[redacted]	[redacted]
Probability of serum phosphate normalisation on burosumab	[redacted]	[redacted]	[redacted]
Lower limb/hip fractures event rates, both arms	[redacted]	[redacted]	[redacted]
Annual burosumab discontinuation after year 1	[redacted]	[redacted]	[redacted]
Utility benefit 1 year after end of treatment	[redacted]	[redacted]	[redacted]
Tapering of morbidity benefit (1 year at start of treatment)	[redacted]	[redacted]	[redacted]
Utility multiplier all Lower limb/hip fractures first year	[redacted]	[redacted]	[redacted]
Tapering of morbidity benefit (1 year after end of treatment)	[redacted]	[redacted]	[redacted]
Cost of disease monitoring (burosumab)	[redacted]	[redacted]	[redacted]
Cost of disease monitoring (SoC)	[redacted]	[redacted]	[redacted]
Cost of lower limb fracture (same cost applied to both arms)	[redacted]	[redacted]	[redacted]
Tapering of mortality benefit (1 year at start of treatment)	[redacted]	[redacted]	[redacted]
Tapering of mortality benefit (1 year after end of treatment)	[redacted]	[redacted]	[redacted]

Figure 41: Tornado diagram for ICER with HST8 PAS price

Legend: Lower ICER – ICER result using lower value from range tested in deterministic sensitivity analysis; Higher ICER – ICER result using higher value from range tested in deterministic sensitivity analysis

3.10.3 Scenario analysis

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties. As seen with the base case results, the model is almost linear with probabilistic results being very close to deterministic results (0.2% difference in incremental costs and 0.7% difference in incremental QALYs). Since the model is run for 14 separate age groups, this makes the runtime for probabilistic analyses 14 times longer than for a model of similar complexity. Given the alignment between deterministic and probabilistic results, the deterministic results are displayed in Table 68.

The results are relatively stable, with most scenarios having an ICER between [redacted]. The ICER is most affected when the utility impact on family and caregivers is not included in the model: in this scenario it increases to [redacted]. Varying the degree of reduction in morbidities also affected the ICER, leading to an increased value of [redacted]. The ICER is also affected when the time horizon for the model is restricted to 20 years. This scenario results in an ICER of [redacted].

Table 67: Scenario analysis results with HST8 PAS price

Parameter	Base case	Scenario	Incremental Cost (£)	Incremental QALY	ICER (£/QALY)
Base Case			[redacted]	[redacted]	[redacted]
Time horizon	Lifetime	20 years	[redacted]	[redacted]	[redacted]
Annual discount rate (costs and health outputs)	3.50%	6.0%	[redacted]	[redacted]	[redacted]
		5.0%	[redacted]	[redacted]	[redacted]
		1.50%	[redacted]	[redacted]	[redacted]
		0.0%	[redacted]	[redacted]	[redacted]
Age distribution	CL303	CL001	[redacted]	[redacted]	[redacted]
Weight distribution	CL303 EU	CL303 All patients	[redacted]	[redacted]	[redacted]
Mortality	Use Hawley at least likely, 50% reduction in mortality for patients treated with burosumab	Use Hawley at least possibly, 50% reduction in mortality for patients treated with burosumab	[redacted]	[redacted]	[redacted]
		Use Hawley at least likely, 0% reduction in mortality for patients treated with burosumab	[redacted]	[redacted]	[redacted]
Spill-over burden	On	Off	[redacted]	[redacted]	[redacted]

morbidities included in model		Include spinal stenosis, spinal surgery, dental abscess,	[redacted]	[redacted]	[redacted]
Mortality taper	On	Off	[redacted]	[redacted]	[redacted]
Morbidity taper	On	Off	[redacted]	[redacted]	[redacted]
Utility taper	On	Off	[redacted]	[redacted]	[redacted]
Treatment continuation rules	Stopping rule applied	No stopping rule	[redacted]	[redacted]	[redacted]
Degree of reduction in morbidities due to serum phosphate normalisation	100%	0%	[redacted]	[redacted]	[redacted]

3.11 Subgroup analysis

No subgroups were included in the cost effectiveness model.

3.12 Benefits not captured in the QALY calculation

Certain aspects of the modelling are conservative and may not reflect all of the value of treatment with burosumab in adults.

- Any benefits of burosumab to mental health and social participation are not captured in the QALY calculation, because these aspects are not addressed by the WOMAC instrument, from which EQ-5D scores were mapped. The improved physical functioning and reductions in pain and stiffness seen with burosumab in CL303 are likely to translate into mental health and social benefits. This has been confirmed anecdotally by patient testimonies from the Early Access Programme,[74] although these have not yet been collected systematically. A 23-year-old man states that: "[redacted] *(see Appendix N p.4)*

- Patients mental wellbeing may also benefit from the knowledge that their phosphate levels are normalised: adults with XLH have spoken about the fear of their condition

worsening as they age, and their fear of sustaining fractures.[20,26] Burosumab treatment may reduce these fears and thus improve mental wellbeing.

- Pain reductions captured through WOMAC may also be conservative: patients who experience less pain may choose to increase their activity levels until they once again reach a limiting level of pain.

- The clinical trial protocol mandated maintenance of baseline analgesic use and dosing. In real life, many patients reduce their analgesic use. Furthermore, based on observations from the EAP, 38.5% of opioid users at baseline had stopped using opioids by one year.[4] Opioid use is known to be associated with many detrimental health outcomes,[47] however, the potential reduction in these opioid (and other long-term analgesic) use related adverse health consequences were not included in the current evaluation.

- The immediate impact of burosumab on fracture healing has been included in the model as a utility improvement to capture reduction in pain, stiffness, fatigue, etc, as captured by improvement in WOMAC scores. The impact on reducing future fracture rates has also been included. However, many of the active and unhealing fractures and pseudofractures at baseline would require costly surgical procedures to handle. The cost savings associated with avoidance of surgical handling of active fractures and pseudofractures at baseline were also not included in the evaluation.

Taking all these factors into account, it is reasonable to assume that the utility gain modelled for burosumab is conservative and potential cost savings associated with reduced opioid/analgesic use and avoidance of surgical procedures for existing fractures at baseline have been omitted from the analysis.

The innovative nature of burosumab is not captured. Burosumab is the first and only treatment to address the underlying pathophysiology of XLH and restore normal phosphate homeostasis and vitamin D activation.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

The cost-effectiveness analyses have undergone both conceptual and technical validation. As described in Section 3.3.2, conceptual validation was provided by in depth interviews with seven global clinical experts with experience in treating XLH and with the use of burosumab. Additionally, interviews covering validation of the model structure, UK-specific resource

utilisation and model assumptions were carried out on three separate occasions. On these meetings, the model concept, the inputs and methods used, and the results were discussed. For more information please see Appendix P and Q.

In addition to conceptual validation, a comprehensive and rigorous quality check was performed once programming was finished. A model validator not involved in the original programming checked the calculation and reference formulas, and an additional team member checked the values of numbers supplied as model inputs.

3.14 Interpretation and conclusions of economic evidence

The results from the cost-effectiveness analyses, show that adult XLH patients and their families receive a total of [redacted] discounted QALYs compared to 7.83 for SoC; which results in an incremental (discounted) QALY gain of [redacted] for patients receiving burosumab. A discounted incremental cost of [redacted] with burosumab treatment applying the current HST8 PAS price approved for children results in an ICER that is higher than currently accepted thresholds. [redacted]

The results of the sensitivity analyses found that the model was most sensitive to assumptions around long-term impact of XLH and burosumab treatment, i.e. the additional utility associated with burosumab treatment (from Year 3), XLH-related age dependent utilities and the mortality ratio of SoC compared to the general population.

Scenario analyses show that for a range of scenarios, the resulting ICER lies very close to the base case. The following three extreme case scenarios had the greatest impact on the ICER: (1) removing the impact on family members and carers, (2) assuming that serum phosphate normalisation does not reduce the occurrence of morbidities associated with XLH, and (3) assuming burosumab has no impact on mortality risk. However, the clinical plausibility of these scenarios is low. Assuming that serum phosphate normalisation does not reduce the occurrence of morbidities contradicts observations of the clinical trials as well as real world studies on the relationship between serum phosphate levels and fracture rates. Since morbidities, especially fractures have been linked to higher mortality, then it could be argued that denying any impact on mortality risk is also implausible. Furthermore, given the nature of morbidities and the burden of disease described by patients, if one accepts an impact on morbidities, then it is implausible for there to be absolutely no impact on carers.

[redacted][13][redacted]

As discussed in Section 3.10 above, there is uncertainty over the extent to which XLH increases mortality in adults compared with the general population, and over the impact of burosumab on morbidity rates and mortality. This is due to the paucity of data on the natural history of this very rare disease. Furthermore, the uncertainty around the impact of burosumab on mortality cannot be resolved since the length of follow-up of burosumab-treated patients needed to provide robust data on mortality is measured in decades rather than years. These uncertainties are a limitation of the analysis, but have been explored in sensitivity and scenario analyses, as described above.

There are also benefits of burosumab treatment that are not covered by the QALY calculation (see Section 3.12). Any benefits of burosumab to mental health and social participation, which may in the long run impact survival are not captured in the QALY calculation, because these aspects are not addressed by the WOMAC instrument, from which EQ-5D scores were mapped. Pain reductions captured through WOMAC may also be conservative: patients who experience less pain may choose to increase their activity levels until they once again reach a limiting level of pain. Furthermore, impact of reduction of analgesic/opioid use and savings associated with avoidance of surgical procedures to treat active fractures at baseline were omitted from the analysis due to lack of data. The innovative nature of burosumab is also not captured. Burosumab is the first and only treatment to address the underlying pathophysiology of XLH[1] and restore normal phosphate homeostasis and vitamin D activation.[7] Taking all these factors into account, it is reasonable to argue that this health economic assessment of burosumab is conservative.

Conclusion

XLH is highly burdensome for affected adults and their families. Ongoing hypophosphataemia in adulthood results in osteomalacia with pseudofractures (painful bone lesions), impaired muscle function, chronic bone and joint pain, stiffness, impaired mobility and disability, depression and early susceptibility to dental abscesses and osteoarthritis.[3]

Many patients require extensive bone surgery for fractures. For highly symptomatic individuals XLH has a profound impact on their physical and mental health and their day-to-day lives.[11,20,21,26,27]

Burosumab, is the first and only treatment that addresses the underlying pathophysiology of XLH and provides significant QALY gains for adults with XLH for whom no other treatment is suitable, and is a cost-effective use of NHS resources.

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5 Appendices

The list of appendices is shown below. Each appendix is supplied as a separate document.

Appendix number	Content
C	Summary of Product Characteristics UK Public Assessment form
D	Clinical SLR report
E	Subgroup analyses from trial
F	Adverse reactions
G	Cost-effectiveness SLR report
H	HRQoL SLR report
I	Costs and resource use SLR report
J	Clinical outcomes and disaggregated results from model (PAS price only)
K	Price details of treatments
L	Checklist of confidential information
M	Patient testimonies: living with XLH
N	Patient testimonies: treatment experience with burosumab
O	Patient survey results
P	Clinical expert elicitation (1)
Q	Clinical expert elicitation (2)
R	Life expectancy analysis
S	Study of burden on family members
T	Alternative HRQoL models
U	Scenario and sensitivity analysis inputs
V	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

Clarification questions

Company responses, 23 June 2023

File name	Version	Contains confidential information	Date
ID3822 Burosumab – EAG clarification responses_redacted ACIC_final 23062023		Yes (CIC, AIC, redacted)	23 June 2023

Section A: Clarification on effectiveness data

Applicability of the company's positioning and trial evidence to the NHS

A1. *From our understanding, the UK Early Access Programme (EAP) criteria for administering burosumab do not require patients to be unsuitable for phosphate treatment, or to have a BPI of 4 or above. This differs from the proposed positioning of burosumab by the company and the inclusion criteria for the CL303 trial. Given this, please comment on:*

a) the applicability of the company's proposed positioning of burosumab to the NHS

b) the applicability of the trial evidence to the company's proposed positioning and the NHS.

Part a). It is correct that the EAP criteria, as set out in the application form, does not explicitly require patients to be unsuitable for phosphate treatment. However, it is stated on page 8 of the application form that patients must have "persistent symptoms despite prior treatment with conventional therapy".[1] The EAP was set up in conjunction with clinical experts to reflect the anticipated positioning of burosumab in the NHS.

The use of burosumab in the NHS in England will follow established clinical recommendations for management of XLH in adults. As noted in document B Section 1.3.6.2, two European consensus statements (which included UK authors) have been published,[2,3] and a draft set of clinical practice recommendations by NHS clinicians (Mohsin et al.[4]) has been shared by the authors for the submission. In all three documents, pharmacological treatment is only recommended for symptomatic patients, and consideration of burosumab is recommended only after insufficient response, complications/intolerance or contraindication to conventional therapy. Mohsin et al state that in symptomatic patients (with musculoskeletal pain and stiffness, or pseudofractures), burosumab should be considered if conventional therapy with phosphate supplementation is not tolerated, has no benefit after 3

months, or has already been tried in the last 24 months for similar symptoms. They also state that average pain should be ≥4/10 for consideration of burosumab (Mohsin p. 11, 12). This reflects the proposed positioning of burosumab in the submission, and the pain threshold is the same as that used in the CL303 trial. Keen et al. 2021 reported that as of 31 May 2021, 103 patients were accessing burosumab treatment via the EAP, from an estimated total of 208 known cases across the five sites.[5]

Part b) The clinical guidance above, and clinical expert opinion on the anticipated positioning of burosumab for adults in the NHS, confirm that there is good alignment between the positioning for the submission, the inclusion criteria for the EAP, and the study population in CL303. The applicability of the trial evidence to the positioning in the submission and anticipated use in the NHS is detailed further in CS Section B1.1.

A2. *Clinical advice to the EAG suggests that WOMAC and BPI scales are not routinely used in the NHS to assess patients with XLH. Please comment on:*

a) How patients would be judged eligible for burosumab if BPI pain score is not measured.

b) How effectiveness of burosumab would be assessed, and how decisions to continue or discontinue treatment might be made, if WOMAC or BPI are not used.

Part a) The BPI-SF (short form) consists of several different scores, each made up of 1 or more items (see Document B p58-59).[6] There is no single 'BPI pain score'. Eligibility for study CL303 was based on the BPI 'Worst pain' score, and not the full BPI-SF questionnaire. The 'Worst pain' score is a single question assessed on a 1-10 numeric rating scale (see document B Table 13), and is therefore very simple to administer. In their draft clinical practice recommendations for the management of XLH in adults in the NHS, Mohsin et al. recommend "Assessment of severe and average pain over the last seven days that the clinician considers is attributable to XLH using VAS 0-10".[4] This is closely analogous to the BPI 'Worst pain' evaluation. In their checklist for follow-up of adult XLH patients (Mohsin p. 21), the BPI-SF pain severity scale is an option for assessing patients' pain at each visit.

The company agrees that the full BPI-SF questionnaire is not routinely used in clinical practice, but the 'Worst pain' score, as used in the trial, is essentially the same as the assessment of 'severe pain' on a 1-10 scale that is recommended by NHS clinicians. Draft clinical guidance also suggests that the BPI-SF pain severity scale is an option for assessing patients' pain at each visit. There should therefore be no problem in assessing patients' eligibility for burosumab in the same way that it was assessed in the trial.

Part b) As discussed above, the BPI 'Worst pain' question or its close equivalent is used in clinical practice. However, pain is only one aspect of burosumab's effectiveness. Continuation of treatment after year 1 in the economic model is based on a requirement of reaching serum phosphate levels above LLN after 24 weeks of treatment and an improvement in WOMAC total score at 12 months after starting treatment. WOMAC score is not routinely used in clinical practice, but clinicians consulted for the submission agreed that WOMAC scores are a good proxy for reflecting the criteria for continuation of treatment that might be used as they capture improvement in pain, stiffness and fatigue (document B, p. 114). In clinical practice, Mohsin et al. recommend that presence of musculoskeletal pain, stiffness and fatigue should be assessed at each visit and the use of burosumab therapy should be reviewed annually within a multidisciplinary team. Pain, stiffness and fatigue are key aspects of XLH patients' impairment in adulthood, constraining their physical functioning and activities of everyday living, including employment. It is expected that patients who have not shown an improvement in pain, stiffness and fatigue after 12 months will not continue burosumab treatment in NHS practice.

CL303 trial design and conduct

A3. *Please clarify whether the incidence of new fractures was systematically assessed in studies CL303, BUR002, and CL304, and provide methods (including imaging, blinding of outcome assessors, number of outcomes assessors per fracture/patient and method for resolving discrepancies where this applies) as appropriate.*

As stated in the company submission, fracture-related endpoints were exploratory only in CL303 and CL304, and related to follow-up of fractures identified at baseline. In BUR02 there were no fracture-related efficacy endpoints. In all studies, new

fractures were reported as adverse events. Further information is provided in the table below.

Table 1 Assessment of new fracture incidence

Study	Assessment of new fracture incidence
CL303	A baseline skeletal survey was conducted to identify pre-existing fractures. Post-baseline radiographs through Week 48 at locations predetermined by the skeletal survey as areas of identified lesion(s) were compared with Baseline radiographs using a predefined list of abnormalities by 2 trained central readers (and 1 adjudicator as needed) who were blinded to treatment assignment. Existing baseline active pseudofractures and fractures were graded as either unchanged, partially healed, healed, or worse, and new findings also were recorded.[7] Assessment is described in the CSR p. 174-175 and also detailed further in response A7. A limitation of the fracture assessment is that only fractures identified in the skeletal survey were systematically followed up. The focus of these exploratory analyses was on healing of fractures identified at baseline, rather than fracture incidence, although new fractures were reported if identified.
BUR02	Fracture incidence was not systematically assessed as fractures were not an endpoint. New fractures were reported as adverse events if they occurred. Javaid et al. 2023 reported on long-term safety and stated that no fractures or pseudofractures were reported as AEs during the study.[8]
CL304	The methodology of fracture assessment were similar to those in CL303. During the 48-week long Open-Label Treatment Period, targeted radiography at locations identified by the skeletal survey were taken at Weeks 12, 24, 36, and 48 to monitor frequency and healing of pseudofractures and/or fractures. During the Treatment Extension Periods, targeted radiographs were taken only at clinic visits following newly diagnosed fractures.[9]

A4. *Please supply a summary of the randomisation procedures for the CL303 trial, including details on how allocation concealment was achieved and how patients, physicians and outcome assessors were blinded to the treatment they received.*

Randomisation

Subjects were enrolled in the study and sequentially assigned an identification number. Subjects were randomised via an Interactive Web Randomisation System (IWRS) and assigned in a 1:1 ratio to the burosumab or placebo treatment groups.[7]

Randomisation was stratified by pain intensity and geographic region. As per the protocol, the pain intensity randomisation stratification was to be based on the mean Brief Pain Inventory (BPI) Question 3, Worst Pain, recorded for the 7 days prior to the Baseline Visit (> 6.0 or ≤ 6.0); however, due to an error in the IWRS, BPI Question 5, Average Pain, was instead used for the randomisation stratification. BPI worst pain score was highly correlated with the average pain score and had minimal impact on the study results.[7]

Randomisation was also stratified by region: North America/European Union (EU), Japan, and South Korea. Stratification by region was not specified in the protocol but was conducted for operational and logistic considerations to ensure balance between the 2 treatment groups, as small numbers of subjects were expected to be enrolled in Japan and South Korea.[7]

Blinding

Double-blind conditions were established so that neither the Sponsor, subject, or site personnel involved in study conduct would know the identity of a subject's treatment. Study parameters to achieve and maintain the double-blind status of the study included:

- Sequential assignment of subject numbers
- Study and site personnel received no knowledge of initial treatment assignment (randomization code was issued) unless unblinding was required for safety reasons
- Management of subject treatment assignment via an IWRS
- Labelling of study drug with the study number and a unique kit number

- Packaging and delivery of study drug supplies to sites in a manner that maintained blinding of site personnel
- Matched appearance of burosumab and placebo
- Central laboratory used for all post-baseline serum and urine parameters; site and sponsor personnel were blinded to key laboratory values associated with expected changes from burosumab treatment during the Placebo-controlled Treatment Period
- Radiographs, ECHOs, renal ultrasounds, and ECGs were centrally read by individuals blinded to treatment assignment and subject data.[7]

During the Placebo-controlled Treatment Period, treatment assignment could be unblinded if serum phosphorus levels exceeded the upper limit normal (ULN). Otherwise, treatment assignment for an individual subject was unblinded by the investigator only in an emergency, and only if knowledge of the treatment assignment was urgently needed for the clinical management or welfare of the subject. In the case of unblinding, the investigator recorded the date and reason for revealing the blinded treatment assignment for that subject in the source documents.

Treatment assignment could be unblinded by the sponsor to satisfy expedited safety reporting requirements of regulatory authorities. The system to unblind a treatment assignment was maintained and executed through an IWRS. The primary analysis of the study occurred after all subjects completed their Week 24 Visit. Selected sponsor personnel were unblinded to treatment assignments to conduct this analysis. After their Week 24 Visit, all subjects received burosumab treatment. Subjects and investigators remained blinded to original double-blind treatment assignments until the Week 48 analysis was completed.

A5. *Section 9.2 of the CL303 clinical study report states that 64.7% of participants in the Burosumab arm and 59.1% in the placebo arm had a major protocol deviation.*

a) Please provide further details on the nature of these protocol deviations, specifically those categorized as 'Procedure Not Done', 'Study Inclusion or Exclusion Criteria', 'Receipt of Prohibited Concomitant Medications', and 'Other'

and comment on how these may impact the reliability of the reported results between the different arms.

b) *If possible, please provide the following appendices from the trial CSR: 16.1.1 Protocol and protocol amendments; 16.2.2 Protocol deviations.*

Part a) Details of protocol deviations categorised as ‘Procedure Not Done’, ‘Study Inclusion or Exclusion Criteria’, ‘Receipt of Prohibited Concomitant Medications’, and ‘Other’ along with the number of protocol deviations occurring in the KRN23 arm and Placebo arm are summarised in the table below.

Some of the deviations could affect the evaluation of safety and/or efficacy but the impact on the reliability of the reported results is expected to be very small since the number of any deviations does not differ significantly in the different groups.

Table 2 Details of protocol deviations

Part b): The requested appendices are supplied with this document.

A6. *Javaid et al. (Journal of Clinical Endocrinology & Metabolism, 2022) indicates that 7 subjects out of 134 randomised in CL303 had previous burosumab use.*

a) *Please provide further details, including when and in what context these subjects received burosumab prior to enrolment.*

b) *Please clarify how many participants in each arm had prior burosumab exposure.*

c) *Please provide results of analyses exploring the potential impact of including/excluding participants with prior burosumab exposure, and comment on the implications for the reliability of the trial results.*

Part a): These 7 patients had been exposed to burosumab previously in another clinical study [redacted] The analysis of prior therapies reported in the CSR did not include previous use of burosumab in another clinical study, which was permitted among subjects who enrolled CL303 [CSR p.126].[7]

Part b): [redacted] patients in the burosumab arm and [redacted] patients in the placebo arm had prior burosumab exposure.

Part c): The data required for the requested analyses are not available at this time. Any impact on trial results of allowing patients with previous burosumab exposure is likely to be minimal, as only 7 of 134 patients (5.2%) had prior exposure. Kamenicky et al.[10] reported that the benefits of burosumab on phosphate normalisation, patient-reported outcomes and ambulatory function appear to be lost if treatment is interrupted but return when treatment is reinstated (see below and Figure 1). This suggests that patients with prior burosumab exposure would be unlikely to retain a treatment effect for a long period after discontinuation, and would therefore not have brought benefits from previous treatment into CL303. However, data on the interval

since discontinuing prior burosumab before enrolling in CL303 for the affected patients are not available.

Kamenicky et al. 2023 reported a post hoc analysis exploring the impact of discontinuing burosumab when transitioning from the end of the CL303 study (at Week 96) to the 48-week open label extension study (BUR02).[10] Some (n=23) received compassionate burosumab treatment between the two studies (a period of 6–18 months), whereas 7 did not (five were under the care of sites that did not participate in the programme, one was taking a treatment break during pregnancy and one declined treatment because they lived too far from the research site). These participants were without treatment for 8-15 months.

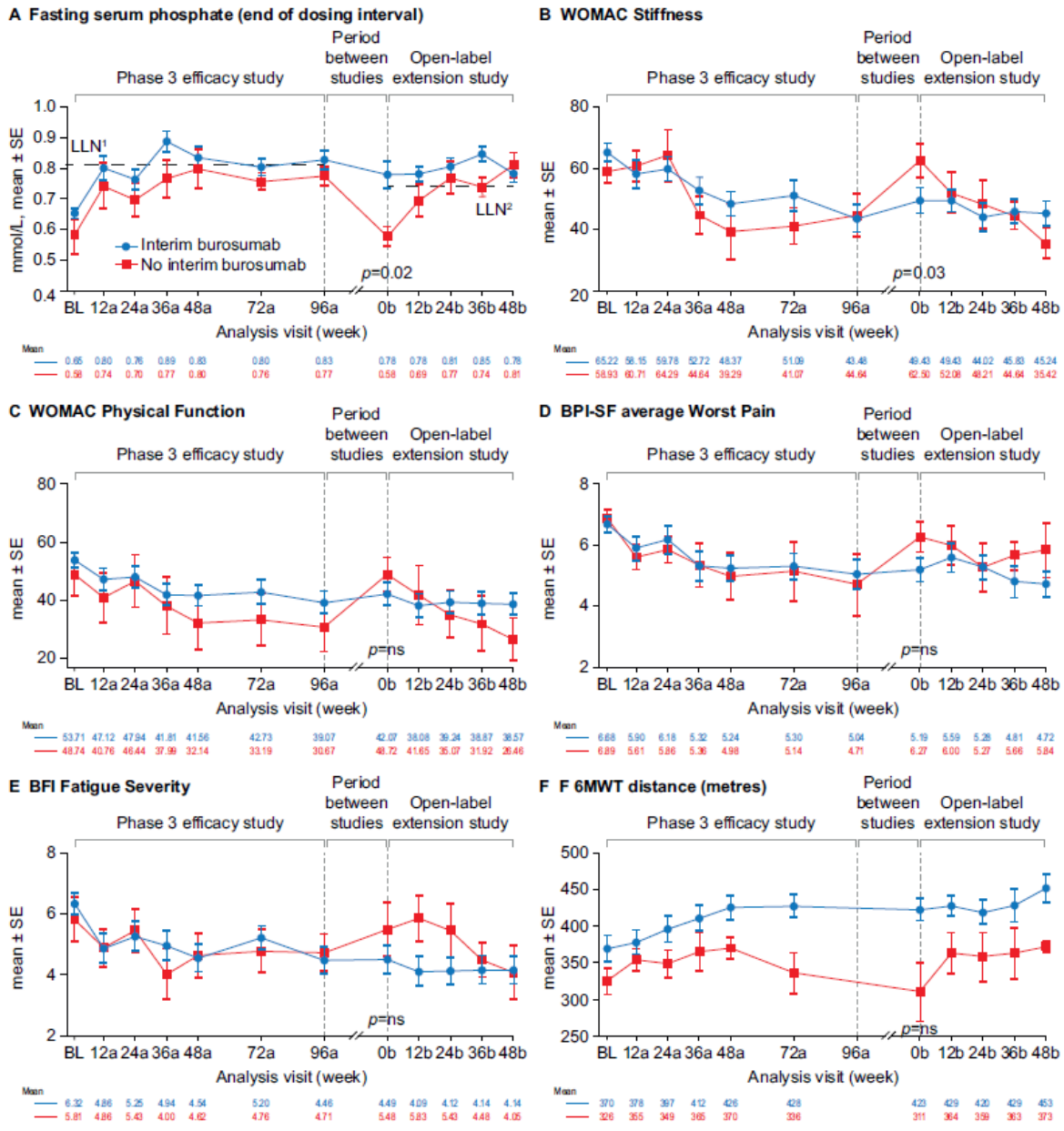


Figure 1 Effect of burosumab treatment interruption on serum phosphate, PROs and 6MWT. (Legend on following page)

Interim burosumab, n=23; no interim burosumab, n=7. Analysis weeks in the phase 3 study and open-label extension are indicated by 'a' and 'b' suffixes, respectively. A decrease in scores indicates improvement on the WOMAC, BPI-SF and BFI. An increase in distance on the 6MWT indicates improvement. BPI-SF and BFI data were captured at a single site visit and were not completed as part of a patient diary at weeks 72a and 96a. Fasting serum phosphate p values are for the difference between the groups (end of dosing cycle) at week 0b (tested using Fisher's exact test); 52% of the interim burosumab group but none of no interim burosumab group had values ≥LLN at the start of the open-label extension period (p=0.01; Fisher's exact test). PROs and 6MWT (tested using the Mann-Whitney U test) $p<0.05$ was considered significant. There was no significant difference between the groups at study baseline. Serum phosphate samples from the two studies were measured at different central laboratories, with different LLN values: 0.81 mmol/L in the phase 3 study (LLN1) and 0.74 mmol/L in the open-label extension (LLN2). BFI, Brief Fatigue Inventory; BL, baseline; BPI-SF, Brief Pain Inventory short-form; LLN, lower limit of normal range; 6MWT, 6-Minute Walk Test; PRO, patient-reported outcome; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Source: Kamenicky et al. 2023.[10]

A7. *Please clarify whether any other imaging techniques were used to assess fractures at baseline and during the first 24 weeks of follow-up (e.g. scintigraphy).*

a) If yes, please provide details (including imaging methods, blinding methods, and numbers of participants/fractures assessed, and timing of assessment).

b) Please comment on the potential risk of bias associated with the accuracy of X-rays compared with more advanced techniques (e.g. scintigraphy) for detecting and monitoring fractures and pseudo-fractures.

Part a): Only radiography was used to assess fractures during study CL303; neither scintigraphy nor any other imaging techniques were used. As reported in the CSR, a radiographic skeletal survey was conducted at the Baseline Visit to allow for determination of subsequent healing or resolution of current pseudofractures and fractures and progression of enthesopathy, and also to identify the number of pre-existing pseudofractures/fractures. Standard radiographs were obtained of the chest, lateral spine, right and left hand/wrist, right and left humerus, right and left radius/ulna, right and left femur/pelvis, right and left tibia/fibula, and right and left foot.

- Targeted radiography at locations predetermined by the skeletal survey as areas of identified active pseudofractures or fractures was performed starting at Weeks 12 and 24 to monitor frequency and healing of pseudofractures and/or fractures. Post-baseline radiographs were compared with Baseline radiographs using a predefined list of abnormalities by a trained central reader who was blinded to treatment assignment.
- Lateral foot x-rays (bilateral) were obtained in all subjects at Baseline (as part of skeletal survey) and at Weeks 24. Size of enthesopathy spurs at both the superior and inferior calcaneus were measured in 2 dimensions.

Part b) The use of X-rays rather than scintigraphy for detecting and monitoring fractures and pseudofractures in adults with XLH is in line with clinical practice in the NHS. Patients would not be routinely offered scintigraphy or other advanced imaging. Scintigraphy is highly sensitive for detecting bone lesions such as pseudofractures, but it is not known what proportion of the lesions detected are clinically relevant (i.e. affect the patient's health state). Clinical expert advice received by Kyowa Kirin indicates that "it is expected that scintigraphy will be more sensitive than X-ray to detect incident fractures, however even when there is cortical union with radiographic healing there is likely to be some uptake on scintigraphy, and so scintigraphy is less sensitive for healing. These differences also depend on the site and duration of fracture. For incident long bone fractures, the time gap between scintographic positive and radiology negative is likely to be a small proportion of all incident cases. Most will develop a periosteal reaction, sclerosis and a fracture line within weeks/ months."

It is possible that clinically relevant pseudofractures were not detected by the use of radiography in the trial. However, such pseudofractures would be associated with pain and functional impairment. Pain scores in the trial, measured through both BPI and WOMAC instruments, improved in patients receiving burosumab, both versus placebo and in the open label extension period, where pain improved over time.

- At Week 24, patients had statistically significant improvements from baseline in WOMAC stiffness, BPI worst pain (average and greatest), BPI pain interference, and BFI worst fatigue (average and greatest), compared with placebo.[11]

- At Week 48, statistically significant improvements from baseline were maintained for all WOMAC and BPI-SF scores.[12]
- At Week 96, statistically significant improvements from baseline were maintained for all patient-reported outcome measures.[12]

Thus, while some pseudofractures (both new and existing) may have gone undetected, the improvements in pain and functionality seen with burosumab are likely to reflect a beneficial effect on clinically relevant pseudofractures, among other effects.

CL303 participant characteristics and results

A8. Priority question: CS Document B, Table 15 shows differences between study arms in baseline characteristics (e.g. BPI worst pain >6.0, opioid use, WOMAC and nephrocalcinosis scores, osteoarthritis and pseudofractures)

a) Please supply analyses of differences between arms at baseline, with statistical significance measures, for each variable listed in Table 15.

b) Please also provide numbers within each arm and test results for baseline imbalance for the following variables:

i. numbers unsuitable for conventional phosphate therapy at baseline;
ii. numbers with no record of phosphate supplement (with reasons);
iii. numbers with serum phosphate levels above LLN at baseline.

c) Please provide an explanation for why these differences may have arisen, and their implications for the quality of randomisation in the trial.

It is acknowledged that there was variability in the baseline characteristics of patients in CL303. To address the question of whether variation in clinically relevant characteristics affects outcomes, Brandi et al. published a post hoc subgroup analysis of the Week 24 outcomes.[13] The baseline variables considered were BPI-SF scores (worst pain, average pain), region (Asia or North America & Europe), sex, race group, age group, WOMAC scores (stiffness, physical function, pain and total), pain medication use, opioid use, active fractures or pseudofractures, and 6-minute walk test distance. The analysis showed that burosumab was largely superior to placebo in the primary, key secondary, and additional efficacy endpoints in these 14

clinically relevant subgroup variables at week 24. Forest plots are given in the paper and its supplement, which are supplied with this document.

Part a) The requested analyses are given in Table 3. All differences are non-significant except for a numerically small difference in baseline serum phosphate, which is slightly higher in the burosumab arm.

Table 3 Demographic and baseline characteristics, CL303

Demographics	Placebo (N=66)	Burosumab (N=68)	Total (N=134)	P-val[g]
Age(Years)				
Mean±SD				
Range				
Female, n(%)				
Race, n(%)				
Asian				
Black or African American				
White				
Other				
Region, n(%)				
North America/EU				
Japan				
South Korea				
Height[a], mean±SD				
Centimetres				
Z-score[b]				
Percentile				
BMI[a] (kg/m), mean±SD				

Demographics	Placebo (N=66)	Burosumab (N=68)	Total (N=134)	P-val[g]
Genetic Status				
PHEX Mutation n(%)				
Pathogenic Mutation				
Likely Pathogenic				
Variant of Uncertain Significance				
No Mutation				
Laboratory measurement				
Serum phosphate (mg/dL)[c], mean±SD				
TmP/GFR (mg/dL)[c], mean ± SD				
Serum 1,25(OH)2D (pg/mL)[c], mean ± SD				
Serum calcium (mg/dL)[c], mean ± SD				
Serum iPTH (pg/mL)[c], mean ± SD				
Genetic Status				
PHEX Mutation n(%)				
Pathogenic Mutation				
Likely Pathogenic				
Variant of Uncertain Significance				
No Mutation				
Laboratory measurement				
Serum phosphate (mg/dL)[c], mean±SD				
TmP/GFR (mg/dL)[c], mean ± SD				

Demographics	Placebo (N=66)	Burosumab (N=68)	Total (N=134)	P-val[g]
Serum 1,25(OH)2D (pg/mL)[c], mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Serum calcium (mg/dL)[c], mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Serum iPTH (pg/mL)[c], mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Conventional therapy ever, n(%)				[redacted]
Phosphate only	[redacted]	[redacted]	[redacted]	
Vitamin D metabolites or analogs only	[redacted]	[redacted]	[redacted]	
Phosphate and Vitamin D metabolites or analogs	[redacted]	[redacted]	[redacted]	
No Phosphate/Vitamin D metabolites or analogs	[redacted]	[redacted]	[redacted]	
Conventional therapy before age 18 years, n(%)				[redacted]
Phosphate only	[redacted]	[redacted]	[redacted]	
Vitamin D metabolites or analogs only	[redacted]	[redacted]	[redacted]	
Phosphate and Vitamin D metabolites or analogs	[redacted]	[redacted]	[redacted]	
No Phosphate/Vitamin D metabolites or analogs	[redacted]	[redacted]	[redacted]	
Conventional therapy duration (years), mean±SD				
Phosphate[d]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D metabolites or analogues[e]	[redacted]	[redacted]	[redacted]	[redacted]
Pain scores and medication				

Demographics	Placebo (N=66)	Burosumab (N=68)	Total (N=134)	P-val[g]
BPI Worst Pain >6.0, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Any Pain Medication at Baseline, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Any Opioids at Baseline, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
XLH manifestations				
Enthesopathy on X-ray, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nephrocalcinosis score >0[f] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Medical history				
Orthopaedic surgery, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Fractures				
Unhealed fracture/pseudofracture at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of fractures/psuedofractures	[redacted]	[redacted]	[redacted]	
Fractures	[redacted]	[redacted]	[redacted]	
Psuedofractures	[redacted]	[redacted]	[redacted]	
Patients with serum phosphate levels above LLN at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

a:Height and BMI not recorded at baseline for one patient in each group. b:Z-score adjusted for sex. c:Normal ranges: phosphate, 2.5-4.5 mg/dL; 1,25(OH)2D, 18-72 pg/mL; calcium, 8.6-10.2 mg/dL; iPTH, 14-72 pg/mL; TmP/GFR, 2.5-4.2 mg/dL. d:Among patients with any prior use of phosphate (n = 62 burosumab, n = 63 placebo). e:Among patients with any prior use of vitamin D metabolites or analogues (n = 62 burosumab, n = 65 placebo). f:On a 5-point scale where 0 = normal and 4 = stone formation solitary focus of echoes at the tip of the pyramid BMI, body mass index; BPI, Brief Pain Inventory; iPTH, intact parathyroid hormone; SD, standard deviation; TmP/GFR, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate
g: P value for Difference between Burosumab and Placebo. Statistical analyses were performed using the chi-squared test, Student t-test

Part b) i. These data are not available; patients were not specifically classified as being suitable or unsuitable for conventional phosphate therapy at baseline. All patients in CL303 were required by the inclusion criteria to have pain of upper limit of mild pain or greater (BPI worst pain ≥4) at screening. Furthermore, patients had high levels of pain, stiffness, functional impairment and fatigue at baseline (see CS Document B Fig 18, p. 84). Thus, those patients in CL303 who were taking conventional therapy at baseline were highly symptomatic in spite of conventional therapy. Phosphate supplements were therefore an inadequate treatment for these patients, which is in line with the positioning of burosumab for the submission.

Part b) ii. [redacted] patients in the placebo arm and [redacted] in the burosumab arm (p=0.0844) had no record of prior conventional therapy 'ever' (Table 3). Reasons for why patients were not taking phosphate supplements at baseline or in their prior history were not reported. As noted in response A9b below, there are many reasons why some adults with XLH do not take phosphate supplements.

Part b) iii. The numbers of patients with serum phosphate >LLN at baseline were [redacted] in the placebo arm and [redacted] in the burosumab arm (p=0.5158; see Table 3). All patients had serum phosphate <LLN at screening in order to be eligible for inclusion. These numbers are very small and their impact on the trial results will therefore be minimal.

Part c): The trial was randomised, using accepted randomisation procedures as described in response A4. Therefore no systematic bias could have occurred in the allocation of patients with particular characteristics to a particular treatment arm.

A9. *CS Document B, Table 15 states that 93.3% of patients had prior phosphate treatment; however, Table 16 states that 110 patients had "no record of phosphate supplement".*

a) Please explain and comment on this apparent discrepancy.

b) Please comment or provide data on the reasons why patients were not receiving phosphate. For instance, were these patients unsuited to phosphate therapy, had stopped using it, or had they refused it, or not been offered it?

Part a) Document B Table 16 is a post-hoc analysis based on whether or not patients were taking phosphate immediately prior to the study, at screening (Screening Visit 1).[14] In contrast, Table 15 refers to whether patients have ever received phosphate therapy. Thus there is no discrepancy between the tables. Note that, as occurs in most clinical studies, not all patients at screening visit 1 went on to be randomised into the trial (N at this visit was 146, whereas the study N was 134).

Part b) Document B Table 16 shows that immediately prior to the study, [redacted] patients who participated in Screening Visit 1 were not taking phosphate therapy at that point. The reasons why they were not taking phosphate are not available. However, Table 15 shows that 93.3% of patients in the study reported phosphate treatment at some time in the past, and 74.6% had received it before age 18 years. Mean (SD) reported duration of phosphate therapy was 16.5 ± 10.4 years. There are many reasons why adults with XLH do not take phosphate therapy. There is limited evidence for the effectiveness of phosphate therapy in adults with XLH.[15] Phosphate supplements are frequently associated with gastro-intestinal discomfort, nausea and diarrhoea. Adherence can be low, due to difficulties in persevering with the regimen, leading to limited engagement with treatment and eventual treatment discontinuation.[16] Long-term treatment with phosphate supplements and decreased production of calcitriol due to excess FGF23 can cause hyperparathyroidism (excessive production of parathyroid hormone (PTH);[2,3] these toxicities are a contraindication to further treatment for some patients.

A10. *Document B, CS Table 15 shows that only 67.9% had pain medication at baseline. Please clarify what proportion of participants were on optimized and stable pain management at baseline.*

Stipulations for concomitant medications are described in the CSR Section 8.5.7. Pain medications (both prescription and over-the-counter) were permitted during the study. However, patients were required to be willing to maintain chronic pain medications at a stable dose(s) and schedule throughout the Placebo-controlled Treatment Period of the study, and any changes were recorded. Pain medication use was recorded by patients in a pain medication diary for 7 consecutive days before the Baseline and Weeks 12, 24, 36, and 48 study visits. There was no requirement

for pain medication to be ‘optimised’ at study start; rather, it was a continuation of patients’ usual medication.

The fact that approximately a third of patients were not reported to be using pain medication at baseline may reflect some patients’ reluctance to take life-long pain medication. All analgesics are associated with risks from long-term use.[17] Non-use of pain medication should not be interpreted as meaning that patients were not in pain: pain of at least the upper limit of mild pain (BPI ≥4) was required for trial entry, and table 15 shows that 71.6% of study patients had BPI worst pain >6 at baseline.

A11. Priority question: The CL303 trial included patients on standard therapies (Vitamin D or phosphate) provided they stopped prior to the washout period.

a) Please provide separate baseline characteristics for patients with and without standard therapies before the washout period (listing characteristics presented in Table 15 and numbers with serum phosphate levels above LLN) by treatment arm.

b) Please provide separate subgroup analyses for patients with and without standard therapies before the washout period for the following trial endpoints: WOMAC total score, BPI score, BFI score, 6MWT distance, fracture healing.

c) Please comment on how the inclusion of treated patients (and the lack of stratification by phosphate/vitamin D treatment prior to the washout period) may lead to bias for any of the trial endpoints.

Parts a) and b). Subgroup analyses for these patients could not be carried out within the time frame given; these will be supplied at a later date.

Part c) This was a randomised trial, so there would be no systematic bias in the distribution between arms of patients who were receiving phosphate therapy immediately before the washout period. Any suggestion of bias is not supported by the data. The placebo arm showed that key laboratory endpoints, WOMAC physical function and stiffness remained stable from 0 to 24 weeks on placebo, and pain from

12 to 24 weeks. This suggests a minimal effect, if any, of previous phosphate / vitamin D therapy on the trial endpoints. If previous treatments such as phosphate / vitamin D therapy did improve trial endpoints, then a progressive decline would have been expected on the placebo arm and this was not seen. This is especially relevant given that the great majority (all but 3 patients in the trial)

had had prior conventional therapy at some point. This clinical observation is supported by the relatively short half-life of both oral phosphate and vitamin D.

A12. Priority question: Please provide data on the number of participants who experienced a clinically meaningful improvement (with definitions) in each arm for the following variables at 24 weeks follow-up, along with appropriate measures of relative effectiveness, precision and statistical significance:

a) WOMAC total score, physical function, stiffness and pain scores

b) BPI score (average and Worst Pain, Pain Interference)

c) BFI score (Worst Fatigue, Global Fatigue)

d) 6-minute walk test (6MWT) distance

Some of this information (key secondary endpoints only) is available in the CSR (Section 10.2.5, reproduced below). The differences between arms in these analyses are not statistically significant. However, the extent of improvement in patient-reported outcomes with burosumab increases over time, as noted in Briot et al.[12], which provides analysis up to 96 weeks for all the requested scores and uses minimally important clinical difference (MCID) values validated in adults with XLH (see CS Document B, section 2.6.2, and Response A16). The 24-week analysis below should therefore be interpreted with caution. Some 48- and 96-week data are also available in the CSR and are given below. Although treatment was open label from Week 24, after which placebo subjects switched to active treatment, participants and investigators remained blinded to the initial treatment assignment until Week 48 to minimise potential bias.

Part a) In the responder analysis for WOMAC Physical Function score (CSR p.156):

- A decrease of ≥ 9.3 nu (the minimally important change) (Bellamy 2012[18]) from Baseline to Week 24 was reported by [redacted]% of subjects in the burosumab group and [redacted]% of subjects in the placebo group (p = 0.3566).

- At Week 48, the proportion of patients with showing a response above MCID (a decrease of ≥ 9.3 nu from baseline) increased to [redacted]% of subjects in the burosumab→burosumab group and [redacted]% in the placebo→burosumab group, reflecting the use of burosumab in both treatment groups between Week 24 and Week 48. At Week 96, a decrease of ≥ 9.3 nu from baseline was reported by [redacted]% of subjects in the Total Burosumab group, demonstrating a consistency in the trends over time.

In the responder analysis for WOMAC Stiffness score (CSR p. 157):

- A decrease of ≥ 10.0 nu (the minimally important change) from Baseline to Week 24 was reported by [redacted]% of subjects in the burosumab group, compared with [redacted]% in the placebo group (p = 0.2112).

- At Week 48, the proportion of patients with showing a response above MCID (a decrease of ≥ 10.0 nu) from baseline increased to [redacted]% of subjects in each treatment group, reflecting the use of burosumab in both treatment groups between Week 24 and Week 48. At Week 96, a decrease of ≥ 10.0 nu from baseline was reported by [redacted]% of subjects in the Total Burosumab group, again demonstrating a consistency in trends over time.

Part b) In the responder analyses for BPI Worst Pain score (CSR p.156):

- A ≥ 15% decrease, which represents a minimally important change (Dworkin et al. 2008[19]), from Baseline to Week 24 was reported by [redacted]% of subjects in the burosumab group and [redacted]% in the placebo group (p = 0.3564). A ≥ 30% decrease from baseline in Worst Pain score, which represents a moderately clinically meaningful change (Dworkin et al. 2008), from baseline to Week 24 was reported by [redacted]% of subjects in the burosumab group, compared with [redacted]% in the placebo group (p = 0.2858).

- At Week 48, the proportion of patients with showing a response above MCID (a ≥ 15% decrease from baseline) increased to [redacted]% of subjects in the burosumab→burosumab group and [redacted]% in the placebo→burosumab group, and a ≥ 30% decrease from baseline was reported by [redacted]% of subjects in the burosumab→burosumab group and [redacted]% in the placebo→burosumab group, reflecting the use of burosumab in both treatment groups between Week 24 and Week 48. At Week 96, a ≥ 15% decrease from baseline was reported by [redacted]% of subjects, and a ≥ 30% decrease by [redacted]% of subjects in the Total Burosumab group, again demonstrating a consistency in the trends over time.

Parts c) and d): Data on the number of patients experiencing a change deemed clinically meaningful (as opposed to whether or not the mean change reaches this level, which is reported by Briot et al.[12]), are not currently available except for those endpoints reported above, and would require further analysis. Some items might not be possible because there is only information on group-level meaningful change and not individual responder definitions for several of these measures.

A13. Priority question: Please provide numbers of all patients who were treated in European centres and results data for the Europe region for the following outcomes:

a) WOMAC total score, physical function, stiffness and pain scores

b) BPI score (average and Worst Pain, Pain Interference)

c) BFI score (Worst Fatigue, Global Fatigue)

d) 6MWT distance

For study CL303, separate analyses of patients treated in European centres are not available at this time, only North America and Europe combined. No systemic differences in PRO outcomes between European and North American patients would be expected; furthermore, the European cohort is made up of patients from four different countries (France, UK, Ireland and Italy), so cultural and other differences within the European group are just as likely as differences between North American (i.e. US) and European patients.

Data for European patients only are available from the open-label extension study, BUR02, which was made up of European participants from CL303 after completion of the 96-week study period. Kamenicky et al. compared baseline characteristics between the BUR02 population and the CL303 population and found no significant differences in age, sex or BPI-SF worst pain scores.[10] This table is reproduced below. These results for these patients are shown in the CS Document B, Section 2.6.2 to 2.6.4.

It should be noted that 87.9% of patients in the placebo group and 85.3% in the burosumab group were in the North America and Europe region. A comprehensive set of subanalyses at Week 24 was published by Brandi et al. 2022,[13] including by region. Brandi et al. note that in the Region analyses, results for North America and Europe favoured burosumab, whereas results for Asia favoured placebo for some outcomes, including BPI-SF Worst Pain and WOMAC Physical Function. They suggested that this may reflect cross-cultural differences, even though approved linguistically validated versions of the PRO instruments were used. For forest plots of the analyses for each endpoint please refer to the Brandi paper and its supplementary material, which are re-supplied with this document.

Table 4 Comparison of baseline characteristics between the overall CL303 population and the European patients in the BUR02 population

Table 1 Demographics and characteristics at baseline in the phase 3 study for the whole study population and the subset who continued into the open-label extension

	Phase 3 study population (n=134)	Open-label extension study population (n=31)
Age (years)*	40.0 (12.2)	40.1 (12.1)
Range	18.5–65.5	18.5–59.9
Female, n (%)*	87 (64.9)	21 (67.7)
Height		
Centimetres	152 (10.7)	154.4 (13.0)
Z-score†	–2.3 (1.3)	–2.0 (1.3)
Percentile	6.8 (12.5)	10.3 (13.6)
Body mass index (kg/m^2)	30.3 (7.6)	27.7 (5.5)
PHEX gene variation		
Pathogenic	95 (70.9)	27 (87.1)
Likely pathogenic	15 (11.2)	1 (3.2)
Significance uncertain	17 (12.7)	2 (6.5)
None	7 (5.2)	1 (3.2)
BPI-SF worst pain score*	6.7 (1.4)	6.7 (1.2)
Any pain medication at baseline	91 (67.9)	25 (80.6)
Any opioid at baseline	30 (22.4)	8 (25.8)
Enthesopathy on radiograph	133 (99.3)	31 (100)
Nephrocalcinosis score >0	73 (54.5)	17 (54.8)
Medical history		
Orthopaedic surgery	92 (68.7)	20 (64.5)
Osteoarthritis	85 (63.4)	20 (64.5)

Data are mean and SD or n (%).
*Not significantly different between the phase 3 and open-label extension study populations (p>0.05).
†Z-score adjusted for sex.
BPI-SF, Brief Pain Inventory short-form.

A14. *Please clarify whether fracture and pseudofracture healing follow-up data at 24 weeks from baseline was available for all patients with active fracture/pseudofracture*

at baseline. If not please supply numbers of missing values per arm (by patient and by fracture/pseudofracture).

The table below shows the missing data for fractures and pseudofractures at Week 24 in the primary analysis set (CSR Table 30).

Table 5 Number of Active Fractures and Pseudofractures Healed Over Time (Primary Analysis Set)

Source: CL303 CSR

BUR002 trial

A15. *Javaid et al. 2022 reports that 47 of the 127 CL303 participants with no prior burosumab exposure were from Europe. We understand that study BUR002, which was a follow-up study which only included trial CL303 participants from Europe, only screened 34 patients.*

a) Please clarify the flow of all patients from CL303 to the end of the follow-up of study BUR002, supported by a CONSORT type diagram including reasons for exclusion/discontinuation as appropriate;

b) please comment on whether the exclusion from BUR02 of patients originally treated in CL303 European Centres may have introduced bias, and if so, the potential direction and magnitude of that bias.

Part a) [redacted] European patients who began CL303 did not enrol in BUR02. Of these, [redacted] patients discontinued during CL303 for reason of withdrawal of consent, and

[redacted] did not enter screening for BUR02 for other reasons (reasons not available). Information on screening and enrolment in BUR02 is available as a table in the BUR02 CSR, Section 10.1, reproduced below (Table 6).

Part b) Table 6 below shows that all European CL303 patients screened for BUR02 were enrolled, so no patients who completed CL303 were actively excluded. However, not all patients completed the 96 weeks of CL303: 119 patients (88.8%) completed the treatment extension period (48–96 weeks).[12] A protocol amendment later allowed patients who did not complete CL303 to be enrolled in BUR02 on a case-by-case basis; no applications for enrolment in these patients were declined, and enrolment was not dependent on response to treatment during CL303. The introduction of bias from the absence of the 6 CL303 patients who completed the study but did not enter screening for BUR02 (for reasons not available) cannot be ruled out, but any bias would be minor. Reasons for not enrolling can include causes such as unwillingness to continue travelling to the study centre, or plans to start a family, and are not necessarily medically related.

Table 6 Patient disposition in BUR02 by therapy received in previous study and all

[redacted]

Table continues overleaf

Source: BUR02 CSR[20]

A16. Priority question: Please provide data on the number of participants who experienced a clinically meaningful improvement (with definitions) for the following variables at the end of the open-label extension period, along with appropriate measures of relative effectiveness, precision and statistical significance:

a) WOMAC total score, physical function, stiffness and pain scores

b) BPI score (average and Worst Pain, Pain Interference)

c) BFI score (Worst Fatigue, Global Fatigue)

d) 6MWT distance

Please refer to response A12.

Safety evidence

A17. Priority question: Please supply a complete tabulation of all types of adverse events that occurred in trial CL303 (i.e. by system organ class and preferred term for serious and non-serious adverse events). Please provide this data by treatment arm, and for both the double-blind and unblinded periods of the trial.

This information is available in the CSR Section 12.2 and is reproduced here. Details of severity are given in summary only; severity gradings for individual adverse events are available in CSR Table 14.3.1.6 (double-blind period).

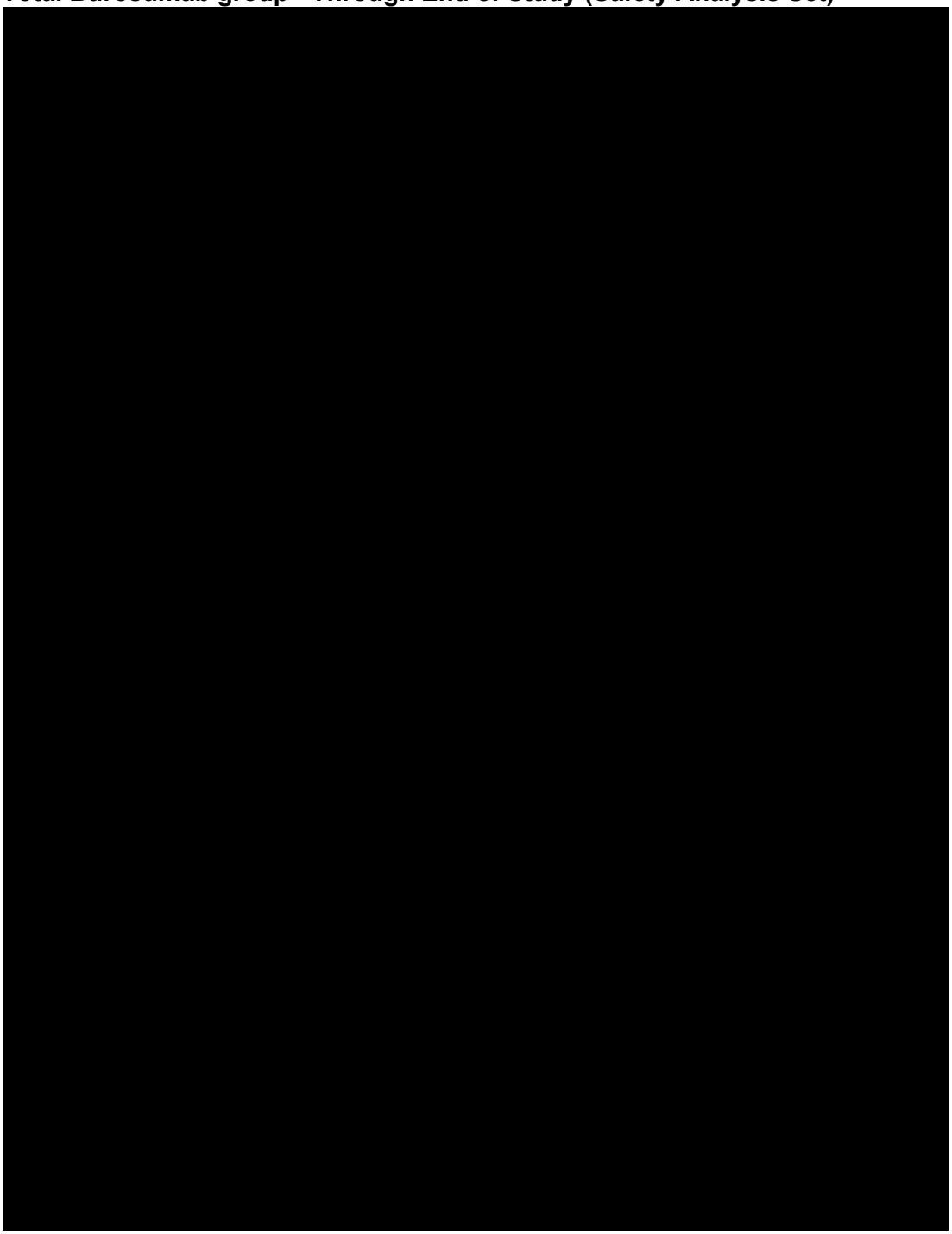
Table 7 Treatment-Emergent Adverse Events Reported for ≥ 5% Subjects in Either Treatment Group -- Placebo-controlled Treatment Period (Safety Analysis Set)

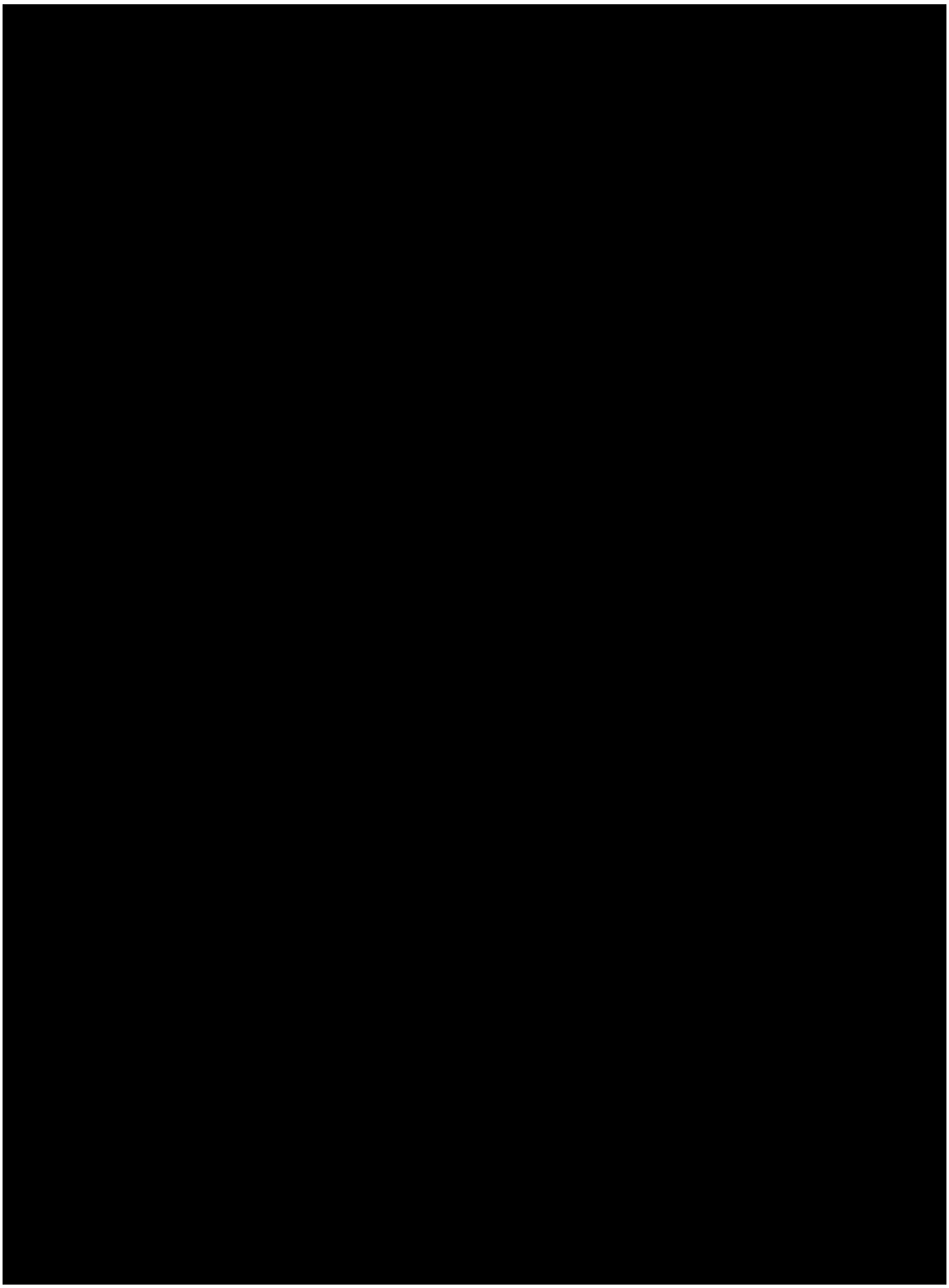
Source: CSR

Table 8 Summary of Treatment-Emergent Adverse Events by severity - Double-Blind Period Safety Analysis Set

Source: CSR.

Table 9 Treatment-Emergent Adverse Events Reported for ≥ 5% Subjects in the Total Burosumab group - Through End of Study (Safety Analysis Set)





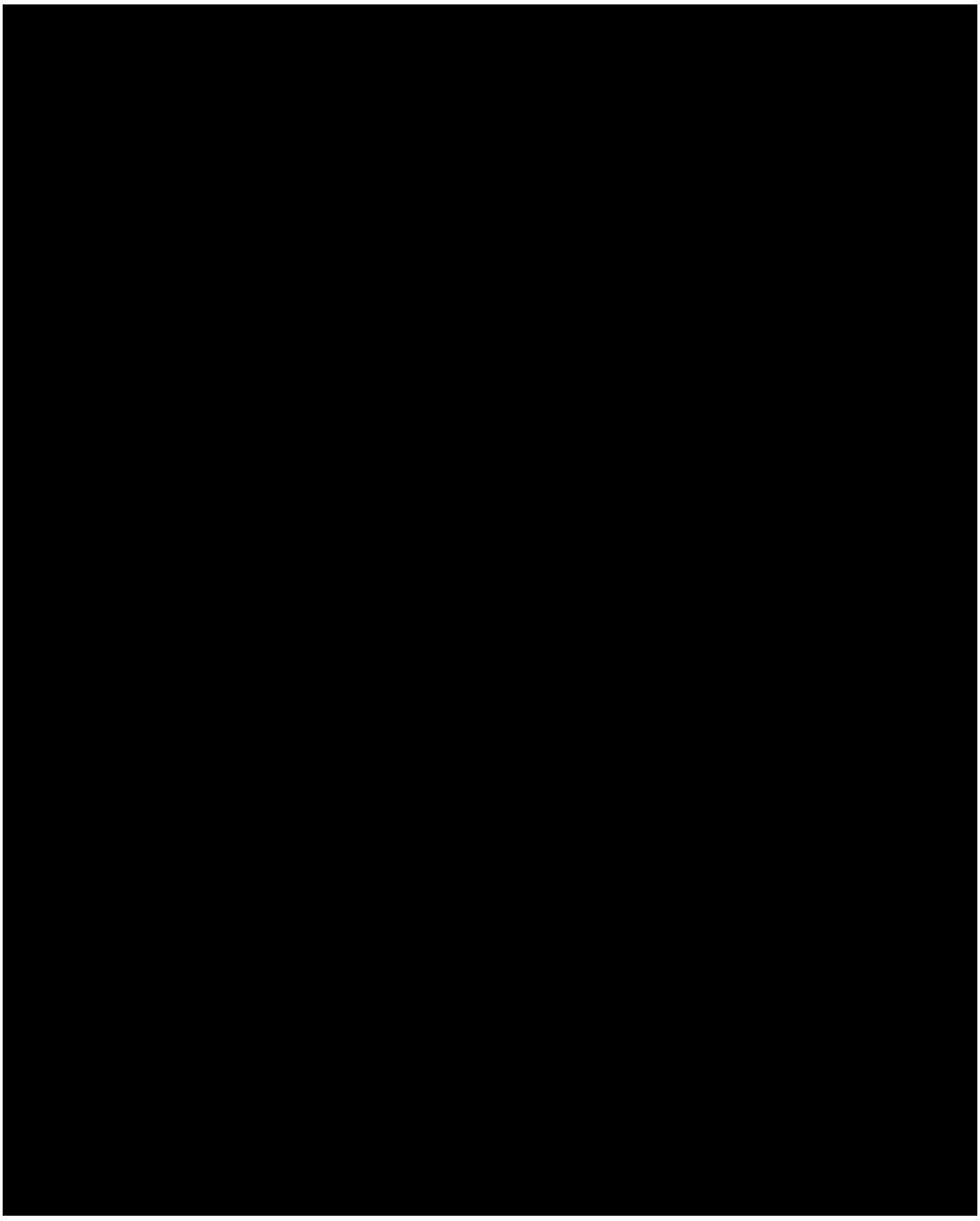
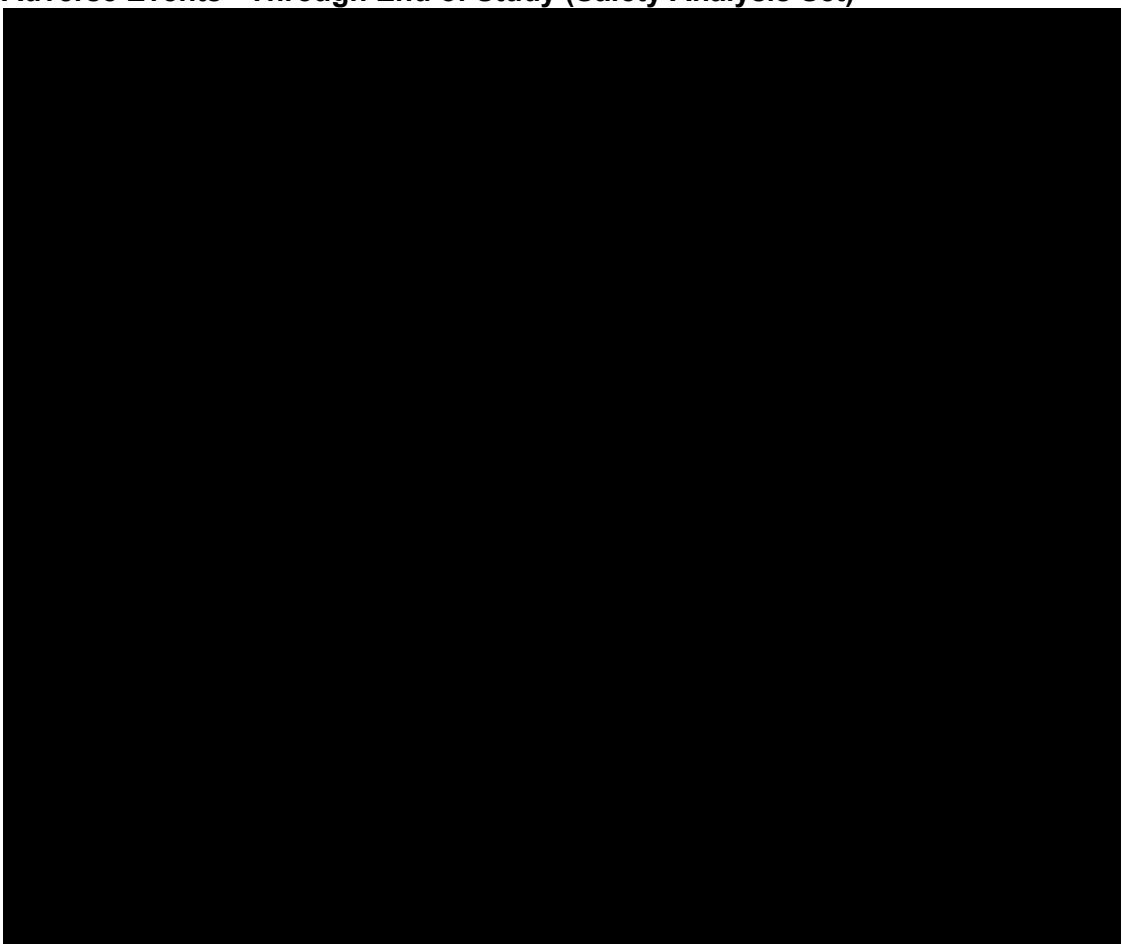


Table 10 Summary of Treatment-Emergent Adverse Events or Burosumab-Emergent Adverse Events - Through End of Study (Safety Analysis Set)



Source: CSR

A18. *The Periodic Safety Report (PSR) from 12 April 2022 submitted by the company states that: Cumulatively, from 03 October 2008 to 18 February 2022, a total of 376 XLH subjects (adults and children) and 30 TIO patients have received burosumab in interventional clinical studies, and that cumulatively, until 31 January 2022, a total of 4,395 patients with XLH or TIO have been exposed to burosumab through the commercially sold product or in EAP. Please provide data on the incidence of fractures in adults XLH whilst receiving burosumab during this period.*

In response to this question a search in the Global Safety Database was conducted for the cases with reported events under the MedDRA High Level Terms (HLT) 'Fractures and dislocations NEC' and 'Fractures NEC'. There were [redacted] cases in adults with XLH of events belonging to the above HLT. Upon review of the [redacted] cases, [redacted] cases reported terms relevant for the event of fractures. The reported terms were Fracture, Stress fracture, Pseudofracture, Pathological fracture, Bone fragmentation, Jaw fracture, and Osteophyte fracture. Distribution is shown in Table 11.

The information reported in these cases is limited, with medical history not reported in the majority of the cases. It is not possible to ascertain if the fractures have appeared after initiation of burosumab, as there is no information reported about the bone health at baseline. The temporal association between administration of burosumab and the appearance of fractures is not reported in the majority of the cases. Some cases reported fall and road accidents as cause for the fractures, while other cases reported fractures as events that in the opinion of the reporter did not worsen, however without the information on start date.

Table 11 Fractures, global safety database

PT Term	Case Numbers
Fracture	[redacted]
Stress fracture	[redacted]
Pseudofracture	[redacted]
Pathological fracture	[redacted]
Bone fragmentation	[redacted]
Jaw fracture	[redacted]
Osteophyte fracture	[redacted]
Total	[redacted]

Early Access Programme

A19. Priority question: We understand that some data from the Early Access Programme is available. Please provide the most up to date baseline characteristics of the UK EAP population, including, where possible for the variables listed in Document B, Table 15, as well as:

a) numbers unsuitable for conventional phosphate therapy at baseline

b) numbers with no record of phosphate supplement (with reasons)

c) numbers with serum phosphate levels above LLN at baseline

As noted in CS Document B p. 104, the burosumab Early Access Programme (EAP) in England currently includes [redacted] (as of April 2023) who have received burosumab via this free of charge route. Data from all participants enrolled in the

EAP will be considered for inclusion in a multicentre, single-arm retrospective real-world data collection capturing deidentified data from adults with XLH being treated with burosumab in routine clinical practice.[21] Data collection is under way, but data from the whole UK EAP population are not yet available to Kyowa Kirin and are not expected to be available within the timeframe of the submission. However, researchers at one centre, UCLH, have made their data available for the submission. Only data from UCLH are presented in the submission.

Part a): this information was not collected

Part b): this information was not collected.

Part c): In CL303, LLN was defined as 2.5 mg/dL (0.81 mmol/L).[7] The UCLH EAP centre reports that [redacted] of patients had serum phosphate above 0.7 mmol/L at baseline. Note that in the EAP, each centre uses their own laboratory's range of normal, and "normal" lab ranges differ from site to site. This information is therefore not available.

Section B: Clarification on cost-effectiveness data

Economic model

B1. Priority Question: The submitted model is not sufficiently flexible to allow patient weight (used to inform burosumab dosing) to vary over time within each discrete age band at which patients start treatment, i.e., as patients age in the model, their weight is not permitted to change over time as they leave the age band at which they started treatment. Please consider providing a revised version of the model that permits patient weight to vary with age over time.

We have undertaken an analysis assessing the impact of age on weight of patients included in CL303. There is significant variability in weight between patients, but age was not shown to be a statistically significant predictor of weight (please see Figure and Table below). Therefore inclusion of the requested functionality is unlikely to impact the conclusions of the analysis.

Figure 2 CL303 participants' age and weight at baseline

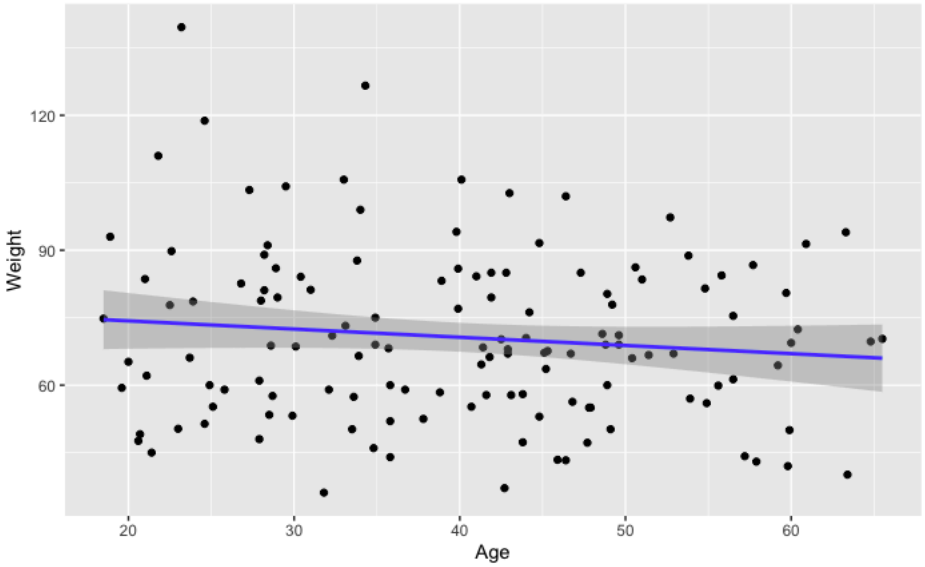


Table 12 Linear regression coefficients to predict patient weight in CL303

	Estimate	SE	t value	p
Intercept	77.9394	5.5922	13.937	<0.0001
Age	-0.1822	0.1338	-1.362	0.176

Published cost-effectiveness studies

B2. *Please clarify why the cost-effectiveness studies of burosumab for the treatment of XLH in adults included in the CADTH Common Drug Review Report (available online here) and the Scottish Medicine Consortium Assessment Report (available online here) were not identified in the literature review.*

Our systematic literature review identified literature from peer-reviewed literature (via MEDLINE, MEDLINE In-Process, Embase, DARE, NHS EED, EconLit, the Cochrane Library and INEHTA); this was supplemented by grey literature searches of conference proceedings. Our grey literature search did not extend to HTA reports. Both the CADTH and SMC models are only available via the respective institutional websites and were therefore not captured as part of the pre-specified systematic literature review methodology.

B3. Please provide a summary of the previous cost-effectiveness models used to evaluate burosumab for the treatment of XLH in an adult population, noting any differences in the evidence and assumptions used in these models compared to the de novo model used in the company submission, and provide justification for the difference.

The submitted model is similar in concept to the CADTH adult model and the model used by SMC in that it models fracture rates and utility benefit associated with treatment based on WOMAC data from CL303 and a reduction in mortality rates. The model submitted to NICE (NICE Model) and the one submitted to SMC use the same structure and assumptions, with the exception of handling of conventional therapy. The NICE and SMC models incorporate more detailed modelling of fracture rates for individual fracture types and utility change over time than the model submitted to CADTH. The NICE and SMC models distinguish between fracture location whereas the CADTH model did not. This was done as the incidence, cost and utility impacts of fractures vary by site.

The NICE and SMC models consider a general excess mortality risk associated with XLH, whereas the CADTH model includes an excess mortality risk associated with fractures. The NICE and SMC models include a general mortality risk as it is likely that the physiological insult of chronic hypophosphatemia due to XLH can increase mortality through a number of pathways, not just fracture risk. The NICE and SMC models do not include the excess mortality risk associated with fractures to avoid double counting. The NICE and SMC models include longer term data on WOMAC scores, and hence utility benefit, as there is evidence that the full benefit of burosumab develops over an extended time period. The NICE and SMC models also considered other morbidities beside fractures as XLH is associated with a range of morbidities.

Both CADTH and SMC models included conventional therapy as comparators for a proportion of the population, but the efficacy estimates of the comparator arms were informed directly by the results of the placebo arm of the CL303 trial. Both authorities commented on the uncertainty of comparative effectiveness estimates if burosumab is compared to (a proportion of patients using) conventional therapy as in their view it remains unclear whether patients on conventional therapy would respond similarly to those in the placebo arm of the trial. The current positioning of burosumab is more in line with clinical recommendations and allows use of the CL303 trial data directly. A comparison of the models is shown in Table 13 below.

Table 13 Comparison of CADTH, SMC and NICE models

Feature	CADTH model	SMC model	NICE model	Justification for difference
Population	≥18 years old with XLH	≥18 years old with a confirmed diagnosis of XLH, persistent and debilitating symptoms	≥18 years old with a confirmed diagnosis of XLH, symptomatic after insufficient response, complications/intolerance or contraindication to conventional therapy	Updated positioning based on UK clinical guidance

Intervention	0.96 mg/kg, 0.94 mg/kg, 0.90 mg/kg of burosumab for first, second and subsequent doses	1 mg/kg burosumab with dose reduction for 6% of population	1 mg/kg burosumab with dose reduction for 6% of population	N/A
Comparator	Standard of care (SoC) of conventional therapy (oral phosphate, active vitamin D, calcimimetic) or no treatments	Standard of care (SoC) of conventional therapy (oral phosphate and active vitamin D) or no treatments	Best supportive care (no treatments)	Positioning based on UK clinical guidance
Mortality benefit	Reduction in fracture-related mortality above age 50	Reduction in excess mortality associated with XLH	Reduction in excess mortality associated with XLH	Hawley et al., 2020 provided evidence of excess mortality associated with XLH
Utility benefit	Based on CL303 (WOMAC mapped to EQ-5D) and fracture disutility	Based on CL303 and BUR02 (WOMAC mapped to EQ-5D) and fracture disutility	Based on CL303 and BUR02 (WOMAC mapped to EQ-5D) and fracture disutility	Longer-term follow-up available from BUR02
Morbidity benefit	Reduction in fracture rates	Reduction in fracture rates (and other morbidities in scenario analysis)	Reduction in fracture rates (and other morbidities in scenario analysis)	N/A
Cycle length	6 months	Annual	Annual	
Health states	Alive without fractures, alive with fracture, death Alive health states' utility captures treatment impact	Alive on burosumab treatment, alive not on active treatment, death Alive health states capture proportion with fractures and other morbidities	Alive on burosumab treatment, alive not on active treatment, death Alive health states capture proportion with fractures and other morbidities	The exact impact of healing fractures is uncertain, the main driver of patients' QoL is reduction in pain, stiffness and fatigue. Differentiation of fracture

				locations and inclusion of other morbidities.
Discontinuation	4.05% every six months	16% at one year 3% annually	7.7% after 24 weeks, increasing to 16.9% at one year 3% annually	Stop criteria based on UK clinical feedback and CL303 proportions, subsequent years based on EAP (UK RWE)
Adverse events	Not considered	Included avoidance of severe adverse events associated with conventional therapy	Not considered	N/A

Patient population

B4. Priority Question: Please comment on whether the cost-effectiveness data is generalisable to a burosumab-experienced population, specifically:

a) **children as they transition to adults (and change from two weekly to four weekly dosing of burosumab)**

b) **patients who recommence burosumab therapy as adults following treatment as a child.**

Part a) Burosumab only obtained its marketing authorisation from EMA in February 2018,[22] and the NICE recommendation for use in children with growing bones in England in October 2018. The clinical evidence available is for children with XLH initiating burosumab at aged 1-12 years, and adults initiating burosumab from 18 years old. There is no trial evidence available for adolescents initiating treatment aged 13-17 years. A recent publication of expert opinion from 20 European specialists has indicated there is currently no clinical consensus on how to handle initiation of therapy, treatment switches and dosing in this adolescent population.[23] According to the marketing authorisation children and adolescents aged 1 to 17

years should be treated using the dosing guidance for children. At 18 years of age the patient should convert to the adult dose and dosing regimen.[24] Please note, that although adults tend to weigh more than children, the reduction in the frequency of administration means that the total dose required every 4 weeks is on average lower for adults than for children between 1-17 years.

Part b) The protocol for CL303 permitted prior use of burosumab [CSR p.126], however only 7 patients enrolled in the trial had been exposed to burosumab previously as adults in an earlier clinical study. All information presented in the submission relates to adults who suffer from debilitating persistent symptoms such as pain, stiffness, fatigue, recurrent and/or unhealing fractures. In untreated children with XLH, the persistent hypophosphatemia leads to abnormal musculoskeletal development, which plays a significant role in the disease burden as an adult. Members of an expert working group with experience in paediatrics, epidemiology, and bone, joint and muscle biology posited that intervention to restore phosphate levels early in life during the critical stages of skeletal development could optimise growth and prevent skeletal deformities, thereby improving mobility, and ameliorating osteoarthritis, enthesopathy, stiffness and pain throughout the patient's lifetime. [25] Therefore, their clinical presentation will be different to those patients who have not received burosumab early in their childhood. It is possible that those who receive burosumab later in their skeletal development will not benefit from optimal correction of skeletal misalignment, and due to the chronic ongoing hypophosphataemia may enter adulthood exhibiting complications similar to those detailed in the starting criteria for burosumab in the over 18 population. However, the proportion of such patients is expected to diminish over time with the availability of burosumab in the paediatric population.

B5. Priority Question: Please supply the following:

a) **The distribution of participant weight by age band used in Table 24 from CL303 (not restricted to EU patients).**

b) **The age distribution for EU participants from CL303, corresponding to the weight distribution presented in Table 46.**

c) **For Burosumab's Early Access Programme, the weight distribution by age band.**

Part a) and b)

Please find below requested tables with age distributions and corresponding average weights. There is no apparent difference between the complete CL303 population, European patients participating in CL303 and the UK EAP participants. There is also no sign of consistent changes in weight with age (see also response to B1).

Table 14: Patient age distribution and mean weight by age band (all patients from CL303)

Age range	Mean weight (kg)
18-23	69.9
24-28	77.1
29-33	74.7
34-38	67.9
39-43	74.8
44-48	63.5
49-53	72.5
54-58	67.1
59-63	67.2
64+	68.5

Table 15: Patient age distribution (EU participants from CL303)

Age range	Number of patients	Distribution of population
18-23	4	9%
24-28	5	11%
29-33	5	11%
34-38	7	15%
39-43	6	13%
44-48	6	13%
49-53	7	15%
54-58	3	6%
59-63	3	6%
64+	1	2%

Part c). Mean weight by age range in the EAP is shown in Table 14 below.

Table 16 EAP mean weight by age range

Age range	n	Mean weight (kg)
18-23	[redacted]	[redacted]
24-28	[redacted]	[redacted]
29-33	[redacted]	[redacted]
34-38	[redacted]	[redacted]
39-43	[redacted]	[redacted]
44-48	[redacted]	[redacted]
49-53	[redacted]	[redacted]
54-58	[redacted]	[redacted]
59-63	[redacted]	[redacted]
64-68	[redacted]	[redacted]
69-73	[redacted]	[redacted]
74-78	[redacted]	[redacted]
79-83	[redacted]	[redacted]
84+	[redacted]	[redacted]

Source: calculated from EAP data set

Survival model

B6. *Please clarify whether the hazard ratio (HR) of 2.88 [95% CI, 1.18-7.00] from Hawley et al. (2020) is based on XLH cases graded as "highly likely", "likely", and "possible". If not, please specify which definition of XLH cases is used to derive this HR.*

The Hawley et al., (2020) publication[26] states that in their base case analysis 9 of the 122 cases died when the "highly likely", "likely" and "possible" definition was used, and 4 of the 64 cases died when the "highly likely" and "likely" definition was used. Based on the context within the manuscript and the observation that 8 deaths were observed in the sensitivity analysis with extended follow-up (less than the number of deaths observed "highly likely", "likely" and "possible population in the base case analysis that censored on transfer from index practice) we are confident that the sensitivity analysis refers to the "highly likely" and "likely" population. This definition

is in line with the definition used in the Kyowa Kirin confirmatory study (see question B7 below).

B7. *Please clarify which definition of XLH cases is used to derive the HR of 2.33 [95% CI, 1.16-4.67] from the Kyowa Kirin confirmatory study, i.e., does it include only "highly likely" and "likely" cases?*

Yes, the HR of 2.33 is the result of the analysis including "highly likely" and "likely" cases only. This definition corresponds with the case definition applied in the Hawley et al., 2020 study included in the base case.

B8. *Please justify the value of a 50% reduction in mortality for burosumab compared to standard of care for the duration of time on treatment.*

Due to the insufficient follow-up available for burosumab treatment in adults, it is not possible to estimate the impact of burosumab treatment on mortality. This will only become a possibility once adults receiving burosumab treatment are observed for decades. In the absence of data, the model inevitably had to rely on an assumption regarding the impact of burosumab treatment on mortality.

As described in section B.1.3.4. of the main company submission document, there are multiple inter-related mechanisms (hypophosphataemia and excess FGF, multimorbidity, physical inactivity, impaired mental wellbeing, opioid use, socioeconomic deprivation) that may drive excess mortality in adults with XLH. Burosumab has been shown to normalise serum phosphate levels; improve physical functioning, stiffness, pain and HRQoL; and promote fracture healing.[10,11] Real-world and trial evidence also shows a reduction in opioid use.[10,27] These benefits directly address many of the likely drivers of increased mortality in XLH. Furthermore, according to clinical feedback, improvements in physical functioning and pain are likely to lead to increased physical activity and improved mental wellbeing during the course of treatment. It has been hypothesised by the clinicians that the increased capacity for employment may also potentially improve socio-economic status of patients. Improvement in all of these aspects was hypothesised to result in a reduction in the excess mortality associated with XLH. The magnitude of the reduction (50%) was based on clinical opinion, based on the fact that treatment with burosumab in adulthood is likely to have variable impact on factors driving mortality

in XLH (CS Appendices P and Q), resolving some of the issues completely (e.g. through addressing opioid use and fractures, leading to increased physical activity), but some of the features of XLH that originate in childhood cannot be altered.

B9. *Please clarify why the rates of treatment effect tapering (build up and waning) differ for morbidities and mortality in Tables 30 and 31, respectively. In particular:*

a) *Please justify the rationale for assuming an ongoing treatment benefit for mortality two years after the end of treatment, while there is no effect on morbidities.*

b) *Please justify the rationale for assuming that it takes longer for the build-up of effect on mortality (75% in year 1 on treatment) compared to morbidities (100% in year 1 on treatment).*

The time period required to observe the impact of burosumab treatment on different outcomes included in the economic evaluation differs. Serum phosphate concentration was observed to increase within two weeks.[7] Once phosphate wasting is eliminated, bone quality starts to improve, but bone remodelling takes slightly longer. The impact of burosumab on mortality is more indirect and the build-up of effect in terms of impact on physical activities, BMI, the observing an impact due to the reduction in opioid use and/or social deprivation may take a longer time compared to impact on bone quality and fractures. Therefore, the economic model applied different assumptions to how quickly improvement in these outcomes may be expected after starting burosumab treatment, and, similarly, how quickly the treatment effect may be lost after discontinuation from burosumab. The expectation of the clinical experts was that the time needed to observe impact on fractures should be shorter compared to the time needed to observe impact on mortality (see Appendix Q of the company submission), since mortality is influenced by multiple inter-related mechanisms (including multimorbidity, potential downstream effects of fractures, physical inactivity, impaired mental wellbeing, opioid use, and socioeconomic deprivation). Similarly, as observed in patients who did not receive burosumab between the end of CL303 and their participation in BUR02, muscle stiffness and symptoms may return quickly when burosumab is stopped.[10] Since

during burosumab treatment the bones are remodelled, the effects on the bones and therefore fracture incidence are likely to wane slower. However, mortality is impacted by many additional factors besides bone quality, and similarly to the delayed impact at treatment start, the effect of reduction in physical activities, increase in BMI, potential increase in opioid use will take a longer time to influence mortality.

Effect of burosumab on fractures

B10. Priority Question: In Table 36 of the company's submission, it states that no new fractures were reported in patients who received burosumab in CL303 and BUR02. However, the EMA assessment report [EMA/423776/2020, page 97 of 151] indicates that six new fractures were reported in the burosumab arm within weeks 0-24, one new fracture within weeks 24-36, and none within weeks 36-48. Please clarify the discrepancy between the data reported in Table 36 and the EMA report.

In Table 36 of the company submission, the statement that there were no new fractures in patients receiving burosumab in CL303 was made in error. We apologise for this error. The sentence should have referred to BUR02 only, and should have clarified that fractures were only recorded in BUR02 as adverse events, not as a study outcome. This is explained on p.93 of the CS, reproduced here: “Mean (SD) exposure to burosumab at the most recently published analysis was 116.22 (30.7) weeks. No new fractures or pseudofractures were reported as AEs during this period. While fracture incidence was not a specified efficacy outcome in BUR02, this observation is supportive of the expectation of a beneficial effect for burosumab on incidence of new fractures, as a result of the improvements to bone mineralisation and osteomalacia resulting from treatment.”

Although some new active fractures and pseudofractures are reported during CL303 as part of safety outcomes, the numbers are very low and decrease over time (see Table 15). At week 48, there are no new fractures or pseudofractures reported in patients who have been taking burosumab since study start (the burosumab to burosumab group), and only one of each in the placebo to burosumab group.

Table 17 Number of active fractures and pseudofractures healed over time (primary analysis set)

Source: CL303 Clinical study report

The model explicitly includes fractures only (pseudofractures are radiological findings and only their impact on patients' quality of life were assumed to be included in the model as part of the improvements observed in WOMAC scores – see also response to B11 below). There was [redacted] new fracture identified in the burosumab -> burosumab group during a 48 week observation period (68 patients * 48 weeks = 62.7692 patient-years of observation) and [redacted] new fracture found in the placebo -> burosumab group between weeks 24 and 48 (24 week observation period) while they were taking burosumab (66 patients * 24 weeks = 30.4615 patient-years of observation). The estimated annual fracture rate based on the CL303 trial would

have been 0.02145 (2 fractures over 90.2308 patient-years). The model assumes that patients treated with burosumab would be experiencing fracture rates observed in the general population. The general population fracture rate applied in the model for 18-year-olds is 0.024 increasing to above 0.050 by the end of the modelled time period.[28] Therefore, the model assumes a higher annual fracture rate than observed in CL303 in its calculations for burosumab treated patients. This is in line with hypothesis of the clinical experts, who were expecting that after bone remodelling XLH patients should experience fewer fractures than the general population due to the structure of their bones (see Appendix Q in the company submission).

B11. Priority question: Please clarify why the model does not make a distinction between fractures and pseudofractures, which are reported separately in the EMA assessment report at baseline and over time from study CL303. Please clarify whether the disutility, resource use and costs associated with fractures in the model is making an appropriate distinction between fractures and pseudofractures.

The model only explicitly includes fractures. All inputs related to fracture rates in both treatment arms as well as the assumed cost and utility consequences relate to fractures only. Pseudofractures are identifiable through radiological investigation only, and require no medical intervention. Therefore pseudofractures were not assumed to have any cost implications. However, pseudofractures may cause pain and influence the mobility of patients. The impact of burosumab on pseudofractures and the healing of active fractures at baseline was included in the model through capturing the impact on WOMAC scores, and therefore only included as part of the quality of life improvement associated with burosumab treatment.

B12. Priority question: Please provide additional clarity on the approach used to model fracture event rates in the model. In particular,

a) **Please clarify why all fractures were modelled as repeat events, without incorporating the timing of events (by assuming a constant rate over time);**

b) Please describe the models, the coefficients included, and the justification for the chosen form of model by fracture site.

c) Tables 28 and 29 of the EMA assessment report suggests that only a proportion of active fractures and pseudofractures are graded as 'healed' by week 48 in CL303, please clarify whether this information is included in the approach used to model fracture event rates.

a): Rates of multiple fractures were estimated based on baseline scan data from the CL-303 trial. The scan data does not provide direct information as to the timing of individual fractures and insufficient cases and variation in age were available to model age dependent rates based on the relationship between age and cumulative number of fractures.

b) All fractures were modelled as repeat events to allow for repeated events within a patient. A test of the null hypothesis of equidispersion in Poisson GLMs against the alternative of overdispersion and/or underdispersion indicated overdispersion for number of fracture sites. This suggests that the incidence of fractures is not an independent event. Following an initial fracture, the risk of subsequent fractures of the same type is higher than in patients who have not had any fractures. The consideration of overdispersion will not affect the estimates of mean fracture rate but will affect estimates of uncertainty in estimates.

Due to evidence of overdispersion, the fit of Poisson, Negative Binomial, and Zero-inflated Poisson models were considered. AIC statistics suggests that the negative binomial model was a better fit for 'Other' fractures, Femur and Pelvis Fractures, Foot fractures, and Tibia/Fibula fractures. The Poisson model was a better fit for Upper limb fractures (humerus, hand/wrist, forearm) and the Zero-Inflated Poisson model was a better fit for vertebral/spinal fractures.

Fracture events were modelled assuming a constant rate over time using a negative binomial model, except for upper limb fractures, where a Poisson model was used. The negative binomial model was also used for vertebral spinal fractures for convenience. Given the low rates for these fractures this had little impact on estimates. Log age was included as an 'offset' controlled for variation in age (time at

risk) for all fracture locations. Note, the coefficient for the offset is constrained to be 1 so it is not reported in Table 10 of submission document B. The estimated model coefficients are shown in Table 34 of submission document B.

Part c): Healing of extant fractures was not explicitly modelled. The QoL benefits were assumed to be captured via the impact on WOMAC scores.

Treatment discontinuation

B13. *Please justify the stopping rule for burosumab, where continuation of treatment after year 1 in the model is based on the requirement of reaching serum phosphate levels above LLN after 24 weeks of treatment and an improvement in WOMAC total score at 48 weeks after starting treatment. In particular, please justify the need for the second hurdle on the WOMAC total score given that there are limited (or no) treatment alternatives for this patient population.*

The stopping rules were derived after multiple consultations with clinical experts (see CS Appendices P and Q). The requirement to achieve serum phosphate levels above LLN after 24 weeks reflects discontinuation in patients in whom phosphate levels could not be normalised with burosumab treatment. Given the mode of delivery (repeated injections) and cost of treatment clinical advice was that it would not be reasonable to continue therapy in patients who do not experience some perceived benefit of treatment.

As hypophosphataemia is the underlying cause of all other morbidities associated with XLH, these patients are not likely to benefit from further treatment. The longer term requirement assesses the downstream implications of improvements in serum phosphate level. With improvement in serum phosphate levels, bone remodelling should take place over time. Improvements in pain, stiffness and physical function are expected to happen and should be assessed over a longer time horizon. The clinical trials showed continued improvements over time with continued treatment. However, if this bone remodelling does not take place within a one-year time frame, the condition of the patient is not likely to improve in the long run, indicating potential issues with bone remineralisation despite increases in serum phosphate levels.

B14. Priority Question: Please provide details of the reasons for treatment discontinuation in the EAP, which was used to inform the annual discontinuation rates reported in Table 25.

Please find reasons for treatment discontinuation for the 16 discontinued patients informing Table 25 in the company submission in Table 16 below.

Table 18 Reasons for discontinuation in EAP

Reason for discontinuation	Number of patients
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

* Adverse events reported were bone pain, insomnia, allergic injection site reaction
Source: calculated from EAP data set

Baseline utility values

B15. *Please clarify whether WOMAC or EQ-5D data are available at baseline from participants in the EAP. If available, please provide the baseline utility values (mean and standard error) for these participants.*

The requested information is not yet available to Kyowa Kirin from all sites participating in the EAP. Researchers from UCLH have provided consent to share EQ-5D data on the patients treated in their centre. WOMAC scores are not available. Please find below EQ-5D values at baseline.

Table 19 EQ-5D-5L values at baseline – UCLH EAP patients

Variable	Baseline value
n	[redacted]
Mean	[redacted]
Median	[redacted]
Range	[redacted]
Standard deviation	[redacted]
Standard error	[redacted]

Source: UCLH

B16. *Please provide the baseline utility values for each of the patient populations that were used to provide WOMAC data at each follow-up time in Table 39, i.e., US patients from CL303 at weeks 120 and 144, BUR02 at weeks 132, 144, 156 and 168.*

The values are provided in Table 18 below.

Table 20 baseline utility values

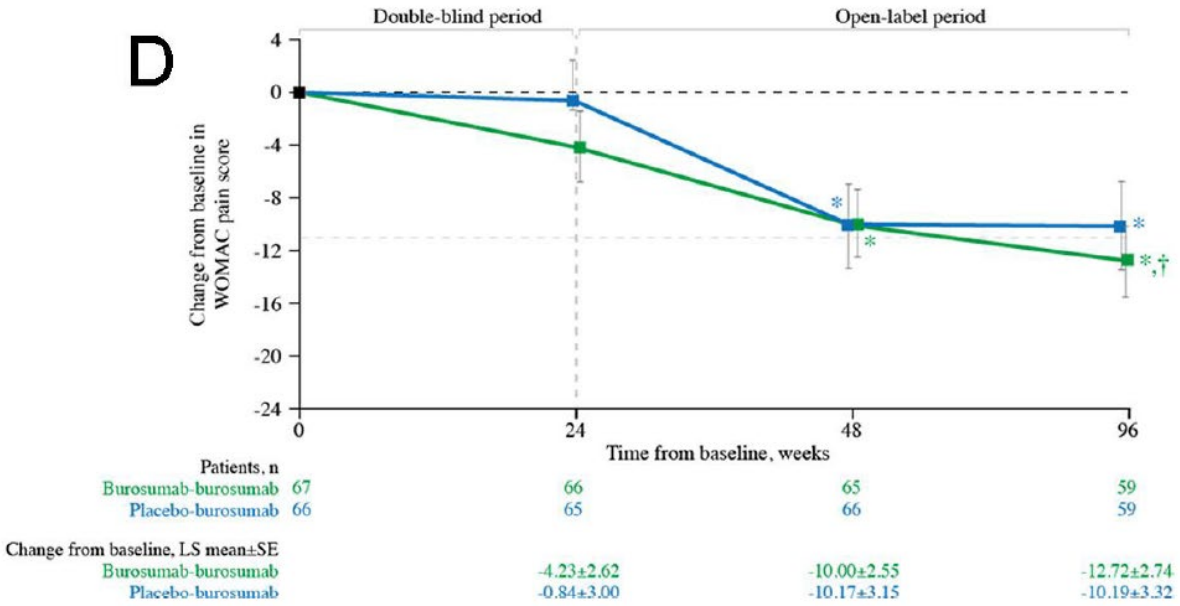
Patient group providing data at time point	Base Utility	
	Mean	SE
120	0.397	0.0315
132	0.393	0.0565
144	0.397	0.0409
156	0.369	0.559
168	0.379	0.0519

WOMAC scores in CL303

B17. *CS Figure 36 shows the change in WOMAC Physical Function and Stiffness score over time from CL303. Please provide the corresponding change in WOMAC Pain score over time.*

Change in WOMAC pain score over time to 24 weeks was not graphed in the study publication or CSR, as the focus was on the BPI pain scores. However, the graph for this period is available as part of the 96-week time period, shown below.

Figure 3 Change in WOMAC pain score over time



Source: Briot 2022[12]

B18. *The EMA assessment report [EMA/423776/2020, page 94 of 151] states that "The reliability of subjective reports of perceived symptoms in an open-label setting is questioned. This is exemplified by the WOMAC Stiffness and WOMAC Physical Function scores in study UX023-CL303, where improvement in LS mean from baseline in the burosumab treatment arm levelled out between Week 12 and Week 24 but increased again between Week 24 and Week 48, implicating that the open-label design may indeed have affected the outcome". Please comment on whether the open-label design might have affected the WOMAC scores in the open-label period of CL303.*

Multiple PRO scores were reported, comprising component scores from the WOMAC, BPI-SF and BFI-SF instruments. Levelling of the improvement in the burosumab arm between weeks 12 and 24 occurred in some but not all scores, and may have been due to chance fluctuations due to the relatively small sample size. The primary analysis time point for the double-blind analysis period was Week 24, and the graphs of PROs over time published by Briot et al (reported in Company Submission document B, Figures 19 [p87-88], 21 [p90-91] and 22 [p92]) show better scores in the burosumab arm than the placebo arm for all PRO measures at this time point. They also show continued improvement over time to 96 weeks. It should also

be noted that patients and investigators remained blinded to the original treatment assignments until the week 48 analysis was completed to minimise bias.[12]

The possibility that the open label design may have influenced patient-reported outcomes after the 24-week double-blind period cannot be ruled out. However, the improvement over time in stiffness, pain and physical functioning is consistent with the physiological effects of long-term phosphate normalisation, which lead to ongoing improvement in bone and muscle health over time[11,29,30] (see CS Section 2.6.5).

To assess the potential influence of the open-label design on patient-reported outcomes, Kyowa Kirin conducted sensitivity analyses using mixed model repeated measures (MMRM) on the End-of-Study (EOS) data. This analysis aimed to compare the change from baseline at each visit timepoint, including those within the open-label period. The results of these analyses can be found in Table 14.2.1.2.1.1.9 and Table 14.2.1.2.2.1.9,[31,32] which are supplied in the reference pack.

Analysing the observed WOMAC stiffness scores, we noted the following standard errors: at week 24, [redacted] for the burosumab group and [redacted] for the placebo group. During the open-label treatment period, at week 36/week 48, the standard errors were as follows: [redacted] for the burosumab→burosumab group and [redacted] for the placebo→burosumab group.

Regarding WOMAC physical function, the standard errors at week 24 were [redacted] for the burosumab group and [redacted] for the placebo group. During the open-label treatment period, at week 36/week 48, the standard errors were as follows: [redacted] for the burosumab→burosumab group and [redacted] for the placebo→burosumab group.

The sensitivity analyses also demonstrated that the 24-week treatment with burosumab resulted in a favorable change compared to placebo in WOMAC stiffness ($p = 0.0181$) and WOMAC physical function ($p = 0.0773$), which aligns with the primary analysis results of WOMAC stiffness and WOMAC physical function scores (CL303 EOS CSR). The non-significant p-values between week 24 (when all patients began receiving open label burosumab) and week 96 indicate that there is no statistically significant difference in the change from baseline between the

burosumab→burosumab group and the placebo→burosumab group in terms of WOMAC stiffness and WOMAC physical function during the open-label treatment period. This suggests that the additional treatment with burosumab from week 24 to week 96 did not lead to a statistically significant difference in WOMAC stiffness/physical function for patients in the placebo→burosumab group compared to the burosumab→burosumab group.

Utilities

B19. Priority Question: Figure 37 shows the change from baseline utility over time, mapped from WOMAC in CL303 and BUR02, based on WOMAC data at each follow-up time from Table 39.

a. **Please clarify whether the WOMAC outcomes from the open label extension study, BUR02, includes participants from study CL304.**

b. **Please clarify why there was a large drop-out of participants providing WOMAC data in CL303 from week 36 onwards.**

c. **Please provide the baseline characteristics and baseline utility values (mean and standard error) of the participants that provide WOMAC data at each of the follow-up time points, i.e., US patients from CL303 at weeks 120 and 144, and BUR02 at weeks 132, 144, 156 and 168.**

Part a) No, they do not include participants from CL304.

Part b) In the utility analysis, the placebo patients who switched from placebo to active treatment at week 24 are excluded from subsequent analysis. Their subsequent trajectory in terms of utility was similar to the patients originally randomised to burosumab. In the trial analysis of WOMAC data there is some drop-off in numbers from week 72, e.g. for WOMAC Physical Function: [redacted]. These do not constitute large drop-out rates over a study of this length, and where not all patients complete the extended study period. A similar pattern was seen in other PROs and importantly in clinical endpoints (e.g. primary endpoint serum phosphate n=119 at week 96).

Part c) Please see B16 for baseline utility values. We are not able to supply the suggested analyses around baseline characteristics at this time.

B20. Priority Question: Figure 39 shows the asymptotic model fit to WOMAC mapped utility change from baseline, based on data at each follow-up time from Table 39.

Please provide the asymptotic model fit to WOMAC mapped utility change from baseline, based only on data from CL303 up to week 96 (i.e., excluding the post-week 96 data from Table 39).

For the asymptotic model fit using WOMAC data up to week 96 only, please provide the predicted mean change from baseline (and standard error) in year 1 on treatment, year 2 on treatment, and year 3+ on treatment for both the non-placebo-adjusted and placebo-adjusted analyses, with and without the stopping rule applied corresponding to Tables 41 and 42, respectively.

Please justify the use of non-placebo adjusted values in the base case.

Kamenicky et al.[10] showed that levels returned to baseline on discontinuation of burosumab, this suggest relatively little regression to the mean effect. In which case the placebo response would only be observed if a placebo were actually administered. As this would not be ethical, we would suggest the unadjusted value is most appropriate.

Please see tables and figures below for the information requested.

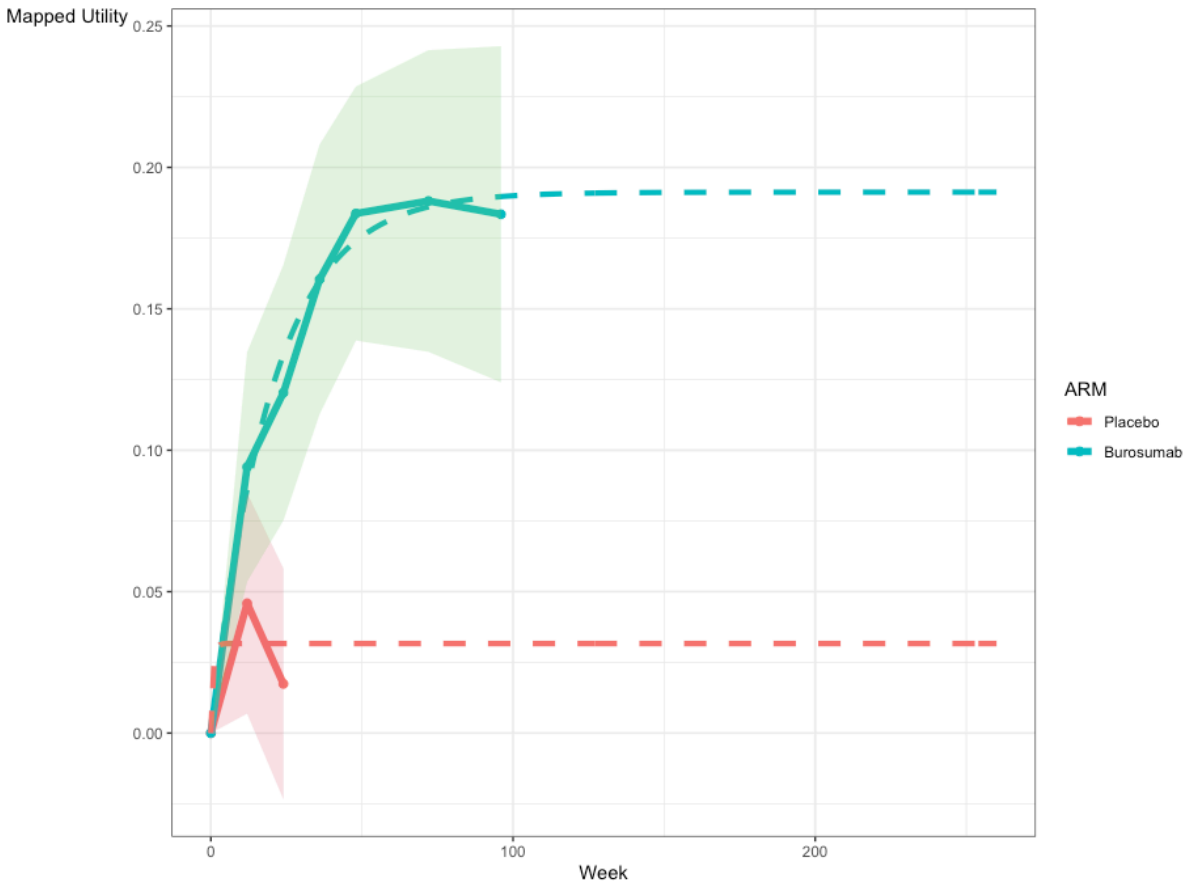
Table 21 Non placebo-adjusted predicted mean utilities mapped from WOMAC whilst receiving treatment with burosumab

	Burosumab (all patients continue) Mean (SE)	**Burosumab (stopping rule applied)** Mean (SE)
Year 1 on treatment	0.141 (0.009)	0.141 (0.009)
Year 2 on treatment	0.153 (0.016)	0.190 (0.016)
Year 3+ on treatment	0.154 (0.018)	0.191 (0.017)

Table 22 Placebo-adjusted predicted mean utilities mapped from WOMAC whilst receiving treatment with burosumab

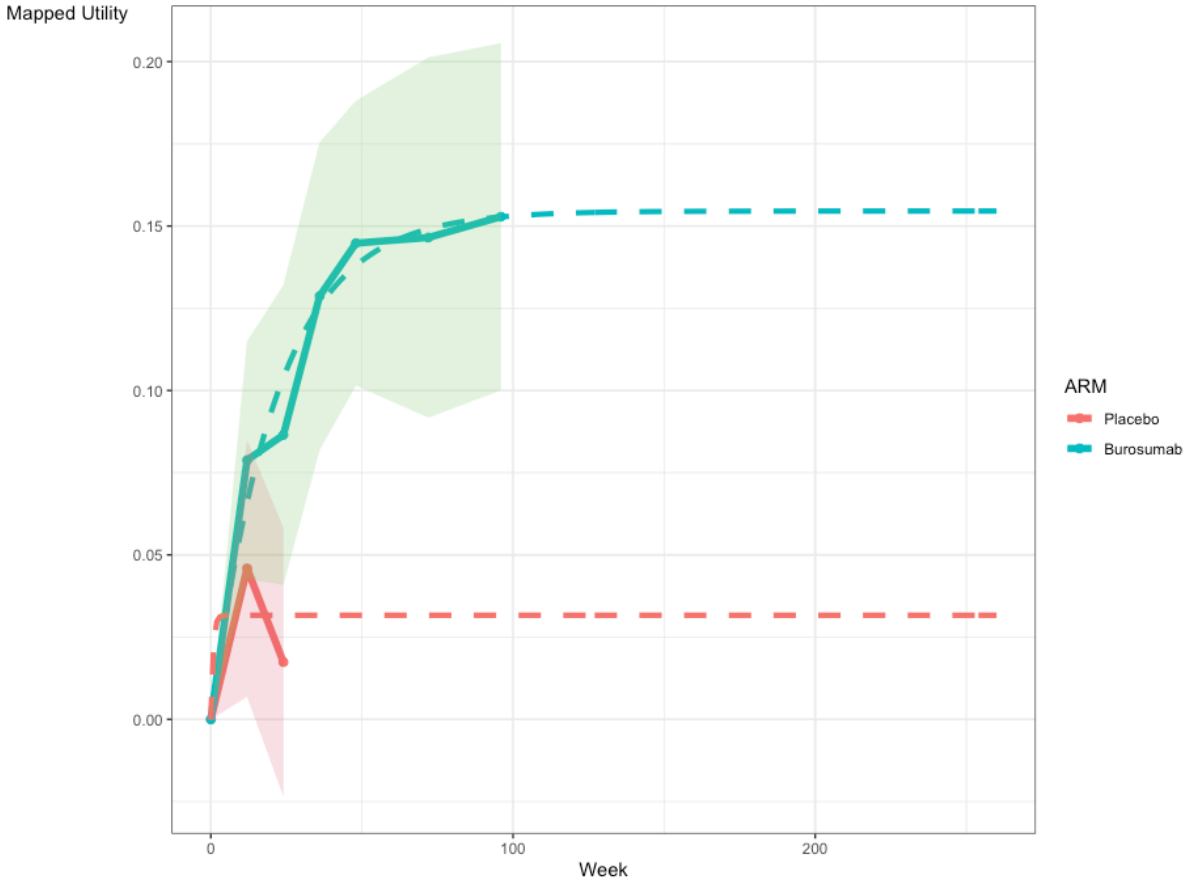
	Burosumab (all patients continue) Mean (SE)	**Burosumab (stopping rule applied) Mean (SE)**
Year 1 on treatment	0.109 (0.015)	0.109 (0.015)
Year 2 on treatment	0.122 (0.020)	0.159 (0.020)
Year 3+ on treatment	0.123 (0.021)	0.160 (0.021)

Figure 4 Change from baseline in utilities mapped from WOMAC scores over time with stopping rule applied at 1 year excluding data from after 96 weeks



Weeks	0	12	24	36	48	72	96
Tx Obs	54	54	54	52	54	48	47
Placebo Obs	65	65	65	0	0	0	0

Figure 5 Change from baseline in utilities mapped from WOMAC scores over time without stopping rule applied at 1 year excluding data from after 96 weeks with no stopping rule



Weeks	0	12	24	36	48	72	96
Tx Obs	66	66	66	64	66	60	59
Placebo Obs	65	65	65	0	0	0	0

B21. *Figure 26 provides the change in EQ-5D domain scores from baseline to one year in adults initiating burosumab based on UCLH experience. If feasible, please provide the EQ-5D utility values (mean and standard error) for baseline and change from baseline utility over time from this study.*

The requested information forms part of a research project conducted by clinicians at UCLH. Researchers from UCLH have provided consent to share EQ-5D data on the patients treated in their centre, shown in Table 21.

Table 23 EQ-5D-5L values – UCLH EAP patients

Variable	Baseline value (all patients)	Baseline value (with follow-up at 1-year)	1-year value
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Standard deviation	[redacted]	[redacted]	[redacted]
Standard error	[redacted]	[redacted]	[redacted]
Mean change		[redacted]	

Source: UCLH

B22. Priority Question: Please explain with greater clarity the approach used to model disutilities associated with fractures (and/or other morbidity events) in the model.

The disutilities for individual morbidities are applied as utility multipliers, which are assumed to be independent of one another. With this approach, the assumption is made that the proportional utility reduction due to morbidities is equivalent for the general population and XLH patients. The absolute disutility will be lower in patients with XLH, due to a lower baseline utility, and is also potentially conservative. It is known that fractures are particularly difficult to treat in XLH patients, so this is likely to be a conservative assumption.

Disutilities associated with morbidities are applied in the year in which the event happens (acute impact). Additionally, a long-term disutility is applied for fractures, spinal surgery and hearing loss/tinnitus, as these events are typically associated with a long-term impact on HRQoL.

However, baseline utility is likely to incorporate previous morbidity events, the utility difference between the burosumab and SoC arms due to morbidities is applied as a benefit to the burosumab arm, rather than as a further disutility for the SoC arm. This does not affect the overall incremental QALYs, only absolute QALYs. The model calculations for the burosumab arm differentiate according to the different impacts:

1. The model calculates the expected age-specific utility value without treatment (this includes the impact of morbidities experienced by patients in the comparator arm)
2. Adds the immediate impact of burosumab treatment observed in the trial (mapped from WOMAC improvement)
3. Adds the long-term impact due to the reduction in morbidity rates: first calculating what is the likely impact of morbidities within the utilities predicted for the comparator treatment arm (see column BH on the SoC Trace sheet in the submitted model), and what is the likely impact of morbidities predicted for the burosumab treatment arm and adding only the net impact of burosumab treatment to the baseline utilities (since these already include the comparator treatment arm morbidity impacts – see column CB on the Burosumab trace sheet in the model).
4. Adds impact on family and caregivers.

B23. *Please justify the assumptions for spillover utility effect on caregivers, specifically:*

a) A value of 20% of utility benefit of burosumab for carers and family members; and
b) The application to two family members for the adult XLH population.

Part a) Very few studies were identified exploring the burden and spillover effects in carers and family members on adults with musculoskeletal conditions (see Company Submission document B Section 1.3.5.6 (p. 36-37). Qualitative studies revealed significant impacts, with caregivers reporting notable impacts to their physical health, work and finances, daily activities as well as emotional and social well-being. This finding was also affirmed by a study conducted by Kyowa Kirin on the impact on caregivers and family members (see Appendix S of the company submission for details). The study estimated the mean difference in observed versus expected EQ-5D utilities for family members of XLH patients was -0.184 (95% CI: -0.339 – -0.029), when compared with age-linked UK general population utility data.

No studies were identified which would have been able to quantify the relationship of improvements in pain and physical function of patients with utilities of family members and caregivers. Therefore, an assumption was applied in the model, i.e. that the improvement of the utility of caregivers and family members would be 20% of the utility benefit of burosumab treatment experienced by the patient. This assumption ensured that the magnitude of benefit for family members and caregivers assumed to be achievable as a consequence of burosumab treatment (0.043 improvement in the long term, as reported in the Table below) remained well below the overall impact of caring for an adult with XLH.

Table 24: Utility improvements for family members if patient receives burosumab

Year	Mean per family member	Mean in model (2 family members)
Year 1 on treatment	0.029	0.059
Year 2 on treatment	0.042	0.084
Year ≥3 on treatment	0.043	0.086

Patient advocates have described the impact of XLH on the family unit as “catastrophic” (see Appendix M of submission). The burden was confirmed by a study which interviewed families of adults with XLH in the UK about their experiences, described in Section B.1.3.5.6 and Appendix S.

Qualitative studies revealed significant impacts, with caregivers reporting notable impacts to their physical health, work and finances, daily activities as well as emotional and social well-being. The study conducted by Kyowa Kirin on the impact on caregivers and family members (see CS as above and Appendix S for details) found that the mean difference in observed versus expected EQ-5D utilities for family members of XLH patients was -0.184 (95% CI: -0.339 – -0.029), when compared with age-linked UK general population utility data. To remain conservative, the utility improvement on family members and caregivers is calculated as 20% of the utility benefit of burosumab treatment experienced by the patient. This assumption ensured that the magnitude of benefit for family members and caregivers assumed to be achievable as a consequence of burosumab treatment (0.043 improvement in the long term) remained well below the overall impact of caring for an adult with XLH.

Part b) A recent study in the UK by Canaway et al. investigated how many people are close to patients near their end of life in order to determine who should be included when estimating spillover effects.[33] The study found that close-person networks at end of life contained eight individuals, three of whom were rated as being the closest. No similar study was identified for musculoskeletal conditions, therefore, again to be conservative, the spillover was applied to only two family members. As the impact on the patient is assumed to be gradually increasing, the impact on family members was assumed to follow the same pattern. This assumption was validated by XLH patient and clinical experts.

Burosumab dosing

B24. *Please provide the proportion of EU participants from CL303 who had dose reductions.*

The study protocol specified dose reductions for patients who developed high serum phosphorus (> 4.5 mg/dL [1.45 mmol/L]). During the placebo-controlled period, no patients in the placebo group and 5 patients in the burosumab group required protocol-specified dose reductions. After initiation of burosumab in the open-label Treatment Continuation Period, 4 patients in the placebo→burosumab group required protocol-specified dose reduction(s). No patients required dose reductions in the Treatment Extension periods (Source: CSR section 12.7.2.1). Of the 9 patients requiring dose reductions at some point in the study, 7 were in the North America/Europe subgroup. The number of EU participants requiring dose reductions is not available at this time but would be small (a maximum of 7).

B25. *Please provide the average dosing and proportion of participants with dose reductions for EAP participants.*

Kyowa Kirin does not yet have access to data collected on patients participating in the EAP. The latest information shared with Kyowa Kirin was that the average dose per cycle for EAP participants was 65mg, which aligns with the average dose calculated within the economic model (65.23mg).

B26. *The submitted model does not take account of the possibility of increasing the dosage of burosumab. A clinical expert who consulted with the company noted that "the dosage may be increased up to the maximum allowable level during the 24-month period" [Appendix Q, page 20 of 22]. Please clarify why the model does not incorporate the option for dose escalation.*

The SmPC explicitly allows for dose increases in the case of children and adolescents aged 1 to 17 years.[24] In the case of adults, only dose decreases are mentioned in the SmPC. The 1 mg/kg dose was also required to remain constant for the duration of the CL303 study except if serum phosphate increased to > 5 mg/dL, in which case dose had to be reduced by half; this is in line with the assumptions made in the model. Furthermore, the average dose required as calculated in the model aligns with the average dose observed in EAP participants (see response to question B25 above), indicating that dose calculations in the model reflect current clinical practice.

B27. *The SmPC recommends that serum phosphate be assessed after two weeks if burosumab dosing adjustment is required [Appendix C, SmPC, page 2]. The cost element for dose reduction is not considered in the submitted model. Please provide a revised model that includes the cost of additional serum phosphate tests for those who need to adjust their dosage.*

The model includes 4 additional serum phosphate tests (with the associated practice nurse time and laboratory measurement costs) for all patients in the first year after initiation of burosumab. Impact on serum phosphate levels can be observed within 2 weeks after receiving burosumab treatment,[7] therefore if dose adjustments are required, these should become apparent within the first year and be included in the cost implications of the 6 serum phosphate tests which are already included for all burosumab patients.

B28. Please clarify whether an increased number of clinic visits are required during the initial titration period. If so, please provide the corresponding resource use and unit costs.

The model includes a total of 6 serum phosphate tests (with the associated practice nurse time and laboratory measurement costs) for all patients in the first year after initiation of burosumab, 4 more assessments than what is assumed for patients not receiving burosumab. A multidisciplinary clinic visit is also assumed as well as kidney ultrasonography for 50% of patients. See Table 23 for summary.

Table 25. Resource use and unit costs associated with burosumab titration period in the model

Resource	Annual usage	Cost	Source
Multidisciplinary team or clinic with accompanying biochemistry	1	£230.27	NHS reference costs 2020/21, Multi-professional Non-Admitted Face-to-Face Attendance, Follow-up (Rheumatology). WF02A, CL.
Lab measurement of serum phosphate	6	£3.63	NHS reference costs 2020/21, DAPS05 Haematology
Kidney ultrasonography	0.5	£69.63	NHS reference costs: Weighted direct and outpatient: Ultrasound Scan with duration of less than 20 minutes, without Contrast, RD40Z
Practice nurse	6	£42.00	PSSRU 2021: Nurse (GP practice)
Total cost	£328.87		

Burosumab administration costs

B29. *Please provide details of the cost elements covered by the KK funded service of nurse-led training for self-administration of burosumab. In particular, please clarify whether the nurse time required to undertake the training is covered. If not, please provide the cost of nurse time required for training.*

All costs related to self-administration training are covered by Kyowa Kirin. This includes a minimum of three and up to six training sessions in the patient's home. Additional training sessions are flexible to the patient's needs within reason. Progress reports are sent to the prescribing clinician after each visit. The nurse time is covered by Kyowa Kirin. In addition, Kyowa Kirin will cover the provision costs of

all ancillaries (ongoing) as well as product and ancillary delivery fees throughout the training and on an ongoing basis for as long as the patient remains on therapy. This includes the provision of needles, syringes etc as well as a sharps box which will be exchanged as required.

Additional services with costs covered by Kyowa Kirin: Should the patient require a dose change for any reason, a request can be made for a nurse visit to observe the new dose being prepared and administered as per SmPC. The clinical team have the option to request an annual 'injection technique assessment' to ensure the patients continue to remain competent and are administering their treatment appropriately. Following initiation, typically three blood samples are required. This can be incorporated into the nurse visit. The blood samples will be couriered to the hospital (if distance within 2 hours travel time). This is due to stability of blood and the requirement to process within four hours of the sample being drawn.) Courier costs are covered by Kyowa Kirin. Should the patient live further from the hospital, usually the bloods would be taken locally. This is arranged by the prescribing hospital.

B30. *Please clarify whether self-administration of burosumab would take place from the start of treatment, i.e., immediately from time 0, or after a number of doses administered initially by a hospital nurse.*

Only the initial dose (1 dose) is given at the Hospital to adult patients. Furthermore, this initiation is only required for newly initiated adult patients who are not currently already receiving burosumab as part of the EAP. The second dose onwards can be incorporated into the training sessions provided by homecare from the second treatment. The homecare nurse can administer treatment during these sessions up until the patient is competent and confident enough to self-administer. Self-administration of burosumab will take place after the patient/carer is deemed competent by the assessing nurse using a competency check list (min 3 visits and up to 6 visits, see response to B29), at which time the clinical team will be notified and the nurse training sessions/visits will cease.

As a highly conservative scenario analysis we added the cost associated with hospital nurse administration (assuming 20 minutes of nurse time at an hourly cost of £46.00 = £15.33) of the first dose (assuming everyone will require hospital administration of the first dose), which increased the ICER by £4 from the original base case of [redacted] to [redacted] using the current HST8 PAS price.

B31. *Please clarify whether patients experiencing clinical events such as injection reactions, dose reductions, or fractures would be required to stop self-administration.*

Any adverse reaction observed or advised to the homecare nurse in the initial administrations will be reported to the clinical team. Following this time, any adverse reactions would be reported by the patient direct to their healthcare team. There is no requirement to stop self-administration. The decision to stop self-administration and/or treatment at any time, for any reason, is a clinical decision by the treating physician.

Section C: Textual clarification and additional points

Additional references and documentation

C1. *Please provide the protocol documents for studies CL303, CL304, BUR002, and if applicable, CL001.*

These are supplied in the reference pack submitted with this response document.

C2. *We did not find a clinical study report for study CL304 in the reference pack. Please provide the latest available clinical study report for this study*.

This is supplied in the reference pack submitted with this response document.

C3. *Please provide the protocol for the UK Early Access Programme as references in Document B: Kyowa Kirin Ltd. UK XLH RWD EAP draft protocol 14 May 2022*

(Contract No 2021-66-UK-CRY). (2022)) and any more recent versions as applicable.

The draft protocol referenced above has been superseded by 'Final v1.4', which is supplied with this document.[21]

Bibliographic searches

C4. *Please provide the search strategy used in EconLit and the interface/website used to access the database (mentioned on page 7 of Appendix D).*

Please see below.

Sr. No.	Search Terms	Search Options	Last Run Via	Results
S1	AB Familial Hypophosphatemic Rickets OR TI Familial Hypophosphatemic Rickets OR AB x linked hypophosphatamia OR TI x linked hypophosphatamia AB XLH OR TI XLH	**Expanders** - Apply equivalent subjects; Apply related words; Also search within the full text of the articles **Search modes** - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit with Full Text	0

C5. *Please clarify if the HTA database (https://www.crd.york.ac.uk/CRDWeb/) or the International HTA database (https://database.inahta.org/) were searched, the interface/website used to access the database and provide the search strategy used (mentioned on page 7 of Appendix D).*

Searched via INAHTA.org using the strategy below.

((Familial Hypophosphatemic Rickets)[mh] OR ((((familial OR hereditary OR genetic) NEAR2 (hypophosphataemi* OR hypophosphatemi* OR hypophosphatami*)))) OR ((('x linked' NEAR2 (hypophosphataemi* OR hypophosphatemi* OR hypophosphatami*)))) OR (((rickets NEAR3 (hypophosphataemi* OR hypophosphatemi* OR hypophosphatami* OR familial OR hereditary OR genetic OR 'd resistant' OR 'x linked')))) OR (((xlh OR hhrh OR hpdr OR adhr))) FROM 1900 TO 2022)

C6. *Please provide the date of the search of conference proceedings (page 7, Appendix D) and the search terms used.*

Last searched in November/December 2022. Proceedings searched are shown below. Search terms used for hand searching:

- **XLH**
- **X-linked hypopho**

Conference	**2019**	**2020**	**2021**	**2022**
American College of Rheumatology (ACR)	8-13 November* Atlanta, Georgia	5-9 November Virtual	1-10 November Virtual	10-14 November Philadelphia, PA
American Society for Bone and Mineral Research (ASBMR)	20-23 September* Orlando, Florida	11-15 September* Virtual	1-4 October Toronto, Canada	9-12 September Austin, Texas
American Society of Nephrology (ASN)	5-10 November Washington DC	19-25 October Virtual	2-7 November San Diego, California	3-6 November Orlando, Florida
British Renal Society	3-5 June Brighton	5-15 October Virtual	October Virtual (abstracts unavailable)	7-9 June Birmingham
British Society for Rheumatology	30 April-2 May* Birmingham	April* (Event cancelled but abstracts available)	26-28 April Virtual	25-27 April Glasgow
European Calcified Tissue Society (ECTS)	11-14 May* Budapest, Hungary	22-24 October* Virtual	6-8 May Virtual	7-10 May Helsinki, Finland

Conference	2019	2020	2021	2022
ENDO Endocrine Society	23-26 March New Orleans, USA	28-31 March (Event cancelled but abstracts available)	20-21 March Virtual	11-14 June Atlanta, Georgia
European Congress of Endocrinology (ECE)	18-21 May Lyon, France	5-9 September Virtual	22-26 May Virtual	21-24 May Milan, Italy
European League Against Rheumatism (EULAR)	12-15 June* Madrid, Spain	3-6 June* Virtual	2-5 June Virtual (abstracts unavailable)	1-4 June Copenhagen, Denmark
International Congress of Endocrinology	NA	Cancelled	24-28 February Virtual	25-28 August Virtual
International Society for Pharmacoeconomics and Outcomes Research (ISPOR and ISPOR Europe)	18-22 May* New Orleans	18-20 May* Virtual	17-20 May* Virtual	15-18 May Washington DC
	2-6 November* Copenhagen, Denmark	16-19 November* Virtual	1-3 December* Virtual	7-9 November Vienna, Austria
World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, WCO-IOF-ESCEO	-	20-22 August Virtual	26-29 August Virtual (abstracts unavailable)	24-26 March Virtual

*Searched via EMBASE (strategy provided below)

ID	Search	Results
#1	'familial hypophosphatemic rickets'/exp	1146
#2	((familial OR hereditary OR genetic) NEAR/2 (hypophosphataemi* OR hypophosphatemi* OR hypophosphatami*)):ti,ab	381
#3	('x linked' NEAR/2 (hypophosphataemi* OR hypophosphatemi* OR hypophosphatami*)):ti,ab	1309
#4	(rickets NEAR/3 (hypophosphataemi* OR hypophosphatemi* OR hypophosphatami* OR familial OR hereditary OR genetic OR 'd resistant' OR 'x linked')):ti,ab	2489

#5	xlh:ti,ab OR hhrh:ti,ab OR hpdr:ti,ab OR adhr:ti,ab	948
#6	#1 OR #2 OR #3 OR #4 OR #5	3514
#7	'american college of rheumatology/association of rheumatology health professionals annual scientific meeting, acr/arhp':nc AND [2019-2021]/py	2962
#8	'annual meeting of the american society for bone and mineral research':nc AND [2019-2021]/py	2219
#9	'annual conference of the british society for rheumatology' AND [2019-2021]/py	891
#10	'ects':nc AND [2019-2021]/py	814
#11	'eular':nc AND [2019-2021]/py	7764
#12	'ispor':nc AND [2019-2021]/py	8337
#13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	22987
#14	#6 AND #13	72

C7. *Please clarify why clinical trial registers were not searched to identify ongoing or completed but not published trials.*

Clinical trial registries were searched. The searches and results are detailed below.

4th January 2022

Clinicaltrials.gov, n=25

X-linked hypophosphatemia OR X-linked hypophosphataemia | Recruiting, Not yet recruiting, Available, Active, not recruiting, Enrolling by invitation Studies | Last update posted from 01/01/2018 to 04/01/2022

ICTRP, n=42

X-linked hypophosphatemia OR X-linked hypophosphataemia

29th November 2022

Clinicaltrials.gov, n=16

X-linked hypophosphatemia OR X-linked hypophosphataemia | Recruiting, Not yet recruiting, Available, Active, not recruiting, Enrolling by invitation Studies | Last update posted from 01/01/2022 to 11/29/2022

ICTRP, n=0

X-linked hypophosphatemia OR X-linked hypophosphataemia

NCT Number	Title	Acronym	Status	Completion Date
NCT03651505	X-linked Hypophosphatemia Disease Monitoring Program	-	Recruiting	Dec-32
NCT03879915	Dental Implants in Patients With X-linked Hypophosphatemia	IMPLANTS-XLH	Recruiting	December 31, 2022
NCT03748966	Calcitriol Monotherapy for X-Linked Hypophosphatemia	-	Recruiting	Mar-24
NCT03745521	Study of Longitudinal Observation for Patient With X-linked Hypophosphatemic Rickets/Osteomalacia in Collaboration With Asian Partners	SUNFLOWER	Recruiting	December 31, 2023
NCT04695860	Anti-FGF23 (Burosumab) in Adult Patients With XLH	BurGER	Recruiting	Dec-22
NCT04273490	Characterising Pain, QoL, Body Composition, Arterial Stiffness, Muscles and Bones in Adult Persons With XLH and Healthy Controls	-	Recruiting	Sep-25
NCT04049877	Retrospective and Prospective Disease Progression and Quality of Life in XLH	-	Active, not recruiting	Jul-21

NCT03920072	Study of the Anti-FGF23 Antibody, Burosumab, in Adults With XLH	-	Active, not recruiting	January 31, 2022
NCT04946409	Burden of Disease and Functional Impairment in XLH	IdeFIX	Recruiting	Oct-24
NCT04842019	Study to Assess the Safety, Pharmacokinetics and Efficacy of KRN23 in Adult Chinese Patients With XLH	-	Recruiting	Sep-23
NCT04146935	Examining the Effect of Burosumab on Muscle Function	-	Recruiting	May-22
NCT03771105	The Impact of Phosphate Metabolism on Healthy Aging	-	Recruiting	November 30, 2022
NCT03775187	Expanded Access to Burosumab	-	Available	-
NCT05050669	Natural History Study of ENPP1 Deficiency and the Early-onset Form of ABCC6 Deficiency	-	Not yet recruiting	Dec-23
NCT04686175	Evaluation of Safety, Tolerability, and Efficacy of INZ-701 in Adults With ENPP1 Deficiency	-	Recruiting	Mar-23
NCT04846647	Study of the Inappropriate Secretion of FGF23 in Patients Followed in Hospital in a Context of Hypophosphatemia	IFEH	Recruiting	Aug-22
DRKS00016074	Muscle fatigability and X-linked Hypophosphatemia		Not Recruiting	07-Feb-22*

EUCTR2019-003190-26-DE	A study to test an antibody (Antibody Burosumab (KRN23)) to treat Hypophosphatemiazu (decreased phosphat level in the blood) in adults		Authorised	05-Jan-21*

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	XLH UK
3. Job title or position	Trustee
4a. Brief description of the organisation (including who funds it). How many members does it have?	XLH UK, registered England and Wales (1196811), exists to help those with X-linked hypophosphatemia (XLH) and their families living in the UK. We organise events and maintain a website with resources and news. We raise awareness by sharing stories of the lived experience. We also contribute to research into the multiple aspects of this rare condition, to better inform the development of new treatments and standards for best care. XLH UK depend on public donations, grants from other charities, and professional organisations to operate and deliver on its promise. XLH UK has approximately 350 members who are mostly patients, carers, and other family members from who live across the UK and Ireland.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	XLH UK's financial year runs from February 1st – January 31st. • From February 1st, 2022 – January 31st, 2023 XLH UK received a £21,000 financial support request from Kyowa Kirin which represented 95% of its income. The financial support, received in January 2023, from Kyowa Kirin has been allocated to deliver on three priorities identified in our 2023 strategic plan: 1. Patient event: £3,000 for venue, equipment and marketing; £6,000 towards evidence underpinning fresh insights.

If so, please state the name of the company, amount, and purpose of funding.	2. Improve awareness of the charity in UK NHS specialist centres: £2000 for materials and printing. 3. Upgrade of website: £10,000 for design of a secure, off the shelf wireframe which can be maintained by non-specialist volunteers. • In our current financial year, from February 1st, 2023 – January 31st, 2024 XLH UK has received no financial support from Kyowa Kirin during our current financial year. Our income to date from public donations and support has been £3,418.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No, neither XLH UK or its trustees have any direct or indirect links with the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	XLH UK is a patient organisation that gathers insights formally and informally about the patient's lived experience. XLH UK also provides practical information and support for carers, individuals and families suffering with XLH. We provide this service to 300+ patients and carers across England, Wales, Scotland, Ireland, Northern Ireland and the Channel Islands. We are fortunate to hear their experiences through our online discussions and events. We also regularly conduct surveys and hold focus groups exploring issues that are relevant to patients with XLH. To support this NICE patient organisation submission, XLH UK have worked to collect evidence from our community through interviews, newsletters, social media channels and healthcare professionals. We have heard directly from 129 patients and carers who have personal experience of living with or caring for someone living with XLH. 90% were completing as adult patients, 41% of those patients have passed XLH to their children. 15% of the 129 patients were completing as a parent, guardian or carer for their child. 75% of patients came from England, 7% of patients came from Scotland and 18% of patients were from the Wales, Northern Ireland, the Channel Islands, and the Republic of Ireland.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	XLH causes progressively debilitating bone/joint abnormalities along with calcifications of soft tissue, chronic bone pain, fractures, muscle weakness, fatigue, tooth loss, hearing loss, and early-onset arthritis. XLH has dominant transmission, so younger patients observe and are affected by physical/emotional/economic limitations of older generations. XLH restricts the ability of patients and caregivers to fully engage in self-care and parenting, as well as pursuing educational and employment opportunities, which in turn adversely affects their emotional wellbeing. 49% of patients/carers surveyed reported limits to their ability to work full-time. *"I never know where I stand with the pain and discomfort. I can feel ... relatively pain-free for a few moments then I can quickly be in agony. Usually if I feel good and allow myself to do more, I will then see the negative impact of that at a later time when the pain kicks in."* (Patient, age 30s) *"I feel anxious when going out, I avoid socialising, I am no longer physically able to do any leisure activities I used to. I am scared I will lose what's left of my independence and social life."* (Patient, age 30s) *"My health has definitely deteriorated in the last decade. I have bone spurs in my spine..., pain in my back and hips, struggle to walk after short periods at work and I have had to reduce my working hours."* (Patient, age 40s, also carer of patient) Virtually all patients surveyed reported regular use of pain relief medication: • opiates (25%) • over-the-counter pain relief (68%) • anti-inflammatories (13%) • anti-depressants (10%) *"So much pain. ... Very depressed and feel like I've had enough and don't want to go on."* (Patient in 50s, also carer of patient) Note that XLH patients have developed a high tolerance for pain, having never experienced a life without it, which currently available treatment does little/nothing to address.

	"I can't work. I am in chronic pain, and I feel useless. I struggle to get through the day. I don't feel like I have a future." (Patient aged 50s) *"I always feel some sort of pain, legs, hips, back shoulders and teeth/gums. The pain can vary but it's always there. The teeth issues ... pain level at times is beyond severe. I have a young family and running around after the children is extremely difficult and painful."* (Patient aged 40s and carer of patient) Although excellent care is now available to children who may have better futures, existing adults are at high risk of the most disabling disease progression, ultimately becoming a burden on society, family, and healthcare. Many paediatric XLH patients have multiple leg surgeries, and then they often need repairs later in life. Adults have orthopaedic and spinal surgery earlier than the general population: knee/hip replacements as early as 30s, spinal surgery in 50s. Adult patients reported a moderate to severe negative impact on the following in the indicated percentage of respondents: • physical health: 86% • mental health: 68% • social life: 63% • relationships: 61% • money/finances: 53% • ability to work/study: 57%

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Current treatment for XLH adults in England is limited and suboptimal, consisting of oral phosphate supplements and activated vitamin D (pills). The treatment is difficult to tolerate due to bad taste, frequency of doses (every 4-6 hours), and serious adverse side effects, including gastrointestinal distress, diarrhoea, kidney stones, nephrocalcinosis, and hyperparathyroidism. It disrupts the daily work/study routine, with frequent required breaks for the bathroom and to take the many doses. Not all patients can tolerate the current treatment. 20% of patients in our survey were on no treatment at all. *"No treatment, disadvantage my phosphate keeps dropping & I keep getting symptoms. Phosphate supplements ... [give me] severe nausea, heartburn & upset stomach."* (Patient, 40s, and carer for patient) *"Had to come off phosphate treatment due to calcium levels being high."* (Patient, 60s) Given the complicated regimen, a realistic view of the current treatment's effectiveness has to consider the difficulty for even the most well-intentioned/motivated patients to adhere to that regimen while working or pursuing additional education. There are bound to be missed doses, which worsens the inherent ups and downs of phosphorus levels. Phosphorus has a short lifespan in the blood anyway and balancing the dose of supplements while not causing damage to the kidneys or parathyroids, means that even with the phosphorus/activated-vitamin D regimen, patients are constantly going in and out of hypophosphatemia every few hours, leading to less-than-optimal bone quality and inadequate energy for muscles and activity. Beyond the inherent difficulties in maintaining a complicated dosing schedule, patients report that the regimen isn't effective. 43% of surveyed adult patients currently take either phosphate plus activated vitamin D or the D alone. Of those taking both, 38% find it ineffective, 25% find it slightly effective and only 4% found it very to extremely effective. *"I am in a great deal of pain. I suffer with my joints, muscles, bones and teeth. I feel that I am falling apart and my current medication doesn't seem to be doing anything to combat this."* (Patient, 30s) *"How can a medication that helps with the XLH yet makes it impossible to stray too far from a toilet be effective. When the side effects create anxieties and embarrassment. It leaves me feeling depressed with extreme low self-esteem."* (Patient, 40s, also carer)

	"The medication helps with pain but I am never entirely pain free." (Patient, 50s) Finally, there is also a significant cost, to both the patient and the health care system, to the current treatment regimen of phosphate and vitamin D. Given the significant potential side effects (hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis, chronic kidney disease, and hyperparathyroidism that may require specialist endocrine surgery that has significant risks), along with variable responses from patient to patient (dosing is trial-and-error, not standardised), the regimen requires close monitoring by health care professionals by way of regular bloodwork and regular kidney ultrasounds. Also, when patients see little improvement to their skeletal health and fatigue from the current pharmacological treatment, they are left with nothing but surgical intervention to correct any unresolved bone deformities that are likely to worsen and contribute to even greater disability.

8. Is there an unmet need for patients with this condition?	There is undoubtedly an unmet need for patients. We believe that Burosumab is the only truly effective treatment for adults because it consistently normalises the blood phosphate levels, since risk-benefit analysis comparing the low effectiveness of the existing treatment with its side-effects often leads to the decision not to provide any treatment to adults. And when patients did get the existing treatment, they report very little benefit. The impact on family and carers is basically the difference between caring for a loved one who has no treatment whatsoever and someone who has an effective treatment. *"Since being on burosumab I am able to work longer hours to a high ability. I need less breaks. I am able to participate in local/community activities. I have been able to travel solo for the first time in my life. Prior to burosumab being available I would have not considered having children but now I [am considering it], consequently having a positive impact on relationships. ... I would not have wanted my children to experience the [pain] I have…"* (Patient, 30s) When asked for the three biggest improvements with burosumab, patients mentioned having greater freedom, feeling happier, being in less pain, and being more mobile. The following percentages of adult patients reported positive impacts on their lives with burosumab: • Physical Health: 81% • Mental Health: 56% • Social Life: 64% • Relationships: 50% • Money/Finances: 42% • Ability to work/study: 69% At present, with no effective treatment for adults, family members and carers frequently have to take time out of their work schedule to support other family members with appointments or home care, or even pause their own career to care for their loved ones. As the patient's health improves with treatment, there will be fewer demands on the family/carers' time. *"Since starting burosumab my mobility has improved I couldn't get out of bed do my personal care or any everyday tasks without help I walked with a walking frame depended on constant pain relief which I have now reduced and I now walk with crutches so a big improvement."* (Patient, 50s)

	Similarly, there will be important improvements to the emotional wellbeing of the family/carers. Carers expressed emotional burdens directly related to their loved ones' health. Some feel anger or sadness that their life is no longer their own, while others were anxious about seeing the patient deteriorate and worried about future generations who could inherit XLH. With better treatment, there is less worry about their loved one's pain, worsening health, disability, and the likelihood of invasive surgery. They will worry less about financial issues, including both the patient's need to take time off from work (or early retirement), and their own need to take time off to support the patient. Further, given that XLH is a genetic disorder, there are frequently more than one family member affected by XLH in a given household, with patients both giving and receiving support. 35% of our community have more than one family member affected by XLH, doubling (or more) the impact on the whole family. As the patient's health improves with better treatment, the burden on the family drops.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We believe burosumab will improve patients' quality of life and experience of care in five key ways: 1) convenience of regimen, which also improves effectiveness by reducing non-compliance; 2) reduced need for corrective orthopaedic surgery; 3) reduced need for pain medication; 4) reduced disability as a result of better bone quality; and 5) increased emotional wellbeing and self-esteem due to increased ability, mobility, function and reduced pain. Burosumab is administered by injection, once every four weeks, compared to the current treatment which is taken multiple times a day, every day (with concurrent gastrointestinal issues), requiring frequent breaks from work, education, and other daily activities. Further, burosumab is simply more effective, both objectively and subjectively (better bone quality, reduced pain). Many disabling symptoms are not significantly improved by the existing regimen, but patients report improvements while on burosumab. Patients who were prescribed burosumab through England's Early Access Programme (available since 2019) and The Scottish Free of Charge Scheme (2021) make up 37% of the surveyed patients. **A stunning 95% of those adults reported burosumab was moderately to extremely effective on their XLH symptoms (compared to 4% who found the existing regimen very effective).** *"It has given me my life back, physically, emotionally, socially, not being in pain is huge and being able to have the confidence to achieve even the most mundane tasks that most people would take for granted. Then my self-esteem was low because I felt I'm letting people down by not physically being able to complete jobs."* (Patient, 60s) *"Burosumab has greatly improved the way I can access the world and the way I feel on a day-to-day basis. I have far more flexibility in my day as it is not all based around the timing of the next dose of medication, I am able to walk further and partake in a wider variety of exercise without extreme pain and finally, I feel like it gives me the freedom to be much more like a normal 19-year-old at university."* (Patient, 19) *"Burosumab has been very effective compared with phosphate for me. Not only am I pain free, and can move more freely without complaining or having any bone aches and pain,"* (Patient, 30s)

	"Treatment could not be easier. Burosumab has allowed me to ... maintain a good quality of life for the first time in my life. ... I no longer have pain, fatigue, and mental exhaustion for the first time in my life. I can finally live my life to the same quality as my peers. I now have zero anxiety about my ageing process for the first time." (Patient, 30s) XLH is a progressive disorder, so the sooner a patient receives effective treatment, the better the likelihood they won't become reliant on family, carers, government disability benefits and other social services. Further, with a more effective treatment, patients see improvements to their emotional wellbeing health, and feel less pressure to make unwanted lifestyle decisions (job changes, home relocation or adaptation to accessible bathroom/kitchen or ground floor bedrooms) due to poor health.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We see very little in the way of disadvantages to burosumab treatment. The main reported adverse effect is a temporary injection site irritation, which can occur with any subcutaneous injection. We are not aware of any patients who found it particularly troublesome, certainly not to the degree that it outweighed the benefits of burosumab, so that they considered discontinuing treatment. While some patients might be uncomfortable with needles, evidence from our survey suggests that XLH patients were overwhelmingly comfortable with the idea of a subcutaneous injection. 92% of patients reported that burosumab was Easy or Very Easy to use. That contrasts with the existing treatment that patients have long found to be extremely burdensome. In theory, the need for regular medical monitoring might be considered burdensome, but currently patients on either treatment are asked for blood tests upon every visit to the specialist hospital, so there would be no significant difference between the two treatments. Most patients are not concerned about the need for blood draws, and the need for kidney ultrasounds will, if anything, be reduced with burosumab, compared to the existing treatment. At present, needing to get the injections administered by a healthcare professional once a month is mildly burdensome in terms of arranging appointments. That is not inherent in the treatment however, and we expect that with appropriate training and guidance, patients will be allowed to self-inject in the future or have partners manage the injection for them. We are aware of only one side effect of burosumab that is even slightly burdensome to the patient. 8% of patients that we surveyed who are currently prescribed burosumab have reported having restless legs in the evenings (Restless Leg Syndrome). However, there are remedial treatments, either by lowering the dose of burosumab or adding another medication specifically for RLS. We are not aware of any patients who have deemed this side effect to be so burdensome as to outweigh the perceived benefits of the burosumab treatment.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes, there may be certain groups of patients who could benefit more or less from the use of burosumab in adults, depending on their severity of their symptoms. For example, patients who have at the very least been prescribed phosphate and vitamin-D but still present with orthopaedic fracture, bone pain and fatigue may benefit more from burosumab because their condition is more severe and may have greater scope for improvement. On the other hand, adult patients who experience mild symptoms of XLH may not see as significant of an improvement in their symptoms with the use of burosumab.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	XLH UK have commissioned independent patient case-studies to help illustrate the impact that XLH has on individuals and their families. Please visit: https://xlhuk.org/patient-stories/ to view our collection. XLH UK has also accompanied this submission with its own independent research titled: **Burden of disease and perspectives on treatment** Filename: XLHUK-Burden of disease and perspectives on treatment.pdf (We understand our research report will be included as an appendix to this submission for the committee's reference).

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• XLH is a devastating progressive disease. The heavy symptom burden affecting both physical and mental wellbeing and the dominant hereditary nature of the disease are two crucial factors contributing to the quality-of-life deficit experienced by patients and carers. Due to the symptom burden, patients often have to give up work or reduce their hours. Those who do work say it is a struggle to manage and are concerned about their ability to continue working. • There are significant unmet needs. No other treatments tackling the underlying cause of XLH are currently available to adults and current symptom management approaches have limited effectiveness. • Burosumab provides a potential significant step change in the management of this disease for adults with XLH: it has proven to be superior at reducing the most burdensome symptoms and can be administered in a way that does not impose an additional burden on family members and, by its nature, supports patients to be independent. • This is a situation where there are clearly additional benefits (e.g., on carers/family members, productivity, convenience, independence etc.) that may not be captured in either the clinical evidence or economic modelling; and these need to be factored in. • 95% of adults on burosumab report it to be moderately to extremely effective.

Thank you for your time.

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Your privacy

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Single Technology Appraisal

NICE clinical expert invitation 1: X-linked hypophosphataemia (adults) - burosumab [ID3822]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating X-LINKED HYPOPHOSPHATAEMIA (XLH) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	UNIVERSITY OF OXFORD/ OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
3. Job title or position	PROFESSOR OF OSTEOPOROSIS AND RARE BONE DISEASES
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with XLH? ☒ A specialist in the clinical evidence base for XLH or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NO
8. What is the main aim of treatment for XLH? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Stop progression Prevent complications Improve physical and mental wellbeing

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in complications Prevention of complications Improved physical and mental function
10. In your view, is there an unmet need for patients and healthcare professionals in XLH?	Yes
11. How is XLH currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Only international guidance NHS facing Pathway for adults in progress through the NHS Rare Disease Collaborative Network (RDCN) for Adult Rare Bone Diseases and XLH-UK Significant impact, transformative
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will reduce current care requirements as patients have slower/ no progression Specialist care network with secondary care spokes Training Network support to ensure adequate expert input for patient selection, drug initiation, evaluation of benefit and stopping criteria
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Significant benefits are expected Yes increased survival

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes increased quality of life
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with significant clinical disease and those with treated paediatric disease to prevent onset of complications.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Burosumab requires early treatment titration with 2 week phosphate peak and 4 week trough.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	These are in draft and summarised below for musculoskeletal pain and pseudofracture and will be finalised by the RDCN. **Musculoskeletal pain and stiffness** – The key aim is to identify the dominant cause(s) for pain from osteomalacia bone ache, (pseudo)fractures, enthesopathy, osteoarthritis, and chronic widespread pain based on history, examinations, laboratory testing and imaging.

	Physiotherapy assessment for reducing pain through general and targeted exercise. Simple analgesia (paracetamol 1g tds) Oral NSAID if < 65 years of age Glucocorticoids or colchicine are not recommended. Shockwave lithotripsy is not recommended for enthesopathic pain due to a lack of data Consider referral to orthopaedics if joint based and not responding to the above measures. Consider 3 month trial of oral phosphate and activated vitamin D unless already tried in the last 24 months for similar symptoms. A baseline blood sample to measure PTH, 25-OH vitamin D, serum adjusted calcium and eGFR, fasting urine for measurement of urinary calcium/creatinine ratio (either fasting morning spot or 24-hour collection) and renal ultrasound to establish pre-treatment status regarding

	possible nephrocalcinosis/nephrolithiasis should be performed. Vitamin D deficiency should be corrected to maintain values ≥50 nmol/L. The aim is to return the phosphate to the lower limit of the normal range without causing worsening hyperparathyroidism and hypercalciuria. Treatment should be started with calcitriol 0.25 µg/day twice daily or alfacalcidol 0.5µg/day in a single daily dose in adults. Doses will need to be titrated as necessary, providing serum and fasting calcium/creatinine spot urine samples or 24-h urinary calcium measurements are regularly monitored to avoid hypercalciuria and the associated risk of nephrocalcinosis/ nephrolithiasis. Calcitriol should be titrated in 0.25 µg/day steps and alfacalcidol 0.5µg/day. Serum and urinary calcium excretion should be measured within a week of a dose change.

	The dose of active vitamin D should be titrated to suppress hyperparathyroidism and maintain the urinary calcium excretion just below the upper limit of the normal laboratory reference range. An ultrasound of the kidneys is recommended in case of persistent hypercalciuria or yearly if the patient is on active vitamin D and phosphate supplements. Phosphate supplements should be given in the form of a drink containing one mmol/ml of phosphate divided into multiple doses throughout the day, e.g. 5-10 ml TDS for adults and 1–3 ml/kg body weight qds for children. The dose of phosphate supplement should be titrated to maintain serum phosphate at the lower end or below the normal laboratory reference range for serum phosphate. Care should be taken to avoid overtreatment. Patients should be advised of the potential for gastrointestinal upset and to consider taking a smaller dose more often.

	Long-term phosphate supplementation is associated with chronic stimulation of parathyroid hormone secretion, potentially leading to 4-gland hyperplasia and autonomous hyperparathyroidism precluding the further use of active metabolites of vitamin D and requiring surgical intervention to remove the hyperplastic glands. Serum calcium, PTH concentrations and 24-hour urinary calcium need to be monitored after one month of therapy initiation, one month after any dose changes and every 6 months. Renal uss every 2 years. Increased ALP in otherwise well-controlled hypophosphatemia may signify poor compliance e.g. when patients improve their compliance shortly before clinic visits. If secondary hyperparathyroidism is present, first correct vitamin D deficiency, then alfacalcidol may be increased, phosphate doses decreased. In case of hypercalcemia or hypercalciuria (as measured by 24-hour urine collections, the active vitamin D derivate dose must be reduced

	In patients receiving active vitamin D analogues and phosphate, monitoring of 1,25(O.H.)2D is not recommended because supraphysiological doses may be required to maintain PTH and calciuria within the desired range. If not tolerated or there is no benefit after three months of treatment, and average pain over the last 7 days is ≥ 4 /10 and clinically attributable to XLH and not arthritis or fracture then then refer to regional MDT to consider/ burosumab (if available). The patient needs have a molecular confirmation of XLH. The patient needs to be given information on the benefits, risks and cautions of burosumab therapy. The most common unwanted effects are back pain, headache, restless leg syndrome and dizziness, constipation, injection site reaction, vomiting, and fever(6). Burosumab is not recommended during pregnancy, and in women of childbearing potential, not using contraception

	The starting dose of burosumab is 1.0 mg/kg body weight (maximum dose of 90 mg) given subcutaneously every four weeks Fasting serum levels of phosphate should be assessed At weeks 2, 4, 8, and 12 after initiation. After a stable dose of burosumab is established, six-monthly monitoring of fasting serum phosphate levels predose is recommended Four weeks after each dose adjustment. The dose should be omitted if the fasting serum phosphate level predosing is above the upper limit of normal. Burosumab can be restarted at approximately half of the previous dose when serum phosphate concentration is below the normal range. Review Burosumab therapy annually within an MDT and consider stopping burosumab after 12 months if average

	pain over the last week has not improved AND there has not been a reduction in analgesic use from baseline. If average pain severity is ≥ 4 /10 over the last week, re-assess the source of pain, referral to pain service/ opioid medication with clear discussion on risks and benefits of therapy **Pseudofracture fracture (needs orthopaedic input)** The aim is to heal the fracture and prevent complications. Management should be coordinated between the orthopaedic and the local bone team. If the conclusion that pseudofracture is at high risk for worsening deformity or complete fracture than refer to MDT for consideration of burosumab (if available).. Give the patient advice to off load the limb, limit activities and seek urgent help if there is a sudden increase in pain

	Consider 3 month trial of oral phosphate and activated vitamin D as above if not tried before where the risk for worsening deformity or complete fracture is low or moderate. If not tolerated / no benefit/ progression, then refer to regional MDT to consider Burosuamb. Consider referral for surgery if evidence of deformity or severe pain is not responding to pharmacotherapy. Three months after radiological evidence of fracture healing, consider switching to oral phosphate and activated vitamin D to prevent recurrence. Consider lifelong burosumab if recurrence of pseudofracture.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes, joint / back musculoskeletal related impact is poorly measured. Impact on carer/ family health related benefits.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes. First in class that addresses the mechanism directly. Unmet need for adults with XLH with effective treatment for pain, function and pseuofractures
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Injection site reactions are usually well managed Restless legs can be managed by dose reduction The longer term impact of phosphate restoration on Cardiovascular disease outcomes is unknown.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes for adults with moderate/ severe musculoskeletal symptoms For adults transitioning from childhood therapy there is no direct data but we know: 1. The complications of adult XLH – osteoarthritis, spinal disease are incurable 2. Complications of adult XLH reflect premature aging 3. In children treated with burosumab with effectively normal skeletons there is the potential to avoid this irreversible complicaitons. Some patients develop a transient severe thoracic pain syndrome that can respond to dose reduction.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No

23. How do data on real-world experience compare with the trial data?	The real world evidence complements the trial data by informing the wider impact of XLH
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	XLH in adults is disease of deprivation, probably due to disability. Excluding access to burosumab will increase disability from physical and mental wellbeing perspectives, worsening inequality.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

XLH in adults causes progressive premature complications with significant impact on physical and mental wellbeing

Burosumab is a first in class agent that significantly improves physical outcomes in adults with significant disease

The potential to prevent skeletal complications in those transitioning from paediatric use of burosumab is expected.

The recent Rare Disease Collaborate Network for Adult Rare Bone Disease presents an implementation framework for NHS delivery of burosumab including an adult diagnosis, assessment, management and monitoring by linking expert centres to provide national coverage.

The wider impact of XLH in adults in underestimated by the research evidence due to lack of standardised assessment pathway.

Thank you for your time.

Your privacy

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Single Technology Appraisal

X Linked Hypophosphataemia (adults) - burosumab (ID3822)

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with X-linked hypophosphataemia or caring for a patient with X-linked hypophosphataemia.

The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **30/10/2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Patient expert statement

Part 1: Living with this condition or caring for a patient with <<this condition>>

Table 1 About you, XLH, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with X-linked hypophosphataemia? ☒ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with X-linked hypophosphataemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	XLH UK registered charity
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with XLH? **If you are a carer (for someone with XLH) please share your experience of caring for them**	I have XLH, as do 6 other members out of 12 members of my close family; my father, 2 children, 2 sisters and nephew have XLH. I have suffered all my life with the symptoms as have my other family members who suffer with varying symptoms due to the condition. We are a close family and I try to support all my family members as much as possible. I suffered with severe leg bowing during childhood causing pain and reduced mobility and many dental issues, as well as depression due to bullying at school etc, due to the very visible disability. I had two operations at 17 and 18 years old to straighten my severely bowed legs, which left me aesthetically much improved. This in turn improved my leg pain and stiffness a little and made me look and feel more 'normal' which in turn improved my mental health. All my family members with XLH are disabled but the severity has varied. I and my father and youngest sister have been able to work throughout our lives and have children. However, my other sister is so severely disabled she has never been able to work and was only able to have one child as her physical disability meant it would be too detrimental to her physical health to have any more children. We all live with daily pain, stiffness and mobility issues. However, the chronic pain my sister has after 7 different surgeries to correct leg bowing, and then a spinal surgery, has left her at 41 years old with constant pain, very little mobility and only able to cope by relieving her pain with morphine and other nerve drugs. She suffers with depression due to the impact this condition has on her life. Many days she is trapped in her home as she can't even walk up and down stairs. I support her with lifts to and from medical appointments, physio, chiropractor, hydro-therapy, GP and hospital appointments etc, as she can not drive. All my life, I have had to support

	and help my sister and her son, as she is unable to do many things for herself. I had to do the same for my father from his late 60s. I had daily pain in my legs, arm, neck and back, and also stiffness and weakness. It was very hard when my children were young as both my children have XLH so both had mobility issues, my son being very disabled up to age 3 years old with severe leg bowing. He therefore needed help to walk, so he had to be in a pushchair where possible or carried, which I found very difficult and impacted my arm bowing and pain. It was also very upsetting to see both my children suffer with pain and unable to live a 'normal' life due to this condition.
7a. What do you think of the current treatments and care available for XLH on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The current treatment had no noticeable positive impact for me or any of my family members. Despite taking the medications (Alfacalcidol and Phosphate) throughout childhood as directed, all members of my family had severe leg bowing requiring various surgeries. I can not say that it would have been worse without those treatments of course but all I can state is that we have all had to have corrective bone surgeries, and a multitude of other symptoms causing pain and reduced mobility caused by XLH including spinal stenosis, arm bowing, nerve pain, spontaneous dental abscesses and more. We all continued the current treatments into adulthood but continued to suffer with all these symptoms resulting in pain and reduced mobility and impacting our ability to live a normal happy life. We continued to have bloods checked every 6-12 months and despite taking current treatment above, our phosphate levels were always too low which meant our phosphate and other vitamins were never 'normal' so I did not know what benefit the current treatment was providing. I stopped the treatment in adulthood for 8 years due to finding no benefit from the treatment but had some awful side effects like stomach pain and diarrhoea, and I didn't notice any difference to my symptoms so from that, drew the conclusion, that it had no benefit. When I started back on the treatments as my symptoms got worse as I was getting older, I still struggled to see a benefit and found the side effects the same but continued with it as I felt it was the only option, despite not really seeing any benefit.

	Both my children had the Phosphate and Alfacalcidol treatment from around age 3 months, and both still had leg bowing, spontaneous dental abscesses etc. and pain and mobility issues. This did not improve until they started on burosumab. I have seen no benefit to the current treatment whatsoever in all honesty.
8. If there are disadvantages for patients of current NHS treatments for XLH (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Taking the phosphate caused me stomach pain and diarrhoea. It also tastes extremely sour and so is very unpleasant to take. I used to take it in a strong-tasting juice to try and hide the taste but it really is very unpleasant. My other family members had the same experience, so I believe this is very common.
9a. If there are advantages of burosumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does burosumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a. There are many advantages over the current treatment. I now have much less pain and stiffness in my legs which in turn results in improved mobility allowing better quality of life - sleep improved - all around better physical and mental wellbeing. Less pain means I can be more active. This improved mobility benefits further physically and mentally. Being more mobile, helped me lose weight and improved mobility improved health all round and reduced depression. I now enjoy life more as I can do things I could not do like walking, playing with my children, riding a bike, tennis etc. My children receiving burosumab treatment has also had an enormous impact to my life. My children are no longer disabled and suffering with pain and mobility issues as well as feeling and looking different to other children. My children now live normal healthy lives at mainstream schools, physically their appearance is no different to a child whose appearance would be considered 'normal'. This has had an enormous impact on my life of course; physically and mentally. They can walk normally and do not have pain so no longer need me to carry or push them in a chair, which is so important for me as I already have arm bowing and irreparable damage due to carrying and pushing my son in a chair when he was age 1-3 years old. I also carried a huge amount of guilt and sadness from passing my children this condition and seeing them suffer. I no longer feel this guilt and sadness as the new treatment has changed their lives entirely and in turn mine.

	9b. Increased mobility is the biggest advantage as I can now live as normal a life as possible which directly impacts my physical and mental health, improving my quality of life. 9c. Yes the new treatment does not have any side effects for me. I self administer the injection monthly at home. It is simple and quick and has no side effects. I no longer have stomach ache or diarrhea from the Phosphate, and more importantly, the treatment does work as my blood tests now always show my phosphate levels are normal and other blood results all normal which I never had on the current treatments.
10. If there are disadvantages of burosumab over current treatments on the NHS please describe these. For example, are there any risks with burosumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No disadvantages or risks as far as I'm aware from my experience. The treatment is far superior to the current as most importantly, the blood results and quality of life I now have prove that it actually works.
11. Are there any groups of patients who might benefit more from burosumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	From what I have experienced and seen in my family, all have seen benefits, but what does seem to the case in my family is that patients with more symptoms (worser cases of xlh), the longer it takes to see the benefits. My sister has taken longer to see the benefits than I did as she is a more severe case. However, we can not know how much worse she would be without the treatment, for example, she had to have spinal surgery – a T10 decompression caused by calcium deposits forming on her spinal cord (caused by xlh) crushing her spinal nerves and causing pain and other symptoms. It was expected that these calcium deposits would grow again but these have not grown back. Her consultant believes this is now because her blood and bone mineralisation is now normal so calcium deposits should no longer occur. If they had, she would have had to endure further spinal surgery which the Surgeon/Consultant has advised carries a high risk of causing paralysis. He said that he would never want to have to operate again. The consultant believes burosumab is the only reason these calcium deposits have not started to grow again. This treatment benefits all of us but in my sister's case, she is benefiting even more as otherwise she would likely end up being wheelchair user. We all find this treatment has improved our symptoms and we all find the new therapy easier to

	administer as its monthly. We have all seen our blood results show that our phosphate levels are normal which has never been the case prior to the new therapy.
12. Are there any potential equality issues that should be taken into account when considering XLH and burosumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No.
13. Are there any other issues that you would like the committee to consider?	I am terrified of being taken off the treatment. I had around 3-4 months of feeling more pain and more disabled when I first started the treatment, but since then, I have improved month on month, and have felt better than I ever have in my life for the last 18 months. I am terrified that my health would deteriorate back to where it was or even worse if the treatment were stopped, as the benefits now are beyond words. I have little or no pain and I am physically and mentally in a much better place. I am now getting older and I do worry that as I get older, things would deteriorate even more with this condition. I watched my father deteriorate from his late 40s to his 80s massively and much more so than other people without the condition resulting in pain, immobility etc requiring surgeries which take much longer recovery for people with XLH. I am worried that my latter years would be

	filled with pain, immobility and a much reduced quality of life if the therapy was not available and I strongly believe that would be the case from my own experience and having seen my father deteriorate in old age, much more than non XLH patients; it is a life-long debilitating condition that accelerates in older age, and results in a very poor quality of life. A further consideration needs to be that this treatment is given to children with xlh from 1 year old. My son [redacted] has been on the treatment since age 3 years old and my daughter has been on the treatment since age 9 years old, around 5 years. Both my children had leg bowing, pain and other issues. My son who is now 8 was severely disabled with leg bowing and severe pain meaning he couldn't walk far at all, about 25 metres without pain. Since starting the treatment at age 3, his legs have straightened again and he has grown normally and he is now a normal healthy boy. He looks the same as other children, goes to school and even plays football in a football team, plays tennis, does swimming. He lives a normal life and looks like every other child of his age. If adults do not have access to this treatment, when my children stop growing, the treatment will be stopped. This terrifies me even more than having it taken away from me. Both my children have had normal bloods for over 5 years now and have gone from being disabled children to being normal and healthy. If the treatment is stopped, their blood levels will return to pre-burosumab days and their Phosphate and other vitamin levels will be low, causing further health issues in adulthood. It will have an impact on all their bones, teeth and their general health. Surely inflicting this on children who are now fit and healthy as a result of burosumab is cruel and unnecessary. Not to mention the costs to the NHS of their ill health in the future years.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I suffered my whole life with pain and immobility and depression due to symptoms of XLH.
- It clusters in families due to being X inherited so many members of a family often suffer with the it making it even harder to support our children and each other; a heavy burden for all.
- The new therapy has been life changing for me and my family members improving pain, mobility and hugely improving our quality of life.
- The current treatment does not work and provides no benefit, just negative side effects in my experience and that of all my family members.
- I am terrified of having the treatment stopped as my quality of life is so much better since starting the treatment and my blood and bone mineralisation are now normal for the first time in my life. I am so scared that I would go back to how I was or even worse now that I am older. Many children have been receiving the treatment for many years including my children and my nephew, and when they stop growing, they now face having the treatment stopped and their health deteriorating. Surely inflicting this on children who are now fit and healthy is cruel and unnecessary. Future costs for the NHS of the ill health of xlh sufferers are likely to outweigh any continued burosumab treatment costs.

Thank you for your time.

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External Assessment Group Report
Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

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Rider on responsibility for report

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Contributions of authors

Alexis Llewellyn took chief responsibility for clinical sections of the report and wrote most of Section 3 of the report.

Anqian Zhou performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 5 of the report.

Thai Han Phung performed the critical review of the economic analyses, and contributed to drafting Section 4 of the report.

Martin Njoroge wrote Section 2 of the report.

Melissa Harden performed database searches and provided information service support.

Simon Walker provided advice and support for the economic modelling.

Mark Simmonds had overall responsibility for the clinical sections of the report, performed additional statistical analyses and takes joint responsibility for the report as a whole.

Claire Rothery performed the critical review of the economic analyses, conducted the EAG additional analyses, wrote Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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Abbreviations

Abbreviation	Definition
6MWT	Six-minute walk test
AE	Adverse event
ALP	Alkaline phosphatase
BALP	Bone-specific alkaline phosphatase
BFI	Brief Fatigue Inventory
BMI	Body mass index
BPI-Q3	Brief Pain Inventory-Short Form question 3
BPI-SF	Brief Pain Inventory-Short Form
CC	Complexity and comorbidity
CI	Confidence interval
CPRD	UK Clinical Practice Research Datalink database
CS	Company submission
CSR	Clinical study report
CTx	Carboxy-terminal collagen crosslinks
DMP	Disease monitoring programme
EAP	Early Access Programme
EMA	European Medicines Agency
ENT	Ear, nose, and throat
EPAR	European Medicines Agency public assessment report
EQ5D	EuroQol health-related quality of life questionnaire
EQ5D-5L	5-level EuroQol health-related quality of life questionnaire
EU	European Union
FAS	Full analysis set
FGF23	Fibroblast growth factor 23
GEE	Generalised estimating equation
GFR	Glomerular filtration rate
GP	General practitioner
HES	Hospital Episode Statistics
HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly specialised technologies guidance
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
IgG1	Immunoglobulin G subclass 1
IMD	Index of Multiple Deprivation
iPTH	Intact parathyroid hormone
KRN23	Burosumab
LLN	Lower limit of normal

LS	Least squares
LYG	Life years gained
MCID	Minimum clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
OR	Odds ratio
P1NP	procollagen type 1 n-terminal propeptide
PAS	patient access scheme
PHEX	Phosphate-regulating endopeptidase X-linked
PRO	Patient-reported outcome
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTH	Parathyroid hormone
QALY	Quality-adjusted life year
RCT	Randomised clinical trial
RWD	Real-world data
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36v2	36-item Short Form Health Survey version 2
SmPC	Summary of Product Characteristics
SMR	Standardised mortality rate
SoC	Standard of care
TA	Technology appraisal
TUG	Timed Up and Go test
UCLH	University College London Hospitals NHS Foundation Trust
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphataemia

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and alternative scenarios, with resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

The EAG notes that it submitted points for clarification (PFC) on the company submission to NICE; the company noted they sent their responses to PFC on 23 June 2023, but the EAG only received these on 11 September 2023 along with factual accuracy checks (FACs), hence after the submission of the EAG report on 3rd August 2023.. This report version therefore incorporates information from the company's FACs and, where feasible, information contained in the company's PFC response as well, where appropriate.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

ID3822	Summary of issue	Report sections
1	Difference between NICE scope and company decision problem in terms of who is eligible for burosumab	Section 2.3.1
2	Definition of treatment failure with conventional therapy and size of eligible adult population to receive burosumab in the NHS	Sections 2.3.3 and 4.2.3
3	Generalisability of the cost-effectiveness data and trial evidence to a burosumab-experienced population	Section 4.2.3
4	Baseline imbalances in the CL303 trial	Sections 3.2.3 and 3.5.1
5	Lack of efficacy of burosumab on patient-reported outcomes.	Sections 3.2.4 and 3.5.1
6	Age and weight distribution of CL303 population	Section 4.2.3
7	Modelling the incidence of morbidities and mortality as independent events	Section 4.2.2
8	Excess mortality for individuals with XLH	Section 4.2.2.2
9	Treatment stopping criteria and long-term discontinuation rates	Section 4.2.6.1
10	Burosumab reduction in fracture incidence rates	Section 4.2.6.2
11	Burosumab effect on mortality	Section 4.2.6.3
12	The effect of burosumab treatment on utility change from baseline and extrapolation of effect over time	Section 4.2.8.3
13	Placebo-adjusted utility values	Section 4.2.8.3
14	Disutility for incident fractures	Section 4.2.8.4
15	Utility benefit on caregivers and family members	Section 4.2.8.4

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are: (i) patient age and weight distribution is based on participants in burosumab's Early Access Programme (EAP) in England rather than the CL303 population in the company's base case; (ii) excess mortality risk due to XLH is based on the CPRD AURUM database with a hazard ratio of 2.33 compared to the general population, which is approximately 30% lower risk than the hazard ratio of 2.88 used in the company's base case; (iii) the same treatment tapering effect is used for mortality and morbidity, whereas these are inconsistent in the company's base case; (iv) the effect of burosumab on utility change from baseline is based on extrapolating WOMAC data up to week 96 from CL303, i.e., excluding post-week 96 data from BUR02 as used in the company's base case; (v) the utility benefit for caregivers and family members is applied to one caregiver/family member rather than two in the company's base case.

The selection of changes made to the EAG base case is based on the available evidence; however, a number of important uncertainties remain. To address the remaining uncertainties, the EAG presents a

number of scenarios on the EAG base case. These include alternative assumptions to the company's base case relating to: (i) a reduction in the incidence of fractures with burosumab of 75% or 50%, compared to the company's assumption of 100% reduction equal to that of the general population; (ii) a mortality benefit associated with burosumab of 0% (no evidence is available to support a mortality benefit), 11% (based on evidence of the effect of treatments for osteoporosis on fracture-related mortality risk) or 25% (to account for additional multi-system effects other than fractures), compared to the company's assumption of 50%; (iii) utility benefits for burosumab based on adjusting the utility change from baseline for the placebo effect observed in CL303 and applying a disutility for incident fractures in the first year of the event only, compared to the company's assumption of non-placebo-adjusted utility values and lifetime disutility associated with fracture events.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the probability of serum phosphate normalisation for burosumab compared to standard of care (SoC) and, thereby, reducing the incidence of fractures and consequent disutility associated with fracture events.
- A reduction of 50% in excess mortality due to XLH for burosumab compared to SoC.
- Improvement in health-related quality of life for burosumab compared to SoC through a reduction in fatigue, pain, stiffness and improvement in physical functioning as captured by changes in WOMAC scores from baseline, mapped to EQ-5D utility values.
- Improvement in health-related quality of life of caregivers and family members that is equivalent to 20% of the patient utility benefit of burosumab and applied to two family members.

Overall, the technology is modelled to affect costs by:

- Greater acquisition and administration costs for burosumab compared to SoC.
- Increasing the probability of serum phosphate normalisation for burosumab compared to SoC results in lower disease management and morbidity costs.

The modelling assumptions that have the greatest effect on the ICER are:

- The utility benefit of burosumab on caregivers and family members.

- Placebo-adjusted utility values.
- Disutility for incident fractures included for one year only.
- Percentage reduction in the incidence of fractures.
- Burosumab's utility change from baseline based on extrapolating WOMAC data up to week 96 of CL303, i.e., excluding post-week 96 data for the extrapolation.
- Percentage reduction in excess XLH mortality risk with burosumab.
- Age and weight distribution based on participants in the EAP.
- No treatment stopping criteria applied in the first year.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Difference between NICE scope and company decision problem in terms of who is eligible for burosumab

Report section	Section 2.3.1
Description of issue and why the EAG has identified it as important	The NICE scope and company scope differ on who might receive burosumab. The NICE scope includes all adults with XLH. The company scope is restricted to patients with at least moderate pain (BPI ≥ 4) and for whom conventional therapy is unsuitable. The EAG notes that burosumab is likely to be used only for people with symptomatic XLH where symptoms cannot be reasonably controlled by other medication. However, the definition of which symptoms are considered sufficiently severe to merit burosumab use is uncertain.
What alternative approach has the EAG suggested?	The EAG considers that patients with a range of uncontrolled symptoms, and not pain alone, would potentially be eligible for burosumab. This might include physical functioning and presence of fractures and pseudofractures.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Future evidence on the effectiveness and safety of burosumab for patients with a wide range of symptoms, including additional evidence from the UK EAP, would be useful.

Issue 2 Definition of treatment failure with conventional therapy and size of eligible adult population to receive burosumab in the NHS

Report section	Sections 2.3.3 and 4.2.3.
Description of issue and why the EAG has identified it as important	Burosumab is positioned in a subpopulation of the licensed indication in adults in those for whom there are no alternative treatment options available, i.e., in those for whom conventional phosphate therapy is unsuitable due to ineligibility, intolerance or insufficient efficacy. This differs from the current entry criteria for the burosumab EAP in England. Although the company's positioning broadly aligns with the EAP population, the EAG considers there to be uncertainty about the precise definition of treatment failure with conventional phosphate therapy for burosumab to be considered as an alternative treatment option, which leads to uncertainty regarding the size of the eligible adult population who may receive burosumab in the NHS. Keen *et al.*, (2021)[1] estimates that approximately 152 patients (49.8%) out of a total of 305 adults with XLH in England may be eligible for burosumab based on the EAP inclusion criteria; however, Keen *et al.*, (2021) also acknowledges that the XLH population in England ranges from 291 to 578 adults and uncertainty remains on the number of patients affected by debilitating symptoms and clinical complications.
What alternative approach has the EAG suggested?	The EAG considers it highly likely that there is a proportion of adults who will continue to take conventional therapy intermittently over time, i.e., some patients may discontinue conventional therapy for a period of time due to insufficient efficacy, but restart therapy at a later point in time as symptoms persist. Therefore, a clear definition of treatment failure with conventional therapy is required in order to assess the size of the eligible adult population for burosumab.
What is the expected effect on the cost-effectiveness estimates?	[redacted]
What additional evidence or analyses might help to resolve this key issue?	A clear definition of treatment failure with conventional therapy may help to assess the size of the eligible adult population for burosumab.

Issue 3 Generalisability of the cost-effectiveness data and trial evidence to a burosumab-experienced population

Report section	Sections 3.2.3 and 4.2.3. Item 3.
Description of issue and why the EAG has identified it as important	The company stated that patients who have received burosumab below the age of 18 years will be expected to meet the same eligibility criteria as other adults for accessing treatment in adulthood. The EAG is concerned that response to burosumab treatment in childhood might affect the ability for patients to continue treatment into adulthood once they reach age 18 years. There is uncertainty regarding the generalisability of the cost-effectiveness data and trial evidence to a burosumab-experienced population.
What alternative approach has the EAG suggested?	There is no viable alternative approach using the data currently available.
What is the expected effect on the cost-effectiveness estimates?	The EAG is unable to predict the expected effect on the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	This issue can only be resolved with evidence of outcomes from a burosumab-experienced population.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 4 Baseline imbalances in the CL303 trial

Report section	Sections 3.2.3 and 3.5.1
Description of issue and why the EAG has identified it as important	The EAG has concerns with baseline imbalances in characteristics between study arms in the CL303 trial. Compared with the placebo arm, participants in the burosumab arm appeared to be older, with consistently worse pain, stiffness and function scores at baseline overall. The proportion of unhealed pseudofractures was higher in the placebo arm. The EAG is concerned that regression to the mean may imply that the effectiveness of burosumab is being over-estimated.
What alternative approach has the EAG suggested?	The EAG seeks reassurance that the trial used appropriate randomisation procedures, and that analyses compensated for baseline imbalances.
What is the expected effect on the cost-effectiveness estimates?	The baseline imbalance may suggest that the utility values for burosumab should be adjusted for the placebo effect observed in CL303 – see Issue 13, which produces significantly less favourable cost-effectiveness estimates for burosumab.
What additional evidence or analyses might help to resolve this key issue?	Analyses of the CL303 trial data that explicitly adjust for baseline imbalance, and consideration of the possibility of regression to the mean would be desirable.

Issue 5 Limited evidence of efficacy of burosumab on pain, physical functioning and fatigue

Report section	Sections 3.2.4 and 3.5.1
Description of issue and why the EAG has identified it as important	After accounting for possible regression to the mean (see Issue 4) and placebo effects, the EAG found no clear evidence of a difference between burosumab and placebo for most patient-reported outcomes (pain, physical functioning and fatigue); most differences between burosumab and placebo appeared not to be clinically meaningful, and were generally not statistically significant. This raises concerns as to how to interpret results in the non-randomised, open-label, longer-term follow-up data.
What alternative approach has the EAG suggested?	EAG Scenario 16 assesses the impact on cost-effectiveness when the utility gain for burosumab compared to baseline utility is adjusted for the placebo effect observed in CL303 (see Issue 13).
What is the expected effect on the cost-effectiveness estimates?	See Issue 13.
What additional evidence or analyses might help to resolve this key issue?	As in Issue 4, analyses of the CL303 trial data that explicitly consider the possibility of regression to the mean and placebo effects would be desirable.

Issue 6 Age and weight distribution of CL303 population

Report section	Sections 3.2.3 and 4.2.3. Item 4.
Description of issue and why the EAG has identified it as important	The age and weight distribution of participants in CL303 may not align with the adult population with XLH in the NHS. Participants in CL303 were younger than participants receiving burosumab in the Early Access Programme (EAP) in England, with 76% of trial participants below the age of 50 years compared to 58% of EAP participants, due to a maximum age restriction of 65 years in the trial's inclusion criteria. The weight distribution of EU participants from CL303 (used in the company's base case analysis) is lighter in weight than EAP, with only 28% of trial participants weighing above 75kg compared to 40% of EAP participants, which has implications for the dosing (and costs) of burosumab.
What alternative approach has the EAG suggested?	The EAG considers participants receiving burosumab in the EAP in England to be more representative of the modelled population than the CL303 trial population, which includes [redacted], as of April 2023. EAG Scenario 3 assesses the impact on cost-effectiveness of using the participant age and weight distribution of EAP rather than CL303.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 3 shows that the ICER increases from the company's corrected base case ICER of [redacted]/QALY to [redacted]/QALY, with the age and weight distribution of participants in the EAP.
What additional evidence or analyses might help to resolve this key issue?	None.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 7 Modelling the incidence of morbidities and mortality as independent events

Report section	Section 4.2.2. Item 1.
Description of issue and why the EAG has identified it as important	The model structure for overall survival based on an excess mortality hazard due to XLH is independent of the models used to predict the incidence of individual morbidities (fractures in the base case analysis), which are nested within overall survival. Whilst this approach may not be inappropriate because any estimate of fracture-associated mortality may not account for potential confounders that are causal to both fractures and mortality, or multi-system effects (other than fractures) of hypophosphataemia that may drive increased mortality, it does result in complete uncertainty about the magnitude of any potential survival benefit of burosumab since there is no evidence to link to the outcomes of CL303.
What alternative approach has the EAG suggested?	An explicit structural link in the model between fractures and mortality would allow external evidence to be considered on how treatments for fractures (or other outcomes) are expected to impact on mortality. In the absence of this structural link, it remains speculative that interventions that reduce fractures will affect mortality in this patient population.
What is the expected effect on the cost-effectiveness estimates?	Expected effect is unclear. The EAG conducted a number of scenarios to assess the impact of alternative assumptions for mortality benefit on the cost-effectiveness of burosumab – see Issue 8.
What additional evidence or analyses might help to resolve this key issue?	An alternative model structure where a structural link is implemented between morbidity events and mortality would offer an alternative estimate of cost-effectiveness.

Issue 8 Excess mortality for individuals with XLH

Report section	Section 4.2.2.2. Item 2.
Description of issue and why the EAG has identified it as important	The excess mortality risk due to XLH compared to the general population hazard of death is based on a hazard ratio (HR) of 2.88 (95% CI, 1.18 to 7.00) from Hawley et al. (2020) [2]. The company's confirmatory study based on extending Hawley et al. by applying the same XLH grading algorithm to patients from both the CPRD GOLD and the larger database of CPRD AURUM, linked to secondary care Hospital Episode Statistics and ONS mortality data resulted in a HR of 2.33 (95% CI, 1.16 to 4.67), which is approximately 30% lower risk than the HR from Hawley et al [2].
What alternative approach has the EAG suggested?	The larger sample of data from the CPRD GOLD and AURUM databases provide greater precision to inform the excess mortality due to XLH. Therefore, the EAG considers it more appropriate to use the HR of 2.33 (95% CI, 1.16 to 4.67), which appears to have been conducted using the same methods and subject to the same limitations as Hawley et al., [2] but includes a larger database and more recent data.

	EAG Scenario 4 assesses the impact on the cost-effectiveness of burosumab using the HR of 2.33 rather than 2.88.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 4 shows that the ICER increases from the company's corrected base case ICER of [redacted]/QALY to [redacted]/QALY, with the HR of 2.33.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 9 Treatment stopping criteria and long-term discontinuation rates

Report section	Section 4.2.6.1. Item 5.
Description of issue and why the EAG has identified it as important	Continuation of treatment in the model is based on a requirement of reaching serum phosphate levels above the lower limit of normal range (LLN) at 24 weeks and an improvement in WOMAC total score at 12 months after starting treatment, while an annual treatment discontinuation rate of 3% is used in years 2 onwards. The EAG considers the first criteria on reaching serum phosphate levels above LLN to be appropriate, but questions whether the second hurdle of requiring improvements in WOMAC is necessary and appropriate given the absence of alternative treatments for this population, the fact that WOMAC is not commonly used in the NHS in XLH, and there may be other benefits to treatment with burosumab (e.g., a reduction in opioid use). The EAG notes that no stopping criteria were applied in either the CL303 trial or the EAP in England.
What alternative approach has the EAG suggested?	The proposed stopping criteria for treatment affects the proportion of patients who remain on treatment at the end of year one and the utility values for patients treated with burosumab after the first year. The EAG considers two scenarios: (i) EAG Scenario 5 with no stopping criteria applied (note that the model was not sufficiently flexible to permit the first criterion on reaching serum phosphate levels, whilst switching off the second criterion on WOMAC improvements); and (ii) EAG Scenario 6 with no long-term discontinuation from year 2 onwards given the absence of alternative treatments for this patient population.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 5, with no stopping criteria applied in the first year (long-term discontinuation rate remains at 3% per annum), increases the ICER from [redacted]/QALY to [redacted]/QALY. EAG Scenario 6, where the discontinuation rate is 7.35% in the first year based on CL303 (without stopping criteria) and no discontinuation from year 2 onwards, decreases the ICER from [redacted]/QALY to [redacted]/QALY. When the stopping criteria are removed in the first year, a lower discontinuation rate results in proportionally greater QALY benefits.

What additional evidence or analyses might help to resolve this key issue?	Evidence on long-term treatment benefits and discontinuation rates for burosumab.

Issue 10 Burosumab reduction in fracture incidence rates

Report section	Section 4.2.6.2. Item 6.
Description of issue and why the EAG has identified it as important	The company assumes a 100% reduction in the incidence of fractures with burosumab (in those with normalised serum phosphate), with rates equal to those of the general population. These rates, however, do not distinguish between hypophosphataemia-driven osteomalacia and fragility fractures from fractures due to trauma experienced by non-affected individuals, or fractures due to osteoporosis, which may have implications for symptomatic treatment management, likelihood of fracture healing, and effects on health-related quality of life. Whilst the EAG believes that it may be clinically plausible that burosumab would lead to a reduction in fractures with improvement in serum phosphate within normal levels the assumption of a 100% reduction is not based on any evidence. Normalisation of the bone may take months or even years to heal (supported by evidence from CL304 that showed that bone structure was not completely normalised at week 48 in bone biopsies), which could contribute to a continued incidence of new fractures despite burosumab treatment.
What alternative approach has the EAG suggested?	EAG Scenarios 7 and 8 assess the impact on cost-effectiveness when a 75% and 50% reduction in the incidence of fractures is assumed, respectively.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 7, with 75% reduction in incidence of fractures, increases the ICER from [redacted]/QALY to [redacted]/QALY. EAG Scenario 8, with 50% reduction in incidence of fractures, increases the ICER from [redacted]/QALY to [redacted]/QALY.
What additional evidence or analyses might help to resolve this key issue?	Longer-term evidence on the effects of burosumab on incidence of fractures and fracture healing rates.

Issue 11 Burosumab effect on mortality

Report section	Section 4.2.6.3. Item 7.
Description of issue and why the EAG has identified it as important	No mortality benefit for burosumab was observed within the short trial duration and small population of CL303 or BUR02; however, the company assumes a 50% reduction in excess XLH mortality risk with burosumab. The company anticipates that by normalising phosphate homeostasis and mitigating the multi-system effects of hypophosphataemia, treatment with burosumab will reduce mortality. The EAG considers that without any evidence of the effects of burosumab on mortality, it is speculative that a mortality benefit exists and the magnitude of any potential benefit is completely uncertain.

What alternative approach has the EAG suggested?	EAG Scenarios 9 to 11 assess the impact on cost-effectiveness when: (i) no mortality benefit is assumed; (ii) 11% reduction in mortality based on evidence of the effect of treatments for osteoporosis on fracture-related mortality risk; and (iii) 25% reduction in excess XLH mortality risk to account for additional multi-system effects other than fractures.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 9, with no mortality benefit, increases the ICER from [redacted]/QALY to [redacted]/QALY. EAG Scenario 10, with 11% reduction, increases the ICER from [redacted]/QALY to [redacted]/QALY. EAG Scenario 11, with 25% reduction, increases the ICER from [redacted]/QALY to [redacted]/QALY.
What additional evidence or analyses might help to resolve this key issue?	Longer-term evidence on the effects of burosumab on mortality.

Issue 12 The effect of burosumab treatment on utility change from baseline and extrapolation of effect over time

Report section	Section 4.2.8.3. Item 9.
Description of issue and why the EAG has identified it as important	After 24 weeks, only open label and single arm data for less than 3 years of treatment are available to support burosumab benefits in relation to symptoms in the long-term with continuous treatment. The lack of comparative data after 24 weeks is a concern in itself, but the EAG's major concern is that the data informing the change from baseline in WOMAC scores for burosumab after week 96, which marks the end of the treatment continuation period of CL303, is based on different patient populations that differ in terms of baseline characteristics and WOMAC scores. The company's asymptotic model fit that is used to extrapolate the utility benefit of burosumab beyond the observed periods appears to be heavily influenced by the post-week 96 data. The EAG considers the WOMAC data up to week 96 from the treatment continuation period of CL303 to be the only reliable source (in the absence of data from the EAP for burosumab in England) to inform the asymptotic model fit to WOMAC mapped utility change from baseline.
What alternative approach has the EAG suggested?	EAG Scenario 15 assesses the impact on cost-effectiveness when post-week 96 data are excluded from the asymptotic model fit to WOMAC mapped utility change from baseline. The corresponding utility value used in Scenario 15 is 0.2 in year 2 onwards, while the company's base case value is 0.211 in year 2 and 0.215 in year 3 onwards.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 15 increases the ICER from [redacted]/QALY to [redacted]/QALY.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up data on the effects of burosumab on health-related quality of life.

Issue 13 Placebo-adjusted utility values

Report section	Section 4.2.8.3. Item 12.
Description of issue and why the EAG has identified it as important	There is uncertainty about whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed in the 24-week period of CL303, where the WOMAC mapped utility change from baseline in the placebo arm corresponds to an improvement in utility of approximately 0.03. The company uses the non-placebo-adjusted utility values in their base case analysis.
What alternative approach has the EAG suggested?	EAG Scenario 16 assesses the impact on cost-effectiveness when the utility gain for burosumab compared to baseline utility is adjusted for the placebo effect observed in CL303. The utility values for patients treated with burosumab from year 2 onwards is also affected by the proposed stopping criteria in the first year. EAG Scenario 17 assesses the impact when no stopping criteria are applied and the utility values are placebo-adjusted.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 16, using placebo-adjusted utility values, increases the ICER from [redacted]/QALY to [redacted]/QALY. EAG Scenario 17, using placebo-adjusted utility values and no treatment stopping criteria, increases the ICER from [redacted]/QALY to [redacted]/QALY.
What additional evidence or analyses might help to resolve this key issue?	Consideration of the significance of the placebo effect in CL303.

Issue 14 Disutility for incident fractures

Report section	Section 4.2.8.4. Item 14.
Description of issue and why the EAG has identified it as important	There is uncertainty about the magnitude and duration of the disutility associated with incident fractures and the assumption of independent effects when multiple events may occur over a lifetime horizon.
What alternative approach has the EAG suggested?	EAG Scenario 19 considers the impact on cost-effectiveness when the disutility for incident fractures is applied in the first year of the event only.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 19 increases the ICER from [redacted]/QALY to [redacted]/QALY.
What additional evidence or analyses might help to resolve this key issue?	Evidence on fracture healing rates over time, which could lead to improvements in health-related quality of life rather than assuming a constant lifetime disutility after the fracture event (post-year 1). A structural link between mortality and fracture events in the model would allow the duration of lifetime disutility associated with fracture events to be adjusted for fracture-specific mortality.

Issue 15 Utility benefit on caregivers and family members

Report section	Section 4.2.8.4. Item 15.
Description of issue and why the EAG has identified it as important	There is uncertainty about the magnitude of treatment benefit on caregivers and family members who support adults with XLH and the number of caregivers. The company's base case assumes a spillover benefit on family members and caregivers equal to 20% of the patient utility benefit of burosumab and applied to two caregivers/family members. The EAG has a concern that the spillover effect may be overestimated by including an effect on two caregivers/family members, where two may be reasonable for a child but less so for an adult, particularly noting that burosumab is administered in a way that supports patients to be independent and less likely to impose additional burden on family members. The EAG also notes that there is no evidence to support a 20% patient utility benefit on caregivers and family members; in the company's research study that was used to compare EQ-5D utility values of informal carers or family members of adults with XLH with age-matched general population utility values, only a small loss in utility was identified (0.081), when carers with XLH themselves were excluded from the analysis.
What alternative approach has the EAG suggested?	EAG Scenario 20 considers the impact on cost-effectiveness when the utility benefit is included for one caregiver/family member only (equal to 20% of the patient utility benefit), while EAG Scenario 21 assesses the impact when no utility benefit on caregivers and family members is included in the analysis.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 20, with utility benefit for 1 caregiver/family member only, increases the ICER from [redacted]/QALY to [redacted]/QALY. EAG Scenario 21, with no utility benefit for caregivers and family members, increases the ICER from [redacted]/QALY to [redacted]/QALY.
What additional evidence or analyses might help to resolve this key issue?	Quantitative evidence of the health-related quality of life burden of XLH on caregivers and family members.

1.6 Other key issues: summary of the EAG's view

No other key issues.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 1 summarises the EAG's preferred assumptions and resulting ICER, while Table 2 presents the results of a number of alternative scenarios on the EAG base case where there is remaining uncertainty.

Table 1 Summary of EAG's preferred assumptions and resulting ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's corrected base-case results	[redacted]	[redacted]	[redacted]
EAG Scenario 3: Age and weight distribution based on participants in the EAP in England	[redacted]	[redacted]	[redacted]
EAG Scenario 4: Excess mortality risk due to XLH based on CPRD AURUM database with a HR of 2.33 compared to the general population	[redacted]	[redacted]	[redacted]
EAG Scenario 14: Same treatment tapering effect on mortality and morbidity	[redacted]	[redacted]	[redacted]
EAG Scenario 15: Burosumab utility change from baseline based on extrapolating WOMAC data up to week 96 from CL303, i.e., excluding post-week 96 data from BUR02	[redacted]	[redacted]	[redacted]
EAG Scenario 20: Utility benefit for one caregiver/family member only	[redacted]	[redacted]	[redacted]
EAG Scenarios 3+4+14+15+20 (EAG base case)	[redacted]	[redacted]	[redacted]

Table 2 Summary of EAG's alternative assumptions and resulting ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
EAG base case (3+4+14+15+20)	[redacted]	[redacted]	[redacted]
Morbidity benefit with burosumab			
EAG Scenario 7: 75% reduction in the incidence of fractures	[redacted]	[redacted]	[redacted]
EAG Scenario 8: 50% reduction in the incidence of fractures	[redacted]	[redacted]	[redacted]
Mortality benefit with burosumab			
EAG Scenario 9: No reduction in mortality	[redacted]	[redacted]	[redacted]
EAG Scenario 10: 11% reduction in mortality	[redacted]	[redacted]	[redacted]
EAG Scenario 11: 25% reduction in mortality	[redacted]	[redacted]	[redacted]
Utility benefit with burosumab			
EAG Scenarios 16+19: Placebo-adjusted utility values + disutility for incident fractures in first year only	[redacted]	[redacted]	[redacted]

Modelling errors identified and corrected by the EAG are described in Section 5.3.1. For further details of the exploratory and sensitivity analyses undertaken by the EAG, see Section 6.1.1.

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents a critique of the company's submission (CS) to NICE from Kyowa Kirin Limited on the clinical effectiveness and cost effectiveness of burosumab (Crysvita®) for treating X-linked hypophosphataemia (XLH) in adults (aged ≥18 years).

Burosumab is recommended by NICE for treating XLH with radiographic evidence of bone disease in children aged 1 year and over, and in young people with growing bones.[3] Burosumab received a full marketing authorisation throughout the EU granted by the European Medicines Agency (EMA) in September 2022.[4, 5] In March 2023, the Medicines & Healthcare products Regulatory Agency (MHRA) granted a marketing authorisation for burosumab, intended for the treatment of XLH, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.[6] Since 16th March 2023, burosumab has been conditionally approved by the Scottish Medicines Consortium to be prescribed within the ultra-orphan pathway while further evidence on its effectiveness is generated. The company is expected to provide an updated submission for reassessment in 2026 for a decision on its routine use in NHS Scotland.

2.2 Background

2.2.1 X-linked hypophosphataemia (XLH)

The company's description of XLH is broadly appropriate and relevant to the decision problem.

XLH is a very rare, lifelong genetically determined metabolic bone disease characterised by low levels of phosphate in the blood (hypophosphataemia), due to excessive production of the phosphate-regulating hormone fibroblast growth factor 23 (FGF23), and reduced production of the active form of vitamin D (calcitriol).[7, 8] Adults with XLH are affected both by the legacy of childhood disease (short stature and lower limb and dental deformities) and by ongoing disease processes driven by hypophosphataemia[7-10], and suffer from early development of osteoarthritis, osteomalacia, pseudofractures (painful, slow- or non-healing bone lesions), impaired muscle function, chronic bone and joint pain, stiffness, impaired mobility and disability, depression and susceptibility to dental abscesses.[9] However, importantly the severity of XLH varies between patients, and not all adults with XLH are symptomatic with clinical advice to the EAG suggesting that 30% of the patients are symptomatic in the UK.

In the UK, using the Clinical Practice Research Datalink (CPRD) database, the prevalence of XLH in adults has been approximated as 0.67 per 100,000 adults (95% CI: 0.45-1.02) between 2012 and 2016, with approximately 298 adults with XLH in England in 2023.[2] However, the true prevalence is expected to be higher, due to better diagnosis and that some patients would not always receive treatment, as shown a survey of 15 XLH treatment centres commissioned by NHS England that identified a minimum of 350 patients currently receiving treatment. Clinical experts estimated that the true prevalence could be up to 1,000 people including individuals diagnosed with XLH not currently receiving treatment or those that are undiagnosed.

The burosumab Early Access Programme (EAP) initiated in England has [redacted] who have received burosumab (as of April 2023).

2.2.2 Burden of disease

The company's description of XLH's morbidity, mortality and carer burden is broadly appropriate and relevant to the decision problem.

XLH has wide ranging effects that usually develop during the first or second year of life and continue throughout life.[11] These effects include: skeletal and dental deformities that are established in childhood, rickets, disproportionately short structure and painful stress and deformity fractures (sometimes known as 'pseudofractures').[9, 11] An analysis of baseline data from study CL303[10] found that 27-40% had a history of fracture among those aged between 18-29 and increased to 65-86% in those aged ≥60 years. Likewise, the prevalence of osteoarthritis increased from 23%-37% among 18-29 year-olds to approximately 70% in those aged over 60. Surgeries such as hip and knee arthroplasty were reported by adults in their 30s. However, not all adults with XLH are symptomatic as mentioned in section 2.2.1.

XLH has also been found to be associated with an increased mortality. An analysis using the Clinical Practice Research Datalink (CPRD) database[2] found a reduced life expectancy, with the estimated median age at death for people likely to have XLH of 64 years (IQR 58-74), compared with 72.5 years (IQR 52-91) for matched controls. However, importantly the mechanism for the increased mortality was not known, in addition to a lack of published evidence on causes of death in people with XLH.

While qualitative studies have documented the patient experience of pain, stiffness and fatigue, and the psychosocial impact of XLH reporting significant impact of their mobility and ability to perform daily activities, limits their social, family and work life and affects their mental health.[12-14]

2.2.3 Burosumab

The EAG considers the company's description of the technology to be clear and appropriate. Burosumab is a recombinant human monoclonal antibody (immunoglobulin G subclass 1 [IgG1]) that binds to and inhibits the activity of FGF23. It is packaged in single vials in strengths of 10mg, 20mg or 30mg (CS Document B p16, Table 2). It is produced by recombinant DNA technology using Chinese hamster ovary (CHO) mammalian cell culture.[4, 5] Burosumab addresses the underlying mechanism of XLH (excessive levels of FGF23) and restores phosphate homeostasis, resulting in increased serum phosphate levels.

The recommended starting dose for burosumab in adults is 1.0 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, given every 4 weeks. After initiation of treatment, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. Fasting serum phosphate should be measured 2 weeks after the previous dose of burosumab. If serum phosphate is within the normal range, the same dose should be continued. If serum phosphate is above the upper limit of normal range, the next dose should be withheld, and the serum phosphate level reassessed within 2 weeks. Once serum phosphate is below the normal range, treatment may be restarted at half the initial starting dose up to a maximum dose of 40 mg every 4 weeks.

2.2.4 Clinical pathway

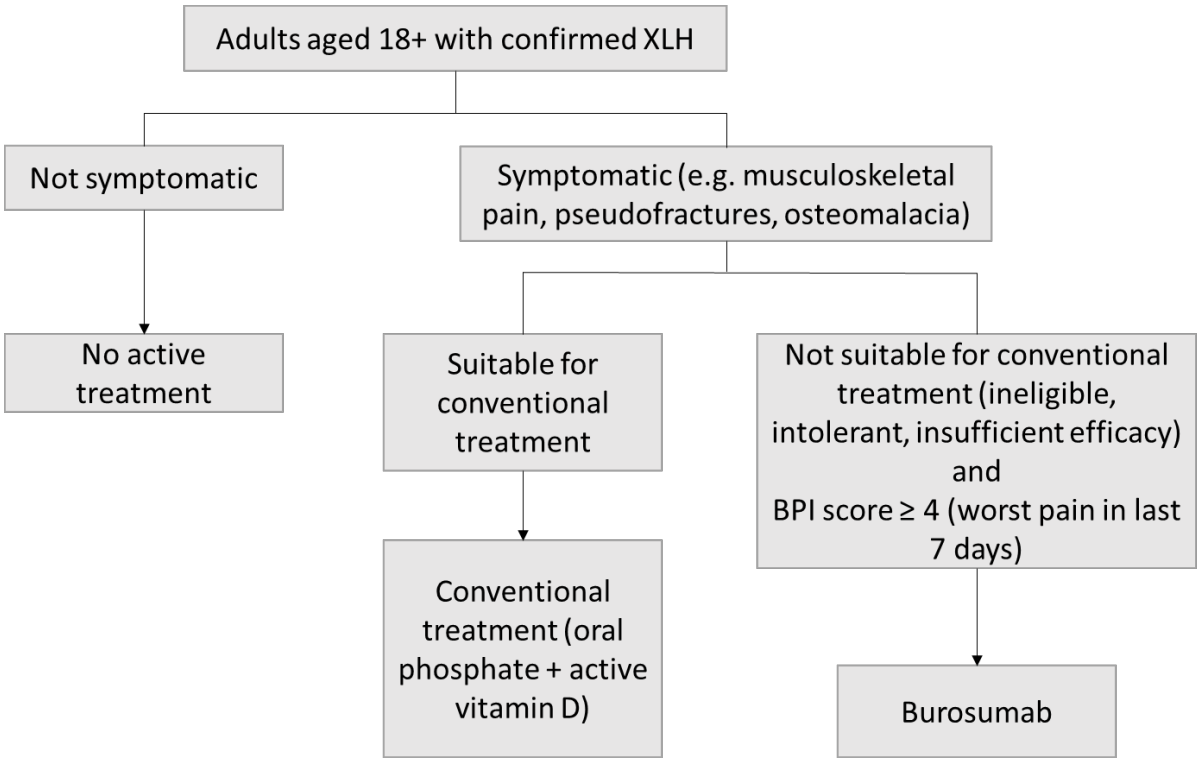
There are no NICE or UK-specific treatment guidelines or clinical pathway of care for adults with XLH. In the NHS, treatment is recommended in symptomatic adult patients using conventional treatment with active vitamin D and oral phosphate. This is because there are no options of tackling the root cause of the issue (excessive production of the phosphate-regulating hormone fibroblast growth factor 23 (FGF23)). The focus with conventional treatment until now has been on the individual needs of patients, e.g., pain, mobility, stiffness, and dental abscesses among other symptoms. However, conventional treatment does not improve enthesopathy or exacerbated the mineralization of enthesis or hearing loss or osteoarthritis.[9, 11] In addition, convention oral phosphate treatment has been found to have adverse effects including intestinal discomfort due to phosphate supplements, with nausea, diarrhoea, hypercalciuria and nephrocalcinosis in between 60-70% of the patients.

The EAG agrees that there is an unmet need as conventional therapy is not well-tolerated and does not correct the underlying cause of disease and thus does not restore phosphate homeostasis, thereby normalising serum phosphate levels and improving symptoms, physical functioning and HRQoL for adults with highly symptomatic XLH. Unlike the current standard of care, burosumab addresses the underlying mechanism of XLH (excessive levels of FGF23) and restores phosphate homeostasis.

2.2.4.1 Intended positioning of burosumab

Figure 1 summarises the company's positioning of burosumab for adult XLH patients (CS, page 45). The company expects that burosumab will be used in highly symptomatic adult patients who meet the criteria for active pharmacological treatment of their XLH set out in clinical guidelines (specifically BPI score of ≥4 (worst pain in last 7 days)), but for whom conventional treatment is not suitable due to ineligibility as they are asymptomatic, intolerance due to adverse events, or insufficient efficacy from conventional therapy.

Figure 1 Proposed company's pathway of care and position of burosumab in therapy



BPI: Brief Pain Inventory

Source: CS, Document B, Figure 7

The EAG notes that this is a subset of the defined population in the final NICE scope. For patients who have received burosumab through the Early Access Programme the clinical pain guideline was described as "there is presence of debilitating symptoms, including, but not limited to, pain, stiffness, and fatigue". Clinical advice to the EAG notes that most patients would be unsuitable for conventional treatment with oral phosphate as it is poorly tolerated and has long-term adverse effects of abdominal distress, diarrhoea, and nausea, leading to discontinuation or reduction in dosage. In addition, the company preferred BPI score of ≥4 (worst pain in last 7 days) reflective of 'persistent and debilitating symptoms' is a very low pain threshold that is not commonly used in NHS practice.

In practice approximately 30% of symptomatic patients would receive phosphate and vitamin D with the rest having no alternative treatment options, other than orthopaedics, fracture management and pain relief. Since burosumab has the theoretical potential of getting at the root cause of the problem thus normalise the phosphate in the blood and appears to have a better adverse effect profile compared to conventional treatment, 80-90% of the symptomatic XLH adult population are likely to be eligible for burosumab making it the "first line" treatment if approved.

It is unclear whether the children with XLH who have been on burosumab (where it is already approved, HST8[3]) and adults who have been receiving it through the EAP would be eligible for burosumab based on the company's preferred positioning. Following FAC stage, the company stated that patients who have received burosumab below the age of 18 years will be expected to meet the same eligibility criteria as other adults for accessing treatment in adulthood. The EAG is concerned that response to burosumab treatment in childhood might affect the ability for patients to continue treatment into adulthood once they reach 18 years of age.

2.3 Critique of company's definition of decision problem

Table 1 of the CS presents the decision problem, including a description of the final scope issued by NICE, the decision problem addressed within the submission and the rationale for any differences between the two. This information, along with the EAG comments on the rationale provided, is presented in Table 3 below.

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with X-linked hypophosphataemia	Adults (aged ≥18 years) with a confirmed diagnosis of XLH who have chronic hypophosphataemia, symptoms that include a Brief Pain Inventory (BPI) "worst pain in last 7 days" score of ≥4 (upper limit of mild pain), and for whom conventional therapy is unsuitable due to ineligibility (e.g. patients with contraindications, such as presence of toxicities developed on conventional treatment such as renal or parathyroid toxicity), or intolerance or insufficient efficacy (i.e. failure to normalise phosphate levels, or persistence of symptoms despite treatment).	Only adults with XLH aged 18 years and older and are symptomatic are considered in this submission. This aligns with the consensus statements on treatment of XLH[9, 11] and UK clinical practice[15].	This population differs from the scope and the UK Early Access Programme (EAP) criteria for administering burosumab which do not require patients to be unsuitable for phosphate treatment, or to have a BPI of 4 or above. The criteria also differ from the trial (CL303) inclusion criteria, which required that chronic pain medications regimens must have been stable for >21 days before screening.
Intervention	Burosumab	As per NICE scope	Not applicable.	The intervention described in the CS is in line with the NICE scope.
Comparator(s)	Established clinical management without burosumab (including vitamin D analogues and phosphate supplementation)	The comparator is best supportive care (primarily consisting of fracture treatment).	This corresponds to established clinical management without burosumab in the submission population, for whom conventional therapy is not suitable.	The comparator described in the CS is narrower that that considered in the NICE scope as it excludes vitamin D analogues and phosphate supplementation. The EAG considers this narrower scope to be reasonable provided burosumab is considered only where phosphate therapy is not appropriate
Outcomes	• fractures	Outcomes included in the base case economic analysis:		Outcomes presented in the CS broadly reflect those listed in the final scope. However, clinical advice to the EAG suggests that WOMAC and BPI scales are

	• pain (including bone pain, joint pain and joint stiffness) • motor skills • tooth loss and pain • neurological complications (including problems with • hearing and balance, and spinal cord compression) • renal function • parathyroid hormone levels • alkaline phosphatase levels • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).	• Fracture incidence (including upper limb, vertebrae/spinal, foot, fibia/fibula, femur/pelvis, and other fractures). • Stiffness, pain and fatigue as reflected in WOMAC scores from the trial. • Mortality • Health-related quality of life for patients. • Health-related quality of life for informal caregivers and close family Outcomes modelled in scenario analyses: • Dental problems (tooth loss and pain). • Spinal stenosis and need for spinal surgery. • Tinnitus and hearing loss. The outcomes above are in line with the draft NICE scope. Those described below are not in line with the draft NICE scope. • Serum phosphate levels modelled. • Joint stiffness and motor function • 6-minute walk test (6MWT) and the Timed Up and Go test (TUG). • Pain is modelled via WOMAC score, which includes pain in its questionnaire.		not routinely used in the NHS to assess patients with XLH, and serum phosphate levels have been used instead of alkaline phosphatase levels as recommended by the NICE scope. Motor skills are measured via the WOMAC score, 6-minute walk test (6MWT) and the Timed Up and Go test (TUG). Fracture healing is also measured (not-prespecified in CL303) The EAG considers that the choice of outcomes is broadly reasonable.
Economic analysis	The reference case stipulates that the cost effectiveness of			The economic analysis is in line with the reference case. Utility

	treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered. The availability of any managed access arrangement for the intervention will be considered.			values used in the model were based on mapping WOMAC scores to EQ-5D using a published utility mapping algorithm and valued using the UK tariff. See Table 13 for details.
Subgroups	No subgroups were included in the scope.	Subgroup analyses were presented as part of the clinical (for sex, Brief Pain Inventory-short form (BPI-SF) Average and Worst Pain, region, race, WOMAC Stiffness, Physical Function and Pain domains and total score, use of opioid/other pain medication, active fractures/pseudo-fractures, and 6-minute walk test distance), but not the economic assessment.		The subgroups were not specified in the NICE scope but are broadly appropriate.

Special considerations including issues related to equity or equality	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances such as with the application of a QALY severity modifier as per the NICE Methods and Processes.		Adults with symptomatic XLH have a long-term disability, which is a protected characteristic under the Equality Act 2010. XLH is also a very rare disease. The UK Rare Disease Framework recognises four key priorities, including helping patients to get a faster diagnosis and improving access to specialist care, treatment and drugs.[16, 17]. Finally, people with XLH are more likely than the general population to suffer socioeconomic disadvantage and are disproportionately located in the lowest two socioeconomic quintiles as measured by Index of Multiple Deprivation (IMD).[18]	The company used a severity modifier. See Section 7.

2.3.1 Population

The EAG is concerned that the modelled population may not be reflective of patients who would receive burosumab in clinical practice. The modelled population is significantly narrower that the population described in the NICE scope, which allowed for any adult with XLH to receive burosumab. Based on clinical advice, the EAG considers restricting burosumab to patients with more severe symptoms, that could not be controlled with conventional pain relief medication, is appropriate.

However, the narrower population addressed in the CS may be inappropriate, as this population is not reflected in the UK Early Access Programme (EAP) criteria for administering burosumab since the EAP criteria has been broader, allowing for "presence of debilitating symptoms, including, but not limited to, pain, stiffness, and fatigue",[19] or the trial participants (CL303) whose inclusion criteria was "required that chronic pain medications regimens must have been stable for >21 days before screening" or clinical advice to the EAG that stated that burosumab has a better adverse effect profile compared to conventional treatment and therefore might be offered as a first-line treatment in the future. However, clinical guidelines state that burosumab should be considered if conventional therapy is not beneficial, not tolerated, or has resulted in complications.[9, 11] In this respect, the company submission population is aligned with current guideline recommendations.

2.3.2 Intervention

The intervention in the company submission is in line with the NICE scope.

2.3.3 Comparator

The company has positioned burosumab to be offered as a second-line therapy in adults with XLH for whom conventional treatment is not suitable and so excludes comparison with the conventional treatment of vitamin D analogues and phosphate supplementation. Given clinical advice, the EAG considers restricting burosumab use to patients who have terminated phosphate supplementation due to inefficacy or side effects, or to patients otherwise ineligible for phosphate therapy, is reasonable.

However, the EAP allows patients to terminate phosphate therapy in order to receive burosumab. There is therefore a lack of clarity as to whether patients who could, in principle, receive phosphate therapy would be eligible for burosumab.

2.3.4 Outcomes

The EAG notes that the outcomes presented in the company submission broadly reflect those listed in the final scope. However, clinical advice to the EAG suggests that WOMAC and BPI scales are not

routinely used in the NHS to assess patients with XLH therefore selection criteria that recommend the use of BPI scales to be eligible for burosumab may be challenging to apply within the NHS. Following FAC stage, the company stated that VAS (0-10) scales may be used as an alternative measurement of pain and would be easy to include in routine assessments.

Serum phosphate levels have been used instead of alkaline phosphatase levels as recommended by the NICE scope. The alkaline phosphatase is an enzyme derived from bone that may or may not be abnormal. It is independent of phosphate levels. With active bone disease, alkaline phosphatase is elevated. The company used serum phosphate as an outcome arguing that serum phosphate level is the primary driver of morbidity in adults with XLH. It is important to note that [redacted]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of the systematic review

The company conducted a systematic literature review to identify all relevant clinical evidence relating to the efficacy and safety of treatments for adults with XLH. Details of the review are reported in Appendix D of the CS.

3.1.1 Searches

The search strategies to identify studies of patients with XLH were included in Appendix D of the CS.

A broad search using terms for the population only was undertaken. This approach was appropriate to identify studies of the clinical effectiveness of treatments for XLH, as well as studies of health-related quality of life and costs/healthcare resource use in patients with XLH. The reporting of the search strategies was not entirely clear in the original CS, however all reporting issues where clarified in the company response to the PfCs.

Table 4 EAG appraisal of evidence identification

Topic	**ERG response**	**Note**
Is the report of the search clear and comprehensive?	YES	- Search strategies were missing for EconLit, however were provided in the company response to the PfCs. - It was not clear which databases were searched for previous health technology assessments and the search strategies were not provided. The company clarified that the International HTA database was searched and provided the search strategy used in their response to the PfCs. - The search terms and date of the search were missing from the search of conference proceedings. These missing items were provided by the company in their response to the PfCs.
Were appropriate sources searched?	YES	- Published studies were sought from the key sources of healthcare literature – MEDLINE, Embase and the Cochrane Library. - Trial register searches for ongoing or completed but unpublished studes were not reported in the original company submission. This was queried in the PfCs and the company provided the search strategies for ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).
Was the timespan of the searches appropriate?	YES	- Database inception to 4th November 2022. - Recent conference proceedings were searched from 2019 to 2022.

Were appropriate parts of the PICOS included in the search strategies?	YES	- A broad search using population terms only (patients with XLH).
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	YES	- Animal only studies were removed from the search results.
Were any search filters used validated and referenced?	NOT APPLICABLE	

3.1.2 Study selection

The review eligibility criteria are reported in Appendix D, Table 4. Studies of adults with a diagnosis of XLH were included. Comparative and non-comparative trials and observational studies were eligible for inclusion. There were no restrictions by date or location, although non-English publications were excluded. All references were screened in duplicate, with disagreements resolved by a third reviewer. Overall, despite some language restrictions, the EAG believes that the study selection process was appropriate and unlikely to miss relevant studies.

3.1.3 Data extraction

The company submission did not specify the process for extracting data from included studies, therefore, the EAG could not assess whether data was extracted reliably.

3.1.4 Quality assessment

Two quality appraisal tools were used to assess the quality of included studies: the NICE critical appraisal tool for RCTs, and the CASP checklist for critical appraisal of observational (cohort) studies. The CASP checklist includes items for both internal and external validity. The external validity of RCTs was not assessed. Results were reported in tables and justifications for decisions were generally not reported. The company submission did not specify the process for appraising the quality of the studies included in the systematic review. Of the three studies that informed the clinical evidence submission and were included in the company's economic model, two (CL303 and CL001) were critically appraised; no critical appraisal of BUR02, the open-label extension of CL303, was presented. The EAG broadly agrees with the company's appraisal of CL001 and CL303, although unlike the company, the EAG is concerned that differences in baseline characteristics between CL303 study arms may have introduced bias to the study results. This is further discussed in Section 3.2.

3.1.5 Evidence synthesis

No meta-analysis was conducted. Given the limited number and heterogeneity of designs of studies that informed the efficacy and safety of burosumab, the EAG considered the lack of meta-analysis to be appropriate.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation

3.2.1 Clinical evidence overview

An overview of the burosumab clinical programme is presented in Document B, Section 2.2. In brief, the company presented six studies: CL303,[20-22] BUR02,[23, 24] CL001,[25] CL203,[26] CL304,[27] and a life course analysis combining data from CL001 and CL303.[10] Of those, two studies (CL303 and BUR02) informed the company's base-case economic model, and one study (CL001) informed scenario analyses.

The main trial that supports the company submission is CL303, a phase 3, randomised, placebo-controlled trial evaluating the efficacy and safety of burosumab in 134 adults with XLH. BUR02 is an open-label extension study, which includes a subset of 34 participants treated in European centres from CL303 and CL304. Study CL304 is a phase 3, single-arm study evaluating the effect of burosumab on osteomalacia in 14 adults with XLH. CL001 is a cross-sectional survey that included 232 adults with XLH, evaluating disease manifestations, treatment history and patient reported outcomes.

Two early phase trials were not presented in the submission. This included KRN23-001 (phase 1/2 dose escalation and its extension, KRN23-001. The EAG considers the exclusion of these small, early phase studies to be appropriate.

Four ongoing studies were also discussed but their results did not inform the company's economic model (Document B, Section 2.11). These include BURGeR. XLH international registry, CL401 DMP and the Early Access Programme Real World Data (EAP RWD). The EAP RWD includes [redacted] (as of April 2023) who have received burosumab in England. Although the company stated that data are not expected to be available within the timeframe of their submission, baseline data was used to inform the economic model (see Section 4.2.3) and preliminary results were presented (Document B, Section 2.6.6.1) for 40 participants treated in one of the centres involved in the EAP (University College London Hospitals NHS Foundation Trust (UCLH)).[28]

This section presents a summary and critique of the following studies: CL303, BUR02, CL001, CL304 and the UK EAP with an emphasis on the studies and outcomes that inform the economic model.

3.2.2 CL303 Study design

Document B, Section 2.3.1 summarises the design of study CL303. Briefly, CL303 was a phase 3, placebo-controlled randomised trial that evaluated the efficacy and safety of burosumab in 134 adults with a diagnosis of XLH. Following two screening visits, participants were randomised 1:1 to either burosumab (1mg/kg) or placebo by subcutaneous injection every four weeks, and entered the 24-week placebo-controlled treatment period. Participants then entered an open-label treatment continuation period (between 24 and 48 weeks) during which they all received burosumab (1mg/kg every four weeks). This was followed by two open-label treatment extension periods, the first from Week 48 to 96 and the second (in the US only) from Week 96 to 149. After Week 96, participants treated in European study centres had the option to take part in the open-label continuation study BUR02.

The primary objective was to establish the effect of burosumab compared with placebo on increasing serum phosphorus levels in adults with XLH. The key secondary efficacy objectives of the study were to evaluate the effect of burosumab compared with placebo on skeletal pain, stiffness, and physical functioning.

3.2.2.1 Participant eligibility criteria

Trial CL303 eligibility criteria are summarised in Document B, Section 2.3.1.1. Adults (18 to 65 years) with a diagnosis of XLH and biochemical findings associated with XLH were eligible for inclusion. Participants were required to have a Brief Pain Inventory Short Form (BPI-SF) worst pain score ≥4 in the last 24 hours attributed to XLH/osteomalacia, and any chronic pain medications regimens must have been stable for more than 21 days before screening. Subjects with recent history (≤6 months) of traumatic fracture or orthopaedic surgery were excluded.

The EAG considers that selection criteria were generally appropriate, but notes that the requirement for Worst Pain score of 4 (upper limit of mild pain) attributed to XLH/osteomalacia is a low threshold for XLH-related pain, according to clinical advice to the EAG. Study CL303 criteria did not require the presence of other symptoms (such as stiffness, physical function, fatigue). This appears to differ from the UK EAP criteria for treatment-naive, which include the presence of 'debilitating symptoms, including, but not limited to, pain, stiffness and fatigue'. At PFC stage the company stated that there is good alignment between the positioning for the submission, the inclusion criteria for the EAP, and the study population. The EAG agrees it is likely that the EAP eligibility criteria and trial criteria broadly align, but notes that the CL303 population was overall younger, fitter and lighter than the EAP population. This is further discussed in section 3.2.3 . The fact that patients were not required to be

unsuitable for conventional phosphate supplementation (as per the company's positioning described in Section 2) may also limit the applicability of the trial to the population who would be eligible to burosumab in practice. At PFC stage, the EAG requested for the company to provide the numbers of participants who were unsuitable to conventional phosphate therapy in CL303; the company replied that this data had not been recorded and was therefore unavailable. They noted that although the EAP criteria do not explicitly require patients to be unsuitable for phosphate treatment, the EAP application form requests information on the presence of persistent symptoms despite prior treatment with conventional therapy.

3.2.2.2 Comparator

In its submission to the EMA, the company justified their choice of placebo as comparator, as opposed to conventional therapy.[29] In brief, an active-comparator trial would not have been practical and appropriate due to differences in method of administration between burosumab and phosphate supplementation with active vitamin D (subcutaneous injection vs. oral treatment), lack of consensus on conventional therapy use in adults, and the limited evidence supporting a favourable benefit/risk profile for treatment with phosphate supplementation and active vitamin D.

The EAG agrees that the choice of a placebo as comparator was broadly appropriate, as it accounts for the risk of placebo effect (particularly for patient reported outcomes). However, the study does not allow to draw any conclusions about the relative efficacy of burosumab compared with phosphate and active vitamin D supplementation, and has limited applicability to patients who would be eligible to phosphate supplementation and active vitamin D. Although the trial design allows the estimation of the placebo effect of burosumab in the short term, the unblinding at 24 weeks means that any longer-term placebo effect could not be accounted for.

3.2.2.3 Randomisation and allocation concealment

Methods of assigning subjects to treatment groups were reported in the trial CSR, Section 8.5.3. Participants were randomised via an interactive web response system (IWRS) and assigned in a 1:1 ratio to burosumab or placebo. Subject numbers were assigned sequentially and study and site personnel had no knowledge of the randomisation code according to the study CSR.

The study protocol specified that randomisation was to be stratified according to mean Brief Pain Inventory (BPI) Worst Pain score (BPI-Q3) during the 7 days preceding the baseline visit. An error in the IWRS led to stratifying by BPI Average Pain (BPI-Q5) score (> 6.0 or ≤ 6.0) over the last 7 days prior to the baseline visit instead. Sensitivity analyses for the primary and key secondary endpoints were implemented to assess the impact of this error and found that it had minimal impact on the primary analyses. Randomisation was also stratified by region (North America/EU, Japan, South Korea). This stratification factor was not specified in the original protocol, but as a protocol

amendment (dated 31 March 2017). The company stated this additional factor was aimed to ensure balance between the two treatment groups, as small numbers were expected to be enrolled in Asian centres.

Despite the use of an IWRS to assign treatment and reported methods to conceal allocation to study arm, the EAG is concerned by imbalances in participant characteristics at baseline between the burosumab and placebo arms. This is further discussed in Section 3.2.3.

3.2.2.4 Blinding

Blinding methods are reported in the study CSR, section 8.5.6. Burosumab and placebo had matched appearance, and all study personnel were blinded to key laboratory values associated with expected changes from burosumab treatment during the placebo-controlled treatment period. After 24 weeks, subjects in both arms received burosumab, and remained blinded to their treatment allocation at baseline.

To assess fracture healing, radiographs were centrally read by two independent reviewers blinded to treatment assignment and subject data. A central laboratory was involved for all post-Baseline serum and urine measurements, and radiographs were read centrally by personnel blinded to treatment assignment. During analysis of the x-ray data, at least one of the two central readers did not consistently use the baseline radiograph as the comparator for grading as intended and instead used the most recent radiograph as the comparator (e.g., the Week 12 radiograph was used as the comparator to evaluate Week 24 fracture/pseudofracture healing grading). The CSR reported that the numbers of fractures/pseudofractures reported as fully healed at Week 24 are unlikely to be affected, because grading followed a strict definition that is independent of previous readings. The EAG agree that the validity of fully healed fracture outcomes is unlikely to be affected by this error; however, fractures/pseudofractures reported to be partially healed, unchanged, or worse at Week 24 may not be reliable due to the inconsistent use of baseline radiograph data.

3.2.2.5 Trial outcomes

Primary and secondary efficacy outcomes are listed in Document B, Table 12. The primary efficacy endpoint was the proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (LLN) (2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dose interval (ie, Weeks 2, 6, 10, 14, 18, and 22), averaged across dose cycles between Baseline and Week 24.

Clinical advice to the EAG confirmed that the primary outcome was a relevant surrogate marker for the target molecule, FGF23, and used an appropriate method for measuring biochemical efficacy. Overall, the definition of the primary outcome was acceptable. The choice of serum phosphate, as opposed to alkali phosphatase, was considered appropriate by the EAG clinical adviser. Unlike

phosphate (chemical derivative of phosphoric acid), alkali phosphatase is an enzyme derived from bone that may or may not be abnormal (depending on the presence of active bone disease), and is independent of phosphate levels.

Patient reported outcome instruments used in study CL303 are summarised in Document B, Table 13. Three main scales were used: WOMAC, BPI-SF and BFI. Key secondary efficacy endpoints were:

- Change from Baseline to Week 24 in BPI Worst Pain score
- Change from Baseline to Week 24 in the WOMAC Stiffness score
- Change from Baseline to Week 24 in the WOMAC Physical Function score

Only one of the three "key secondary outcomes" (Change from baseline to Week 24 in BPI-Q3 (Worst Pain) score) was specified in the original protocol. In protocol amendment that took place after the primary analysis database lock/double-blind treatment period, change from baseline in WOMAC physical function and WOMAC stiffness score were added as "key secondary outcomes" to the protocol. A justification for this decision is summarised in the EMA assessment report;[29] the company's decision to update the list of secondary outcomes was partly driven by the results of study CL001, which highlighted the clinical relevance of stiffness in adult XLH. Overall, the EAG believes that the decision to upgrade these outcomes after the database lock is not scientifically valid, and the risk that it was driven by the study results cannot be excluded. In response to request for clarification, the company provided further details on protocol deviations (including 'Procedure Not Done', 'Study Inclusion or Exclusion Criteria', 'Receipt of Prohibited Concomitant Medications'); based on the data presented, the EAG broadly agrees with the company that the reliability of the relative efficacy and safety results is unlikely to be substantially affected by those deviations.

Other secondary outcomes included changes from baseline to post-baseline visits in BPI, WOMAC and BFI scores, and pharmacodynamic and biochemical markers.

The BPI, BFI and WOMAC scales were not designed to measure outcomes for in subjects with XLH. The company conducted a study to assess the reliability and validity of these scales in adult XLH using CL303 data. The results of this study were presented as conference abstracts and posters only. [30-32] A summary and critique of the evidence presented by the company on the reliability and validity of the BPI, BFI and WOMAC scales for adult XLH is presented in Appendix 1. Overall, the EAG believes that the company did not provide sufficient evidence to assess whether these scales were validated for adult XLH.

Although CL303 attempted to rule out pain not related to adult XLH at screening, it does not appear that BPI and WOMAC scales measured XLH-specific pain and accounted for other confounding sources of pain at follow-up.

"Exploratory" endpoints, not pre-specified in the protocol, included:

- Active fractures and pseudo-fractures
- Change from baseline in six-minute Walk test
- Change from week 24 to visits after week 24 in Timed Up and Go (TUG) test

Skeletal x-ray surveys were conducted at baseline, and targeted radiography was performed at follow-up for identified active pseudofractures or fractures. The incidence of new fractures and pseudo-fractures was not pre-specified and this outcome does not appear to have been measured systematically after treatment initiation, although fractures outcomes at follow-up were reported as safety events.

Serum phosphate outcomes were measured every two weeks from baseline, before each of the burosumab injections and at the midpoint between doses, and were also reported as percentage of subjects with serum phosphate level above the LLN just before the next dose.

Other biochemical markers included serum bone-specific alkaline phosphatase (BALP, a bone-specific isoform of alkaline phosphatase and marker of bone disease), serum procollagen type 1 n-terminal propeptide (P1NP, a marker of bone formation) and serum Carboxy-terminal collagen crosslinks (CTx, a marker of bone resorption).

Safety endpoints are described in the CSR, Section 8.8.3.3.

3.2.2.6 Statistical analysis

A summary of the statistical analysis method is presented in document B, Section 2.3.1.4, with further details presented in the CSR, Section 8.8. For the primary analysis of the primary outcome (proportion of participants achieving a mean serum phosphate concentration above the (LLN) of 2.5 mg/dL), analyses were conducted for the primary analysis set, which consisted of all randomised participants who received at least one dose of study drug during the placebo-controlled treatment period. The consort diagram reported in CS, Appendix D, indicates that all randomised participants received at least one dose of study drug. The primary endpoint was analysed with the Cochran-Mantzel-Haenzel test, adjusted for actual randomisation stratification factors: BPI average pain score, and region (North America/EU, Japan, South Korea).

Key secondary endpoints were analysed as a group using a generalised estimating equation (GEE) repeated-measures analysis, and the Hochberg adjustment was used for multiple testing. Fixed factors adjusted for baseline measurements included treatment, BPI average, region, visit and interaction of treatment-by-visit. Other secondary outcomes were analysed with GEE models. It does not appear that other covariates, including those with imbalances at baseline, were accounted for (PFC response).

Sensitivity analyses of the key secondary endpoints were conducted to assess the impact of the randomisation stratification error. Additional sensitivity analyses used last observation carried forward (LOCF), baseline observation carried forward (BOCF), and modified baseline observation carried forward (mBOCF) methods to impute missing data.

The CSR stated that WOMAC Stiffness, 6MWT, and fractures were reanalysed for the placebo-controlled treatment period because additional or corrected data were provided for these endpoints after the Interim Database Lock for the primary analysis. The impact on WOMAC Stiffness was minimal at 24 weeks (LS mean (SE) difference between burosumab and placebo: -8.1 (3.24) (p=0.0122) in the initial analysis, vs. -8.3 (3.25) (p=0.0106) in the re-analysis) and appears to have affected only one patient for 6MWT. The impact of data corrections for the fracture outcomes is uncertain.

In addition to the primary analysis set, analysed populations included the Safety Analysis Set, which consisted of all randomised subjects who received at least one dose of the study drug. Subjects were analysed based on the actual treatment received. This analysis set was used for all safety endpoints. Other analysis sets (Pharmacokinetics Set and Postprandial Substudy Analysis set) are defined in the CSR, Section 8.8.5.2. All 134 participants were included in the Primary and Safety Analysis Sets.

The EAG believes that the statistical methods were broadly appropriate. However, a number of baseline imbalances were identified between the study arms (see Section 3.2.3 for further detail), and statistical analyses did not account for most of these differences or explore their potential impact on the study results.

In addition, the analysis methods used assumed normal distributions for the outcomes. The company used the Shapiro-Wilk test of normality and found that the change scores were non-normal for all measures (BPI Worse Pain Score, WOMAC Physical Function and WOMAC Stiffness) for the burosumab arm, and non-normal for WOMAC stiffness for placebo.[29] This limits the validity of these outcomes. The EAG requested from the company as PFC that they provide data on the number of subjects who experienced a clinically meaningful improvement in each arm at 24 weeks follow-up for WOMAC, BPI, BFI, as well as 6MWT, as they consider these measures to be more robust measures of efficacy than mean changes from baseline, particularly when mean change scores are not normally distributed. Data were reported in the company's response to PFC and are summarised in section 3.2.4.

3.2.2.7 Exposure

In both treatment groups, the median weight-based dose of study drug was 1.0 mg/kg (mean: 0.99 mg/kg; range: 0.6 – 1.1) at the Baseline Visit and remained between 0.9 and 1.0 mg/kg (mean: 0.87-

0.98 mg/kg; range: 0.2 – 1.2) at follow-up visits. The protocol included criteria for treatment assignment unblinding and dose adjustments due to elevated serum phosphorus levels over upper level of normal (ULN) (>4.5 mg/dL [1.45 mmol/L]). During the 24 weeks blinded period, 5 (7.4%) subjects in the burosumab group and no subject in the placebo group had treatment unblinded. Across all treatment periods, burosumab doses were reduced to 0.5 mg/kg in 11 (8.2%) subjects and subsequently maintained at that dose in 10 out of 11 participants.

3.2.3 CL303: Participant characteristics and applicability of the evidence

A summary of key baseline characteristics of the CL303 participant in Table 5, Table 6, Table 7 below. Further details are presented in Document B, Section 2.3.1.5.

Table 6 shows the age distribution of CL303 participants compared with the EAP population included in the company's model. Overall, CL303 participants were younger than adults currently receiving burosumab in England, with a higher proportion of subjects younger than 30 year (26% vs. 14%), and a lower percentage of subjects 60 years or older (9% vs. 22%) in the CL303 trial population. Clinical advice to the company indicated that CL303 participants had lower weight and were fitter overall compared with UK clinical practice, and may therefore be less representative than the EAP population. A clinical adviser to the company also stated that age and weight were the most important factors for the model population to align with the clinical practice population in the economic model. This limits the applicability of the CL303 population to UK practice. This is further discussed in section 4.2.3.

Clinical advice to the EAG noted that the distribution of male/female participants was reflective of clinical practice. Most participants were from North American and European centres. No phosphate-regulating endopeptidase X-linked (PHEX) mutation was identified for seven (5%) trial participants, including six in the burosumab group and one in the placebo group. However, the seven subjects were clinically diagnosed with XLH and met the inclusion criterion for support of the diagnosis of XLH. Four of the subjects (all in the burosumab group) had directly related family members with an inheritance pattern consistent with X-linked disease.

Approximately 10% of subjects had no exposure to phosphate with vitamin D metabolites. The company reported that no data was available on the proportion of participants that were unsuitable for conventional treatment with phosphate supplementation and activated vitamin D, and that [redacted] had a record of prior conventional therapy. Seven participants had prior exposure to burosumab ([redacted]). Data on the interval since discontinuing prior burosumab before enrolling in CL303 are not available, therefore it is difficult to assess whether prior burosumab treatment may have introduced bias. Further details, including separate baseline characteristics and subgroup data for subjects with and without standard therapy prior to the washout

period, and for subjects with prior burosumab exposure, were requested as a PFC. The company stated that data on separate baseline characteristics and subgroup analysis of patients with and without standard therapies prior to the washout period could not be provided within the time frame given, but will be supplied at a later date; data for the subgroup of patients with prior burosumab exposure were said to be "not available at this time" (no reasons provided).

Just over two thirds of participants had pain medication at baseline; the EAG asked for the company to confirm whether all participants were on optimized and stable pain management at baseline as PFC. The company replied that there was no requirement for pain medication to be optimised at study start

Table 5 Demographics and baseline characteristics of study CL303 participants

	Burosumab (n = 68)	**Placebo (n = 66)**	**Total (n = 134)**
Demographics			
Age (years)			
Mean ± SD	41.3 ± 11.6	38.7 ± 12.8	40 ± 12.2
Range	20.0-63.4	18.5-65.5	18.5-65.5
Female, n (%)	44 (64.7)	43 (65.2)	87 (64.9)
Region, n (%)			
North America/Europe	58 (85.3)	58 (87.9)	116 (86.6)
Asia (Japan, South Korea)	10 (14.7)	8 (12.1)	18 (13.4)
Height[a], mean ± SD (centimetres)	152 ± 9.5	153 ± 11.8	152 ± 10.7
BMI[a] (kg/m^2), mean ± SD	30.0 ± 7.5	30.6 ± 7.8	30.0 ± 7.6
Genetic status			
PHEX mutation, n (%)			
Pathogenic	45 (66.2)	50 (75.8)	95 (70.9)
Likely pathogenic	8 (11.8)	7 (10.6)	15 (11.2)
Variant of unknown significance	9 (13.2)	8 (12.1)	17 (12.7)
No mutation	6 (8.8)	1 (1.5)	7 (5.2)
Serum phosphate (mg/dL)[a], mean ± SD	2.0 ± 0.30	1.9 ± 0.32	2.0 ± 0.31
Medical history			
Phosphate + vitamin D metabolites or analogues, ever, n (%)	59 (86.8)	62 (93.9)	121 (90.3)
Orthopaedic surgery, n (%)	45 (66.2)	47 (71.2)	92 (68.7)
Osteoarthritis, n (%)	47 (69.1)	38 (57.6)	85 (63.4)
Fractures			
Unhealed fracture/pseudofracture at baseline, n of participants (%)	32 (47.1)	38 (57.6)	70 52.2)
Number of fractures/pseudofractures	65	91	156
Fractures	14	13	27

	Burosumab (n = 68)	Placebo (n = 66)	Total (n = 134)
Pseudofractures	51	78	129
Mobility			
6 minute walk test (6MWT) meters, mean (SD)	356.8 (109.5)	367.4 (103.4)	NR
Pain medication			
Any pain medication at baseline, n (%)	47 (69.1)	44 (66.7)	91 (67.9)
Any opioid at baseline, n (%)	17 (25.0)	13 (19.7)	30 (22.4)
Non-opoid pain medications (NSAIDs/paracetamol)	47 (69.1)	43 (65.2)	90 (67.2)
Neuropathic pain medication/antidepressants	4 (5.9)	3 (4.5)	7 (5.2)
Other pain medications	7 (10.3)	1 (1.5)	8 (6.0)

Source: Insogna et al. (2018);[7] Portale et al. (2019)[62]

[a]Normal ranges: phosphate, 2.5-4.5 mg/dL; 1,25(OH)2D, 18-72 pg/mL; calcium, 8.6-10.2 mg/dL; iPTH, 14-72 pg/mL; TmP/GFR, 2.5-4.2 mg/dL.

Table 6 Age distribution: CL303 and EAP

	CL303	EAP
18-29	26%	14%
30-39	20%	22%
40-49	30%	23%
50-59	15%	20%
60-69	9%	18%
70-79	0%	3%
80-89	0%	1%

Source: Company submission economic model

Although most baseline characteristics were balanced between arms, there were several notable exceptions: participants in the burosumab arm were older on average (but not statistically significant: p = 0.22), and there were more subjects in the oldest age range (> 50-65 years) in the burosumab group vs placebo (16 vs 10). Burosumab participants had fewer pathogenic PHEX mutations, and less experience of ever receiving phosphate and vitamin D. The percentage of patients with active fracture/pseudofractures and number of pseudofractures were significantly higher in the placebo arm. The percentage of patients experiencing severe pain at baseline (BPI worst pain >6.0) was substantially higher in the burosumab arm compared with placebo, and a larger percentage used opoids at baseline in the burosumab group. The percentage of patients with unhealed

fractures/pseudofractures at baseline, or with a history of orthopaedic surgery, was higher in the placebo arm.

Table 7 presents baseline values of patient reported outcomes at baseline. The mean (SD) WOMAC average score on a normalized scale from 0 (best health state) to 100 (worst) was 49.1 (18.2) across arms, with worse scores for the WOMAC Stiffness subscale (63.1 [20.5]) compared with Pain (49.3 [16.8] and Physical function (47.4 [20.0]). Average BPI Pain severity scores were moderate overall (mean 5.1), although 71.6% of subjects reported BPI Worst Pain scores of >6 (severe pain). The average Global Fatigue score was 5.1 (2.0) across both arms, indicating moderate fatigue overall. Overall, compared with placebo, burosumab arm subjects had somewhat worse physical function, stiffness, pain, pain interference and fatigue scores. The EAG requested the results of statistical tests for baseline imbalances as a PFC but results were only presented for BPI worst pain >6.0 (p=[redacted]) .

The EAG extracted data from the trial CSR for PROs to investigate any potential imbalance between trial arms at baseline. The results are reported in Section 3.5.

Table 7 Patient reported outcomes at baseline in study CL303

	Burosumab (n = 68)	**Placebo (n = 66)**	**All participants (n = 134)**
WOMAC[a], mean (SD)			
Total score	51.8 (18.3)	46.2 (17.7)	49.1 (18.2)
Physical function	50.8 (19.7)	43.9 (19.9)	47.4 (20.0)
Stiffness	64.7 (20.3)	61.4 (20.8)	63.1 (20.5)
Pain	50.7 (18.0)	48.0 (15.5)	49.3 (16.8)
BPI-SF[b] worst pain (average)			
Mean (SD)	6.8 (1.3)	6.5 (1.4)	6.7 (1.4)
≤6.0, n (%)	15 (22.1)	23 (34.8)	38 (28.4)
>6.0, n (%)	53 (77.9)	43 (65.2)	96 (71.6)
BPI-SF[b] worst pain (greatest)			
Mean (SD)	8.1 (1.2)	8.0 (1.5)	8.0 (1.3)
BPI-SF Pain Severity (average) Mean (SD)	5.2 (1.5)	4.9 (1.5)	5.1 (1.5)
BPI-SF[b] pain interference, mean (SD)	5.2 (2.2)	4.8 (2.2)	5.0 (2.2)
BFI[c] scores, mean (SD)			
Global fatigue	5.4 (2.0)	4.9 (1.9)	5.1 (2.0)
Worst fatigue (average)	6.9 (1.7)	6.7 (1.5)	6.9 (1.6)
Worst fatigue (greatest)	8.2 (1.4)	8.2 (1.3)	8.2 (1.4)
Fatigue interference	5.0 (2.3)	4.5 (2.3)	4.8 (2.3)

[a]WOMAC range 0-100, where 0 represents best health. [b]BPI-SF range 0-10, where 10 indicates worst pain. [c]BFI range 0-10, where 10 represents worst fatigue BPI-SF, Brief Pain Inventory-Short Form; WOMAC, Western Ontario and McMasters Universities Osteoarthritis Index.

Source: CS Document, Table 20, and Briot et al. (2021)[22]

Overall, the EAG found that the study arms in CL303 were not fully balanced at baseline. Compared with placebo, participants in the burosumab arm were older overall, less pre-treated with phosphate supplements, more heavily treated with painkillers, worse physical functioning, although with fewer pseudofractures. Imbalances might be due to use of two stratification factors at randomisation in a relatively small sample.

3.2.4 CL303: Trial results

This section presents a summary and critique of the outcomes of CL303 as listed in the NICE scope.

3.2.4.1 Fractures

Fracture and pseudo fractures outcomes are presented in Document B, section 2.6.3, with further details in the CL303 CSR. A summary of outcomes is presented in Table 8 below.

At week 24, more active fractures were healed in the burosumab arm (7/14 [50%]) compared with placebo (0/13 [0]), and more active pseudofractures were healed with burosumab (21/51 [41%] vs. 7/78 [9%]). The combined rate of healed fracture/pseudofractures was 43.1% in the burosumab arm, compared to 7.7% with placebo; in a post-hoc exploratory analysis, using a hierarchical generalized linear mixed proportional odds model for repeated ordered binary responses, the company reported that the odds of a fracture/pseudofracture being graded as fully healed was significantly higher in the burosumab group compared with the placebo group (OR 16.8; 95% CI 4.9-57.0). Although this effect estimate is very large, it combines fractures and pseudofractures, which have a different clinical significance and prognosis. No relative estimates between burosumab and placebo were presented for fractures and pseudofractures separately, although estimates from such analyses would be even more imprecise due to the smaller numbers of events and subjects. Comparisons are limited by the number of participants (e.g. only 8 subjects had active fractures at baseline in each arm) as well as baseline imbalances in the number of active pseudofractures between study arms (51 for burosumab vs. 78 for placebo); the severity of the fractures (e.g. non-union) at baseline was also unknown.

Further fracture healing results (including rates of partially healed, unchanged, or worse fractures/pseudofractures) were reported in the CSR. However, as discussed in Section 3.2.2, the number of fractures/pseudofractures reported to be partially healed, unchanged, or worse at Week 24 may not be reliable due to the inconsistent use of baseline radiograph data.

Additional new fractures/pseudofractures were found in both arms by week 24; 6 (8.8%) in the burosumab arm and 8 (12.1%).[29] One additional fracture was reported at week 24-36.

The 24 weeks follow-up period may not have been sufficient to assess the relative effectiveness of burosumab for this outcome. In study CL304, bone structure was not completely normalised at Week 48 according to bone biopsies, suggesting that normalisation of the bone may require more time than the duration of the blinded period in the CL303 trial. In addition, although skeletal radiographic surveys were conducted at baseline, and targeted radiography at follow-up for identified active pseudofractures or fractures, there was no schedule of assessment for new fractures/pseudofractures, and bone scintigraphy, which is more sensitive than x-ray, was not used. Therefore, some additional events may have been missed.

For the EAG's reanalysis of fracture data, see Section 3.5.2.

Table 8 CL303 Fracture outcomes

	Burosumab (n=68)	**Placebo (n=66)**
Active fracture complete healing		
Baseline n (%) subjects with active fracture	8 (11.8%)	8 (12.1%)
Baseline n of fractures	14	13
Follow-up n (%) of subjects with fracture healing	4/8 (50%)	0/8 (0)
Follow-up n (%) of healed fractures (24 weeks)	7/14 (50%)	0/13 (0)
Active pseudofracture complete healing		
Baseline n (%) subjects with active pseudofracture	29 (42.6%)	34 (51.5%)
Baseline n of pseudofractures	51	78
Follow-up n (%) of subjects with pseudofracture healing	15/29 (51.7%)	5/34 (14.7%)
Follow-up n (%) of healed pseudofractures (24 weeks)	21/51 (41%)	7/78 (9%)
Fracture/pseudofracture complete healing		
Baseline n (%)subjects	32/68 (47.1%)	38 (57.6%)
Baseline n of fracture/pseudofractures	65	91

Follow-up n (%) subjects with healed fracture/pseudofracture	16/32 (50%)	5/38 (13.2%)
Follow-up n (%) of healed fractures/pseudofractures (24 weeks)	28/68 (43.1%)#	7/76 (7.7%)
New fractures/pseudofractures		
Follow-up n (%) (24 weeks)	6 (8.8%)	8 (12.1%)
New fractures		
Follow-up n (%) (24 weeks)	3 (4.4%)	2 (3.0%)

[#] OR 16.8 (95% CI 4.9-57.0) based on hierarchical generalized linear mixed proportional odds model for repeated ordered binary responses

Sources: CL303 CSR,[21] EMA EPAR [29]

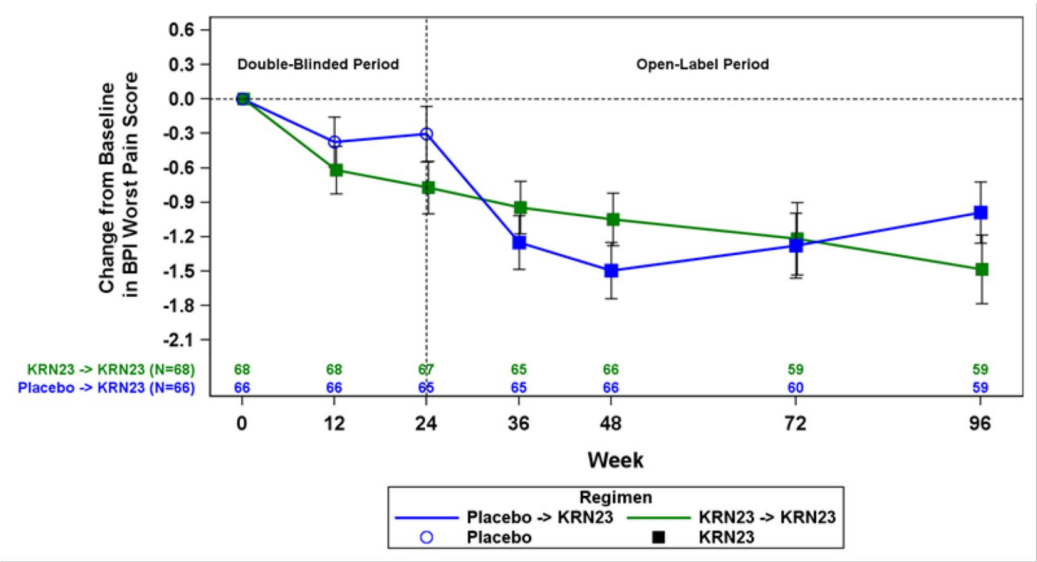
3.2.4.2 Pain

Pain results are reported in Document B, Section 2.6.2.3, with further details reported in the CSR, Section 10.2. Pain was captured using the BPI-SF questionnaire (including BPI Worst Pain, Pain Severity, and Pain Interference), as well as the WOMAC Pain subscale (described in Section 3.2.2). Overall, there was no statistically significant difference in improvement in pain scales between burosumab and placebo at 24 weeks follow-up. Improvements in BPI Worst Pain items, Pain Severity and Pain Interference at 24 weeks were small overall, with LS mean (SE) difference between burosumab and placebo of -0.5 (0.28) for BPI Worst Pain, -0.4 (0.25) for BPI-SF Pain Severity and -0.2 (0.29) for Pain Interference (negative mean values favour burosumab). These results were not statistically significant and did not reach the MCID thresholds presented by the company (1.72 for Worst Pain, 1.0 Pain Interference).[32] Results for WOMAC Pain scores (reported in CL303 CSR, Section 10.2.2) were comparable (burosumab: -6.67 [17.6]; placebo: -2.38 [15.5], LS mean difference not reported) and did not reach the company's MCID thresholds (11 for Pain scale). [31] The location and type of pain (e.g. bone pain, joint pain) was not captured in the BPI and WOMAC pain assessments.

Figure 2 presents results for BPI Worst score over time up to 96 weeks follow-up. The reductions in pain scores observed at 12 and 24 weeks during the blinded period in the placebo group show evidence of a small placebo effect. Pain scores in the unblinded period varied substantially between follow-up points for participants randomised to placebo, whereas the burosumab arm followed a small

linear improvement. Similar trends were found for BPI Pain Severity and BPI Pain Interference scales (see CL303 CSR, Figures 8 and 9). Reasons for this pattern are largely uncertain.

Figure 2 Least Squares Mean (SE) Change from Baseline in BPI Worst Pain Scores over time in study CL303 (Primary Analysis Set)



KRN23 = burosumab
Note: All subjects received burosumab beginning at the Week 24 visit; however, they remained blinded to their previous treatment assignment.

BPI Worst pain scores ranged from 0 to 10; lower scores indicate better health

Source: CL303 CSR Figure 5.

Clinical advice to the EAG noted that adults with XLH have pain from many sources (e.g. skeletal deformity, osteomalacia, osteoarthritis, pseudofractures and fractures, enthesopathy), not all aspects of which may resolve with burosumab treatment given their cause and chronicity. This may explain the lack of clinically meaningful improvement in pain outcomes in burosumab treated subjects.

3.2.4.3 Stiffness

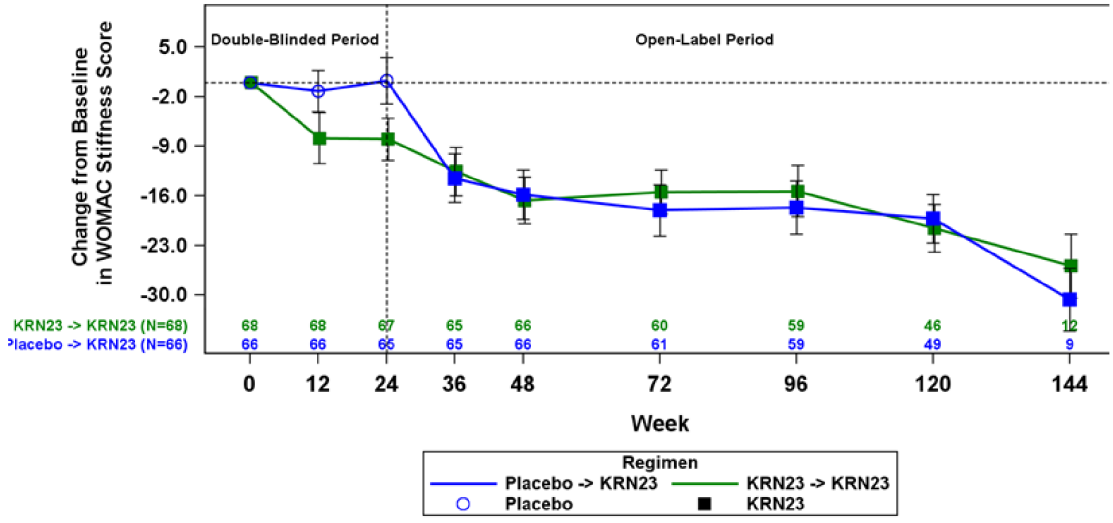
Stiffness outcomes are reported in Document B, Section 2.6.2.2 with further details reported in the CSR, Section 10.2. Stiffness was measured using the two item Stiffness subscale from the WOMAC questionnaire (Stiffness after first waking and later in the day), which is described in Appendix 1.

At 24 weeks follow-up, there was a statistically significant difference in improvement in Stiffness measurements between burosumab and placebo, with a LS Mean (SE) difference (Burosumab-Placebo) of -8.31 (3.251), p=0.0106. The average improvement in WOMAC Stiffness score did not meet the company's threshold for MCID (10-15 points decrease) at 24 weeks.[31] A decrease of ≥ 10.0

points from baseline in WOMAC stiffness score was observed in 55.9% of subjects in the burosumab group, compared with 45.5% in the placebo group; the difference between study arms was not statistically significant (p = 0.2112). The percentage of subjects with reduction of ≥ 10.0 points from baseline in stiffness score in the placebo arm during the blinded period suggests a strong placebo effect. Figure 3 shows that average Stiffness score improvements continued after unblinding at 24 weeks and reached the MCID threshold in both study arms from 48 weeks.

As per the pain outcomes, the analyses for WOMAC Stiffness did not adjust for baseline differences in participant characteristics (e.g. the burosumab arm had worse pain scores and slightly worse Stiffness scores) and concomitant pain medications (as discussed in Section 3.2.3). As discussed in Appendix 1, the reliability and validity of WOMAC stiffness in adult XLH is uncertain. Results beyond 24 weeks are at higher risk of bias due to the unblinding of participants and the evidence of a strong placebo effect, and due to the loss to follow-up rate at later assessment points (most notably at 144 weeks, where only 21 out of an initial 134 participants were assessed). In addition, after unblinding, subjects assigned to the placebo arm had a steep improvement in Stiffness between 24 and 48 weeks, suggesting a regression to the mean effect. Results for further follow-up (week 120 and 144) show further reductions (see CSR 10.2.1), although these may not be reliable due to significant loss to follow-up.

Figure 3 LS Least squares mean (SE) Change from baseline in WOMAC Stiffness scores over time (Primary Analysis Set)



Data are LS mean (SE) change from baseline; lower scores indicate better health. The MCID value is indicated by the pale grey horizontal dashed line. LS, least squares; SE, standard error.

Source: CL303 CSR

3.2.4.4 Fatigue

Fatigue outcomes are reported in Document B, Section 2.6.2.4., with further details reported in the CSR, Section 10.2. Fatigue was measured using BFI, which is described in Appendix XX.

At 24 weeks follow-up, there was a no statistically significant difference in improvement in BFI Global Fatigue scores between burosumab and placebo (LS Mean (SE) difference (Burosumab-Placebo) of 0.1 (0.28), p=0.7912). At 24 weeks follow-up, an improvement in worst fatigue (average and greatest) was observed in both arms, but there was no statistically significant difference in mean change from baseline in BFI subscales (Worst Fatigue and Fatigue Interference). Figure 3 22, shows that average fatigue score improvements continued after unblinding at 24 weeks in both study arms.

As per the pain outcomes, the analyses for BFI results did not adjust for baseline differences in participant characteristics (e.g. the burosumab arm had worse pain scores and slightly worse Stiffness scores) and concomitant pain medications (as discussed in Section 3.2.3). As discussed in Appendix 1, the reliability and validity of BFI in adult XLH is uncertain. Results beyond 24 weeks are at high risk of bias due to the unblinding of participants and the evidence of a placebo effect in Worst Fatigue scores.

3.2.4.5 Motor skills

Motor skills were measured in CL303 using the 6-minute walk test (6MWT) and the WOMAC Physical Function subscale (described in Section 3.2.2). The Timed Up and Go test (TUG) was also performed, but it is of limited relevance to this assessment as it was completed in only a small number of participants (nine across study arms at Week 24).

6MWT

Results for 6MWT are reported in CS Document B, Section 2.6.4.1, with further details reported in the CSR, Section 10.4.2.1. The total distance walked during a premeasured course for 6 minutes was recorded in metres and the percent predicted value for the 6MWT was calculated using normative data adjusted for age, sex and height.[33]

At Week 24, the mean (SD) actual distance walked was 381.5 meters (108.46) in the burosumab group and 369.4 meters (103.39) in the placebo group. The LS mean (SE) change from Baseline to Week 24 was 14.8 meters (7.67) in the burosumab group and -5.0 meters (7.54) in the placebo group. The difference in change from Baseline to Week 24 in distance walked favoured burosumab compared with placebo and was statistically significant (LS mean (SE) difference 19.8 meters (7.67), p = 0.0108). The difference in percent predicted value at 24 weeks favoured burosumab and was statistically significant (LS mean (SE) difference of 3.2% (1.10) (p = 0.0042)). The company did not comment on whether an improvement of 19.8 meters in distance walked in 6 minutes compared with placebo was clinically significant.

The EAG believes that the average 6MWT improvement observed in the burosumab arm of CL303 has limited clinical significance. Evidence from the adult XLH EAP used a distance of 80 meters as MCID,[28] which is comparable with thresholds used in osteoarthritis assessments. [34] The EAG requested from the company that they provide data on the number of subjects who achieved a clinically meaningful improvement in 6MWT; the company responded that no data were currently available.

Figure 4 presents results for 6MWT by distance walked and percent predicted up to 144 weeks from baseline for both study arms. This shows that the difference in change in 6MWT percent predicted (which adjusted for age, sex and height) between the study arms [redacted]. As with pain and stiffness outcomes, estimates beyond 24 weeks are at higher risk of bias due to the lack of blinding; [redacted] means that results at these follow-up points are unlikely to be reliable.

Figure 4 Change from baseline in 6MWT (A) distance walked, (B) percent predicted in study CL303

Data are LS mean (SE) change in meters walked from baseline; 6MWT, 6-minute walking test; KRN23, burosumab; SE, standard error.
Source: Study CL303 CSR

WOMAC Physical Function

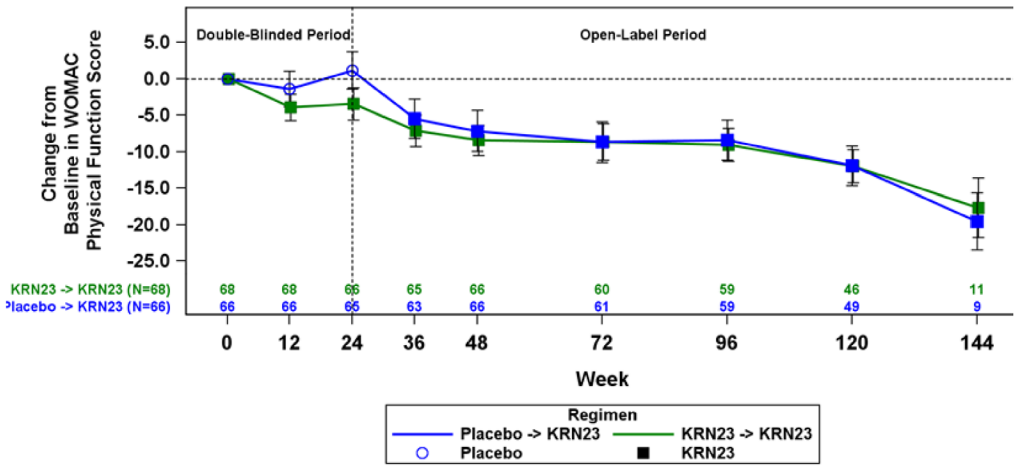
WOMAC Physical Function subscale results are reported in Document B, Section 2.6.2.2, with further details in the CSR, Section 10.2.1. The self-reported WOMAC Physical Function subscales and its 17 items is described in Appendix 1. Overall, there was no statistically significant difference in mean change from baseline in Physical Function between burosumab and placebo at 24 weeks (LS mean (SE) difference of -4.90 (2.479) (p=0.0478, not statistically significant at the 0.025 threshold). LS Mean estimates did not reach the company's MCID threshold for this outcome (8-10).[31] The CSR reported responder analyses using a similar MCID threshold.[35] A decrease of ≥ 9.3 points from baseline in WOMAC Physical function score was observed in 35.3% of subjects in the burosumab group, compared with 27.3% in the placebo group; the difference between study arms was not statistically significant (p = 0.3566). The decrease in the percentage of subjects with a WOMAC score reduction of ≥ 9.3 points in physical function score in the placebo arm suggests a moderately strong placebo effect.

As discussed in Section 3.2.3, baseline WOMAC Physical Function scores were worse in the burosumab arm compared with placebo (mean 50.8 [19.7] vs. 43.9 [19.9] respectively; p=0.046). The company's analyses did not account for baseline imbalances, which limits their reliability.

Figure 5 shows an improvement in WOMAC Physical Function in both study arms after 24 weeks timepoint that remained stable between 36 and 96 weeks, and LS Mean estimates reached the company's MCID threshold (8 to 10 points) from 48 weeks for the burosumab group, and from 72 weeks for the placebo group who switched to burosumab at 24 weeks. However, as with other reported PROs, results in the open-label period are at higher risk of bias due to the unblinding of participants, placebo effect, and the reduced number of subjects at later assessment points (particularly at 120 and 144 weeks).

The EAG agrees with the company that the WOMAC Physical Function scale is broader in scope than the 6MWT, as it covers a wider range of aspects affecting physical function in XLH. However, as a subjective, self-reported scale, it is at higher risk of bias, particularly after unblinding at 24 weeks.

Figure 5 Least Squares Mean (SE) change from baseline in WOMAC Physical Function score over time in study CL303 (Primary analysis set)



Data are LS mean (SE) change in WOMAC physical function from baseline. Lower scores indicate better health.

Source: CL303 CSR, Figure 5

3.2.4.6 Biochemical markers

Serum phosphate

Serum phosphate outcomes are reported in Document B, Section 2.6.1.1. The percentage of participants achieving mean serum phosphate concentration above the LLN average across the midpoints between monthly doses (the trial primary outcome) was significantly higher in the burosumab arm compared with placebo (94.1% vs. 7.6%); the difference was statistically significant ($p<0.001$). A greater percentage of participants maintained a mean serum phosphate concentration level above the LLN just before the next dose (67.6% vs. 6.1%, p-value NR).

During the placebo-controlled treatment period, 5 (7.4%) subjects in the burosumab group and no subject in the placebo group had elevated serum phosphorus levels over upper level of normal (ULN) (>4.5 mg/dL [1.45 mmol/L]), resulting in treatment unblinding and dose adjustment, as per the trial protocol. Across all treatment periods, the dose of burosumab was reduced to 0.5 mg/kg in 11 (8.2%) participants and subsequently maintained at that dose in 10 of the 11 subjects.

CS Document B, Figures 14 and 15, shows that [redacted].

Biochemical marker of bone remodelling

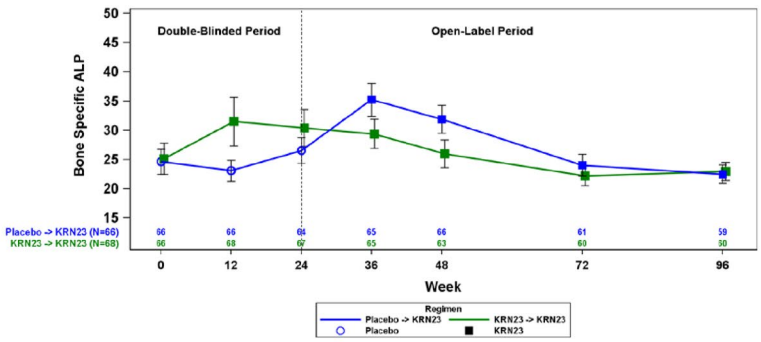
Three biochemical markers of bone remodelling (BALP, P1NP and CTx) were presented by the company. Of those, one was specified in the NICE scope (alkaline phosphatase [AP], measured as serum bone-specific alkaline phosphatase [BALP]). P1NP and CTx, respectively markers of bone

formation and bone resorption, were presented alongside BALP in Document B, Section 2.6.5, with further details reported in CL303 CSR, Section 10.3.5.

Figure 6 presents changes over the trial periods in serum BALP. [redacted]in changes from baseline in bone-specific alkaline phosphatase BALP levels were found between burosumab and placebo at 24 weeks (LS Mean (SE) difference (Burosumab-Placebo) 10.15 (13.656), p=0.4574).

Figure 6 shows that initial increases in serum BALP following burosumab initation in the burosumab arm reduced over time. A similar pattern was observed in the placebo arm following initiation of burosumab at 24 weeks, and for P1NP and CTx. The company stated that this likely reflected the normalization of bone mineral homeostasis over time. The clinical adviser to the EAG agreed that this was a reasonable interpretation based on the evidence presented.

Figure 6 Mean (SE) Serum BALP concentrations (ng/mL) over time (Primary analysis set)



The company stated that BALP is an important marker in XLH-related bone disease in children as it is an indicator of rickets. However, it is less indicative of bone disease in adults, and is less sensitive to changes in bone remodelling than P1NP and CTx. The clinical adviser to the EAG agreed that P1NP is a more sensitive marker of bone formation than BALP, and that CTX is a sensitive marker of bone resorption.

Parathyroid hormone levels

At week 24, mean (SE) plasma Intact parathyroid hormone (iPTH) concentrations in the burosumab and placebo groups were 81.5 (4.73) pg/mL and 99.0 (5.40) pg/mL, respectively. LS mean (SE) changes in plasma iPTH concentrations from Baseline to Week 24 were -9.4 (7.02) pg/mL in the burosumab group and +8.3 (7.04) pg/mL in the placebo group; the difference between groups (burosumab-placebo) in change from Baseline at Week 24 was statistically significant (p = 0.0013). Five subjects (7.4%) had increased blood parathyroid hormone in the burosumab arm (during the

double-blind and open label period); one subject (1.5%) in the placebo arm had increased blood parathyroid hormone after switching to burosumab in the open-label period.

The company reported that adverse events that were related to transient or intermittent increases in parathyroid hormone levels above baseline values but were not associated with any clinically relevant changes in serum-calcium values or clinical signs and symptoms, and no action was taken with the study medication as a result of these adverse events.

Renal function

Renal function results, presented as estimated glomerular filtration rate (eGFR) levels, are reported in the CSR, Section 12.7.1.6. Overall, eGFR levels remained consistent throughout the placebo-controlled period, and no meaningful differences were observed between the burosumab and placebo treatment groups at any time point. One mild (Grade 1) event of decreased eGFR was reported in the placebo group during the 24-week placebo-controlled period and was resolved after 16 days.

3.2.4.7 Health-related quality of life (for patients and carers), and WOMAC Total scores

EQ-5D was not collected in trial CL303. To derive utilities for the economic model, WOMAC scores from CL303 and BUR02 were mapped to EQ-5D. This is further discussed in Section 4.2.8.

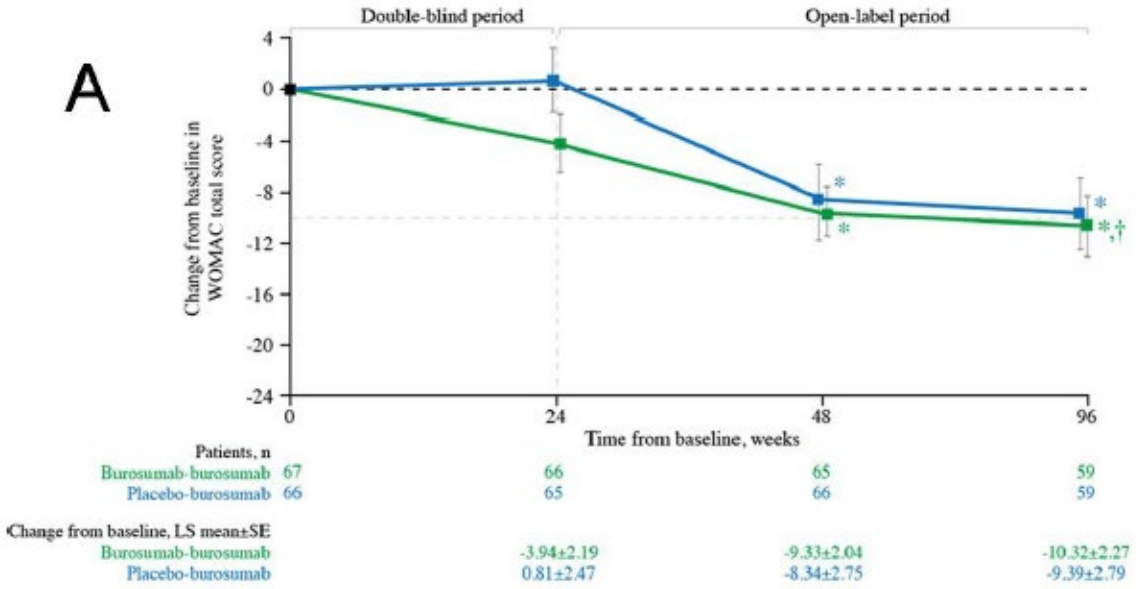
The results for each reported WOMAC subscale in CL303 participants have been discussed above, in sections 3.2.4.2 (WOMAC Pain), 3.2.4.3 (WOMAC Stiffness) and 3.2.4.5 (WOMAC Physical Function). This section provides a brief summary and critique of WOMAC Total scores.

Figure 7 presents the change from baseline WOMAC Total score in both trial arms. At 24 weeks follow-up, there was no statistically significant difference in change from baseline in WOMAC total score between burosumab and placebo. The average improvement from baseline was similar between the two study arms at 48 and 96 weeks, and reached the company's threshold for MCID (≥-10 points) in the burosumab arm at 96 weeks.

The EAG requested as a PFC the percentage of subjects in each arm who reached a clinically meaningful improvement in WOMAC scores; these were provided in the company response and are summarised in section 3.2.4.

As discussed above, the analyses for WOMAC scores did not adjust for baseline differences in participant characteristics (e.g. the burosumab arm had worse pain scores and slightly worse Stiffness scores) and concomitant pain medications. As discussed in Appendix 1, the reliability and validity of WOMAC stiffness in adult XLH is uncertain. Results beyond 24 weeks are at higher risk of bias due to the unblinding of participants and placebo effect, and due to the loss to follow-up rate at later assessment points.

Figure 7 Change from baseline in WOMAC Total score in study CL303



Source: Briot 2021[22]

3.2.4.8 Safety data

A summary of adverse reactions was presented in CS Document B, Section 2.10. The EAG received a more complete summary of adverse events (including by system organ class, preferred term and seriousness) in response to PFC. This section summarises the key points from CS Document B and the trial CSR.

Overall, burosumab was well-tolerated, with no discontinuations due to adverse events. No dose-limiting toxicities occurred. Most participants in each group (94.1% burosumab, 92.4% placebo) had at least one adverse event up to week 24; most were mild to moderate. There were no deaths in the double-blind and open-label periods, and no Grade 4 (life-threatening) treatment-emergent events were reported. Four participants (two in each group) had serious adverse events during the double-blind period, none of which were considered by the investigator to be related to study treatment; these included back pain and irritable bower syndrome in the burosumab arm, and breast carcinoma and upper respiratory tract infection in the placebo arm.

In the burosumab arm, 5.9% of participants experienced hyperphospatemia and required dose reductions; all events were classed as mild by the investigator. No participants in the placebo group experienced hyperphosphatemia. Restless legs syndrome were reported for 11.8% of participants in the burosumab arm, and in 7.6% in the placebo arm.

Before initiation of burosumab treatment, 20 subjects (10 in each arm) were tested positive for anti-drug antibody status. At any visit after initiation of burosumab, 21 subjects (10 in the burosumab arm,

and 11 in the placebo arm) tested positive for anti-drug antibody status. All samples positive for ADA tested negative for neutralising antibodies, indicating no neutralising activity.

Tooth loss and pain

Overall, there was no evidence that burosumab improved tooth loss and tooth pain outcomes. During the placebo-controlled period, one event of tooth loss (1.5%) was recorded in the placebo arm; 9 (13.2%) burosumab group participants had a treatment emergent tooth abscess, compared with 6 (9.1%) for placebo. Tooth pain was not reported as a separate outcome.

Neurological complications (including hearing and balance, and spinal cord compression)

Overall, there was no evidence of a difference in neurological complications between burosumab and placebo, although events were rare.

At baseline, a total of 27 subjects (20.1%) had history of either spinal stenosis, cord compression, or another event likely to be related to either spinal stenosis or cord compression. Six subjects (two in the burosumab arm and four in the placebo group) had seven TEAEs (five serious and two non-serious) related to spinal stenosis. Most events took place during the open-label period. One event of spinal column stenosis was considered to be related to the study drug. Four subjects underwent surgery to address the event, and two subjects were medically managed. All six subjects had a prior history of spinal stenosis, cord compression, or a related condition.

During the placebo-controlled period, one event (1.5%) of sudden hearing loss was reported in the placebo arm (placebo-controlled period), and one event (1.5%) of hypoacusis was reported in each arm. Two events (2.9%) of vertigo took place in the burosumab arm, and one (1.5%) in the placebo group.

3.2.5 BUR02

The design of BUR02 is reported in CS Document B, Section 2.3.2. BUR02 is an open-label extension study evaluating efficacy and safety of participants from European sites in studies CL303 and CL304 providing a further 48 weeks of follow-up. Of 35 participants, 31 came from CL303 and four from CL304. Participants moved to BUR02 as soon as possible after the completion of CL303 or CL304. Interim burosumab treatment was provided during the interval between the studies via an EAP to 24 participants.

The primary efficacy outcome was the serum phosphate concentration at the end of each dose cycle (mean trough serum phosphate), which is more conservative than the CL303 primary outcome (mean serum phosphate levels at mid-point between doses). Secondary outcomes included PROs (WOMAC, BPI-SF, BFI), 6MWT and pain medication use. No targeted X-rays were performed due to the absence of ongoing pseudofractures or fractures. Analytical methods were similar to CL303, with

PROs and functional endpoints evaluated as change form CL303 baseline and with a GEE model adjusting for the same fixed factors, adjusted for CL303 baseline measurements. The impact of treatment interruption to burosumab treatment was explored using the Fisher's exact test to compare the numbers of participants in the two groups with values above the LLN at the start of the open-label extension study. WOMAC scores were the only outcomes from BUR02 that informed the company's economic model. Therefore, the critique below focuses specifically on the WOMAC scores.

Of 35 participants, 25 (71.4%) completed the study. Ten subjects prematurely terminated the study, due to consent withdrawal (n=2) or "other" reasons (n=8, no further details). No withdrawals were due to adverse events.

Participant characteristics of BUR02 (reported in Kamenicky 2023) were broadly comparable with CL303 population, although they had somewhat lower mean BMI (27.7 in BUR02, vs. 30.3 in CL303). Similarly to CL303, BUR02 participants were younger and lighter overall compared with the EAP population, which limits the applicability of the evidence to UK clinical practice.

CS Document B, Figure 20, summarises selected PROs results for participants in CL303 and BUR02. This showed that average improvements from baseline in WOMAC Stiffness, WOMAC Physical Function observed in the open-label phase of CL303 were maintained up to 48 weeks of the extension period. However, the figure does not present results for WOMAC Total score and WOMAC pain outcomes, which were less favourable to burosumab in CL303, and appears to exclude results for the 4 participants included in CL304. In addition, the figure did not present the number of subjects at each follow-up points. Table 14.2.2.6.2 in the BUR02 CSR provided the most complete data on change from baseline in WOMAC scores. This shows that the number of participants with a WOMAC score at each of the scheduled follow-up visits during the BUR02 study were very limited, ranging from 0 to 3 for WOMAC Total score. Therefore, CS Document B, Figure 20 is likely to be significantly affected by missing data and may not be reliable.

Table 9 presents changes from baseline of the BUR02 study to the latest available endpoint, for a total of 31 subjects, WOMAC total scores and all three WOMAC subscales by treatment received at baseline in CL303/CL304 and across all BUR02 participants. This shows that the reductions in average WOMAC scores observed in CL303 were broadly maintained during BUR02, with greater reductions WOMAC Stiffness than WOMAC Physical Function and WOMAC Pain scores. Across all participants evaluated, a MCID threshold was reached only for WOMAC Stiffness. This differs from the results expressed as LSM presented in Document B, Figure 20, which shows that an MCID was reached and maintained for WOMAC physical function and BPI pain interference scores from 36 weeks follow-up. The EAG hopes that this apparent discrepancy can be resolved during technical engagement.

These results have a number of limitations. Numbers of subjects included in BUR02 were small, and there appears to be significant levels of missing data for WOMAC scores. The number of subjects with a clinically meaningful improvement in WOMAC from baseline were not reported, which limits the interpretability of the results. Like with CL303, the lack of blinding in this open-label extension study and uncertainties around the reliability and validity of WOMAC in adult XLH also limits these findings. Overall, the EAG found that the results from BUR02 are at high risk of bias and may not be reliable to inform the company's modelling of the effect of burosumab on stiffness, physical function and pain.

Table 9 WOMAC Total Score change from baseline to end of study or early termination in BUR02 by treatment received from the previous study and overall

		Placebo in double-blind period (CL303) (n=18)	Burosumab in double-blind period for CL303 and CL304 (n=17)	All (n=35)
WOMAC Total score	n evaluated	16	16	30
	Mean (SD)	-12.05 (13.570)	-3.35 (16.045)	-7.99 (15.170)
WOMAC Stiffness Score	n evaluated	17	14	31
	Mean (SD)	-19.85 (23.410)	-8.04 (20.573)	-14.52 (22.615)
WOMAC Physical Function Score	n evaluated	16	14	30
	Mean (SD)	-10.84 (13.015)	-3.57 (15.976)	-7.45 (14.684)
WOMAC Pain Score	n evaluated	17	14	31
	Mean (SD)	-12.94 (15.817)	-0.71 (18.277)	-7.42 (17.789)

Source: BUR02 CSR, Table 14.2.2.6.2

3.2.6 CL001

CL001 was an international natural history cross-sectional online survey. The survey included the WOMAC questionnaire, BPI-SF, and the 36-Item Short Form Health Survey version 2 (SF-36v2) and disease manifestations.

The study included 232 adults with XLH (and 90 parents/caregivers of a child with XLH) identified through an international disease-specific patient advocacy organization. Characteristics of the patients

are given in Table 10. Overall, adults with XLH in CL001 were older than in CL303 (mean [SD] 45.6 [12.9] vs. 40.0 [12.2]) and closer in age to the UK EAP. A higher percentage of the CL001 adult XLH population were female compared with CL303 (76.3% vs. 64.9%). At the time of survey, 64% of the 232 adults were receiving oral phosphate, active vitamin D, or both, and 10% had participated in a clinical trial with burosumab, although none were currently undergoing burosumab treatment. No information on weight and BMI was reported.

Table 10 Characteristics of patients in CL001

	CL001 (adults, n=232)
Age, mean (SD) years	45.6 (12.9)
Female, n (%)	177 (76.3)
Age at symptom onset, mean (SD) years	3.2 (7.2)
Age at diagnosis of XLH, mean (SD) years	9.3 (13.5)
Current use of oral phosphate and active vitamin D, n (%)	110 (47.4)
Current use of oral phosphate, n (%)	114 (49.1)
Current use of vitamin D, n (%)	149 (64.2)
Current use of burosumab, n (%)	0 (0)
Over the counter pain medication	69%
Prescription pain medication	21%

Source: Skrinar 2019 [25]

Table 11 presents WOMAC and BPI scores for CL001 and CL303. Overall, WOMAC and BPI scores in CL001 were moderate, and CL001 adult participants had better self-reported pain, stiffness and physical function than in CL303.

Table 11 Mean WOMAC and BPI-SF scores in CL001 and CL303

	CL001 (n=232)	CL303 (n=134)
WOMAC Pain	39.5	49.3
WOMAC Stiffness	50.3	63.1
WOMAC Physical Functioning	40.8	47.4
BPI Pain Severity	3.7	5.1
BPI Pain Interference	4.2	5.0
BPI Worst Pain	5.1	8.0

WOMAC range 0-100, where 0 represents best health. bBPI-SF range 0-10, where 10 indicates worst pain.

Sources: Skrinar 2019,[25] CS Document B, Table 20

Table 12 summarises morbidities recorded in CL001 and in CL303 at baseline. Overall, compared with CL303, CL001 had a higher percentage of participants with prior orthopaedic and dental surgery, worse percentage of hearing loss and tinnitus, and a worse history of nephrocalcinosis and hyperparathyroidism. CL001 participants also had lower percentage of subjects with osteoarthritis, enthesopathy, and similar percentages of spinal stenosis, excessive cavities and kidney stones. Information on medical history was self-reported rather than based on medical records, and may therefore be subject to recall bias.

Table 12 Morbidities in CL001 and CL303 at baseline

	CL001 (n=232)	CL303 (n=134)
Osteoarthritis	54%	63.4%
Surgery	94%	69%
Fracture history (all types)	44%	NR
Enthesopathy	27%	99.3%
Spinal stenosis	19%	20.1%
Dental abscesses	82%	63.4%
Excesssive cavities	52%	55.2%
Root canal surgery	72%	55.2%
Tinnitus	46%	4.5%
Hearing loss	34%	3.7%
Craniotomy/craniectomy	6%	0.7%
Nephrocalcinosis	21%	11.9%
Kidney stones	14%	13.4%
Hyperparathyroidism	29%	3% (5.2% secondary)

*Spinal stenosis, cord compression and related events

Sources: Skrinar 2019,[25] CL303 CSR[21]

Participants were identified through a patient advocacy network, which may not reflect the larger population of individuals with XLH and include patients with a greater disease burden. The extent to which the CL001 population compares with the EAP and UK clinical practice is uncertain; the EAG requested from the company that they provide further details on the characteristics of subjects included in the UK EAP; the company reiterated that data for whole UK EAP population are not expected to be available within the timeframe of the submission..

3.2.7 EAP

Data on 40 adults who received burosumab at UCLH as part of the UK EAP were analysed. Results are summarised in CS Document B, Section 2.6.6.1.

Results were presented in a conference poster only, and reporting was insufficient to compare the characteristics of this cohort against the CL303 population. The mean age of the cohort was 42.8 years (SD 14.6). Baseline and 12-months measures of EQ-5D-5L, 6-minute walk test (6MWT), and timed up and go (TUG) and serum bone profile were recorded. A subset of 23 subjects had paired whole-body scintigraphy. Opioid medication use was also monitored. Paired parametric or nonparametric descriptive statistics were used.

At 12 months follow-up, there was an improvement from baseline in median 6MWT (median change 38.2m, p=0.048) and 32% of subjects exceeded the MCID of 80 meters. The change in TUG was not statistically significant. Of 20 opioid users at baseline, 9 (45%) had stopped by one year (p=0.008), with no new opioid use at one year. Of 23 subjects with paired scintigraphy, two showed healing of a fracture, three partial healing, and two had suspicious new foci.

A statistically significant improvement from baseline in best health imagined score (EQ5D-5L) was observed, from 55.9 to 63.9 (p=0.03) at one year; the authors did not comment on the clinical significance of this result. Improvements from baseline were reported for the following the following EQ5D domain scores: Mobility (p=0.03), Usual Activities (p=0.01), and Pain (p=0.005); overall, there was no evidence of improvement in Self-care and Anxiety/Depression domains.

To the EAG's knowledge, these are the first available results from the UK EAP. These show encouraging improvements in a number of outcomes, including in motor skills/mobility for a subset of patients, and a substantial reduction in opioid use. However, the paired scintigraphy results (which are more sensitive and specific than x-ray) indicate that fracture healing was limited, and that burosumab did not prevent the occurrence of new fractures at one-year follow-up. The lack of comparator group and lack of blinding means that the results from this cohort are at high risk of bias. Results from this study were limited to 40 out of the [redacted] participants (as of April 2023) who received burosumab in England within the EAP. The EAG requested further results from the company as PFC ; the company replied that data from the whole UK EAP population and are not expected to be available within the timeframe of the submission.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison or multiple treatment comparison were conducted. The EAG considers the absence of an indirect/multiple treatment comparison justified, in view of the evidence presented and the company's placement of burosumab in the clinical pathway.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

3.5 Additional work on clinical effectiveness undertaken by the EAG

In addition to reviewing the evidence on trial CL303 presented in the CS, the EAG also re-analysed data presented in the submitted CSRs for the CL303 and BUR02 trials.
This was intended to address two key concerns of the EAG:

1. Imbalance in outcomes between trials arms at randomisation, and its impact on trial results
2. Incomplete reporting of pain and function outcomes

3.5.1 CL303: Pain and function outcomes

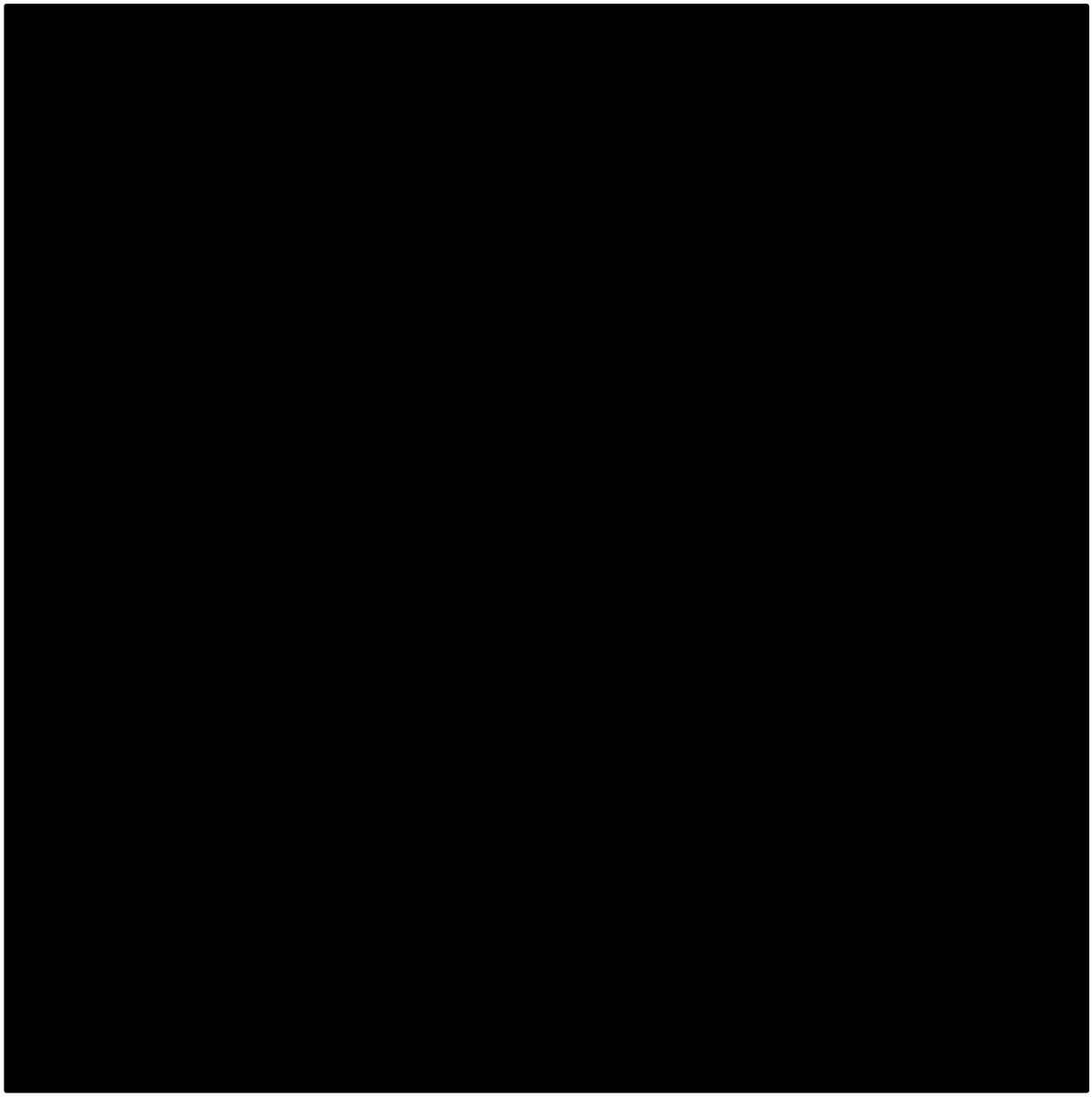
Data were extracted from the CL303 CSR section 10.2 on all pain and physical function outcomes reported. Baseline data, and results at 12- and 24-weeks follow-up were extracted.

We performed standard t-tests to investigate any potential imbalance between trial arms at baseline. The p-values for this analysis are shown in Figure 8. In this analysis

[redacted]

suggesting some uncertainty as to whether these differences occured by chance.

Figure 8 T-tests for baseline imbalance in patient reported outcomes and 6MWT in CL303



A summary of the results for all outcomes is shown in Figure 9, showing mean score in both arms, with the 95% confidence intervals for the mean score. The EAG notes some key characteristics of these data. For some outcomes, and particularly for the pain scales, [redacted]. For example, BPI Worst Pain in the placebo arm [redacted] at randomisation to around [redacted] at 12 or 24 weeks. [redacted]. The differences between placebo and burosumab arms at 24 weeks are generally small. A further concern is that [redacted]. In some cases (such as WOMAC physical function), although scores on the burosumab arm improve over time, [redacted] at 24 weeks.

This suggests that regression to the mean may be a cause of improvements in the burosumab arm for some outcomes.

Figure 9 Summary of all pain and function outcomes extracted from the CL303 CSR

The EAG performed two analyses to compare burosumab and placebo arms: a change from baseline analysis (to compare with the CS) and an analysis comparing the outcomes at 24 months (without correction for values at baseline). In both cases we note that these analyses are based on summary CSR results only, and we could not replicate the fuller analysis presented in the CS and adjust for baseline imbalances without access to the original data set.

The analysis comparing change from baseline in burosumab vs. placebo is shown in Figure 10, with the dots indicating the mean difference between arms, with the 95% confidence intervals for the mean

differences. Most outcomes showed a modest benefit in favour of burosumab. However, most benefits were small compared to placebo (typically [redacted] points on the BPI scale for pain outcomes) and [redacted].

Figure 10 Results of the change-from-baseline analyses of study CL303

By comparison, Figure 11 presents the comparison of burosumab and placebo arms by outcomes at exactly 24 weeks (without accounting for baseline scores). In this analysis difference between burosumab and placebo were notably smaller (typically [redacted] for BFI pain scores) than in the change from baseline analysis, and no outcome showed [redacted] effect.

Figure 11 Results from the EAG analysis at 12 and 24 weeks in study CL303

In a perfectly randomised trial there should be little difference between a change-from-baseline analysis and an end-of-trial analysis. Hence the fact that the two analyses in Figure 10 and Figure 11 give different results raises concerns as to the robustness of the trial analysis. The difference may be at least partly caused by the imbalance in the arms at baseline.

Regression to the mean could be present. This occurs when people have unusually extreme outcomes at randomisation, and such patients will generally regress to a more typical level without treatment. For example, in Figure 9 for physical function placebo arm patients have a mean score of 40 to 45 at all times. In the burosumab arm the mean score declines from 50.8 at randomisation to 43.3 at 24 weeks. If scores between 40 and 45 are typical for untreated patients this reduction could be due to regression to the mean, rather than a benefit of burosumab.

3.5.2 CL303: Fractures

We also examined data on fractures and pseudofractures reported in the CSR for trial CL303. We calculated the odds ratios for complete healing, partial or complete healing and incidence of new fractures for burosumab against placebo at 24 weeks, using logistic regression. The results are shown in Figure 12. There was [redacted]that burosumab increased the chances of partial and complete healing of pseudofractures (Complete healing: OR [redacted]), but see discussion in Section 3.2.4.1. Burosumab probably improves healing of fractures, although [redacted]There was, however, no evidence that burosumab prevented new fractures. The EAG notes that this contradicts assumptions made by the company in its economic model.

Figure 12 Odds ratios for incidence of fracture and pseudofracture at 24 weeks follow-up in study CL303

[redacted]

3.6 Conclusions of the clinical effectiveness section

3.6.1 Decision problem

The EAG has some concerns with the definition of the decision problem and how the company has specified the population in which burosumab could be used.

The NICE scope set the population as any adult with X-linked hypophosphataemia. The company proposed restricting this to people with symptoms, specifically those with at least moderate pain (BPI ≥ 4). Based on clinical advice, the EAG agrees that burosumab is only likely to be used in patients with symptoms that cannot be controlled with regular pain relief medication. However, the EAG notes that the current EAP scheme for burosumab in the UK permits patients with a wider range of symptoms to join. We consider that the EAP inclusion criteria represent a more plausible scheme for prescribing burosumab in the UK.

The company also proposes excluding patients receiving phosphate from eligibility, and restricting consideration to patients unsuited to phosphate therapy, or to patients unable to tolerate it or where it was ineffective. Consequently, the company's preferred comparator was best supportive care, rather than vitamin D analogues and phosphate supplementation. The EAG agrees, based on clinical advice, that burosumab is most appropriate for people who cannot be treated with phosphate supplementation. However, we note that both the CL303 trial and the EAP scheme include patients who had been receiving phosphate and who stopped treatment (for any reason) to receive burosumab. There is therefore some uncertainty as to whether such patients would receive burosumab, and also uncertainty in the efficacy of burosumab in people who are genuinely unable to receive phosphate supplementation.

3.6.2 Trial evidence

The EAG had a number of concerns with the data from the key CL303 trial.

CL303 participants were younger and lighter than the population of adults who are currently eligible for burosumab under the EAP. This limits the applicability of the trial evidence to UK clinical practice.

A number of differences between arms at randomisation were noted: the burosumab arm was older, and had worse stiffness, pain score and physical functioning overall, as well as a lower number of pseudofractures compared with placebo. A higher percentage of opioid use was reported in the burosumab arm at baseline. Although tests for baseline differences only found a statistically significant imbalance for the WOMAC physical functioning score, these tests did not estimate the potential cumulative effect of these differences, and the trial analyses did not adjust for these

variables. The direction and magnitude of bias associated with the lack of adjustment for baseline imbalances is uncertain. Potential regression to the mean effects were observed, and patient reported outcomes during the open-label follow-up period are at high risk of bias due to lack of blinding.

CL303 found a significant improvement in serum phosphate normalisation in burosumab treated patients. Although the trial found an improvement in P1NP and CTx concentration compared with placebo at 24 weeks, indicating improved bone formation and bone resorption, bone disease markers (BALP) were not significantly different to placebo.

CL303 showed promising evidence that fracture and pseudofracture healing were significantly improved in burosumab treated patients compared with placebo at 24 weeks. However, comparisons are limited by the low numbers of active fractures at baseline as well as a significantly larger percentage of pseudofractures in the placebo arm. Similar numbers of new fractures/pseudofractures were recorded in the burosumab and placebo arms; although this finding is uncertain as this outcome was not pre-specified and does not appear to have been measured systematically, this indicates that normalisation of the bone was not achieved by the end of the 24 weeks follow-up period despite burosumab treatment. This is consistent with data from trial CL304, which indicated that bone mineralisation was not normalised after 48 weeks of treatment with burosumab.

Data from the EAP showed a significantly lower rate of fracture healing with burosumab at 52 weeks follow-up compared with CL303; although this data is preliminary and limited to a single-centre, it used a more sensitive method to measure fracture healing and was conducted in a population that is potentially more reflective of UK clinical practice. Further data from the broader UK EAP cohort would help to clarify whether the CL303 results may be replicated in UK clinical practice.

There was little evidence that subjects treated with burosumab had statistically significant improvements in physical functioning compared with placebo at 24 weeks and there was little evidence that burosumab was more effective than placebo at reducing pain and fatigue; none of the improvements observed in the burosumab arm during the double-blind period were large enough to exceed the minimally important clinical difference thresholds. At 24 weeks follow-up, there was a statistically significant difference in improvement in WOMAC Stiffness measurements favouring burosumab compared with placebo, although this result had limited clinical significance, and the validity and reliability of the WOMAC Stiffness sub-scale is uncertain in adults with XLH. Evidence from CL303 indicated that burosumab was safe and well tolerated.

Overall, due to the trial design, there was no clear evidence for relative efficacy and safety of burosumab compared with placebo beyond 24 weeks follow-up. Patient-reported outcome results for subjects receiving burosumab after the 24 weeks blinded period are at high risk of bias due to the lack

of blinding. The attrition rates observed after 96 weeks mean that results beyond this point may not be reliable.

3.6.3 CSR analysis

Analysis of the clinical study report data for the CL303 trial of burosumab by the EAG raised some concerns as to the quality of evidence in favour of burosumab. It further highlighted concerns with imbalances in the trial at randomisation, with patient-reported outcomes being worse in the burosumab arm, although this was only statistically significant for WOMAC physical functioning. The EAG is concerned that regression to the mean could therefore be leading to over-interpretation of any effects in burosumab patients. Our analysis also identified substantial placebo effects, particularly for pain outcomes, which may likewise mean effects of burosumab may be over-interpreted.

The EAG analysis of outcomes at 24 weeks (without correcting for change from baseline, to avoid regression to the mean effects) found that differences between burosumab and placebo for all pain and function outcomes did not achieve a statistically significant difference.

The EAG found evidence that burosumab was more effective than placebo at healing pseudofractures, and possibly fractures generally, at 24 weeks. Due to limited data, there was no evidence that burosumab prevented new fractures and pseudofractures.

3.6.4 Summary

The EAG identified the following key issues with the evidence submitted:

1. The NICE scope and company scope differ on who might receive burosumab. The EAG notes that burosumab is likely to be used only for people with symptomatic XLH where symptoms cannot be reasonably controlled by other medication. However, exactly what symptoms will be considered sufficiently severe to merit burosumab use is uncertain.
2. The company propose restricting burosumab to patients unable to receive phosphate supplementation, so the comparator is best supportive care only. The EAG agrees that burosumab may be best suited to patients who cannot tolerate phosphate, or for whom it has been ineffective. However, this conflicts with the current entry criteria for the burosumab EAP, and exactly what level of efficacy or adverse effects would constitute a lack of effect or intolerance of phosphate supplementation is uncertain.
3. The EAG has concerns with the conduct of the CL303 trial. There were differences in patient populations between burosumab and placebo arms at randomisation, particularly for patient age, although this was not statistically significant. Pain and function outcomes were consistently higher in the burosumab arm at randomisation, leading to concerns that regression to the mean could be influencing interpretation of the effect of burosumab.

4. When accounting for potential placebo effects and regression to the mean, the EAG found no clear evidence that burosumab was more effective than placebo for any pain, fatigue or physical function outcome. Differences appeared not to be clinically meaningful and were not statistically significant. This raises concerns as to how to interpret results in the non-randomised longer-term follow-up data.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company's review did not identify any studies for the cost-effectiveness of burosumab in adults with XLH. Details of the company's search strategy are reported in Appendix D1.1 and study selection and results reported in Appendix G.

Points for critique

The company's review of cost-effectiveness evidence used the same database searches as for the clinical evidence (see Appendix D1.1). Economic evaluation databases such as NHS EED were included. According to the company's PRISMA diagram on Figure 1, Appendix D, the company did not identify any studies from EconLit and NHS EED.

The company's approach to the identification of previous cost-effectiveness evidence is poorly reported and the EAG considers that all relevant publications have not been identified. The EAG notes, in particular, that the cost-effectiveness studies of burosumab in adults with XLH included in the Canadian Drug and Health Technology Agency (CADTH) Common Drug Review Report [36], the Scottish Medicine Consortium (SMC) Assessment Report [37], and the Australian Pharmaceutical Benefits Scheme (PBAC) report [38] were not identified in the literature review, or reported in the CS. The EAG requested clarification for the omission of these reports; the company response states that the grey literature search did not extend to HTA reports, which the EAG considers to be an important omission in the company's pre-specified systematic literature review methodology.

Within the timelines of the EAR, the EAG is unable to conduct a comprehensive literature review to identify previous cost-effectiveness studies of burosumab in adults with XLH; however, through targeted literature searching, the EAG have identified the cost-effectiveness studies for CADTH, SMC and PBAC. These differ from the company's cost-effectiveness analysis in the following key elements:

- The comparator in each of the cost-effectiveness studies include conventional therapy or no treatment;
- The CADTH model incorporates a structural link between morbidity events and mortality;
- Increased mortality risk associated with fractures is only after the age of 50 years in the CADTH model;
- The Global XLH natural history study (CL001) is used to inform the incidence of morbidity events in the SMC model;
- A lower annual discontinuation rate for burosumab is included in the CADTH and PBAC models, including no discontinuation from year 1 onwards in the CADTH model;

- Utility values are captured as changes in WOMAC scores from baseline, mapped to EQ-5D using data from CL303 up to week 96 only, i.e., excluding data from BUR02.
- A utility benefit for caregivers and family members does not appear to be included in the CADTH and PBAC models.

The appropriateness and implications of these differences between previous cost-effectiveness studies and the CS are discussed in the relevant sections below.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a model to compare the cost-effectiveness of burosumab for the treatment of adults (≥18 years of age) with a diagnosis of XLH compared to best supportive care (referred to as standard of care, SoC). A state transition cohort model with annual cycles is used to track patients' treatment status (i.e., whether receiving burosumab or SoC) and survival over time. In order to account for the distribution of ages at which patients may start treatment, the model is run discretely for a range of starting ages. The age-specific results are aggregated according to the proportion of the adult population with XLH in each age category to obtain estimates of total population costs and health effects.

The impact of burosumab treatment is captured in four ways:

- Increasing the probability of serum phosphate normalisation for burosumab compared to SoC and, thereby, reducing the incidence of fractures in the base case analysis (and other morbidities of dental problems, spinal stenosis and hearing loss in a scenario analysis) and consequent disutility associated with the morbidities and resource use and costs associated with management of morbidities.
- A reduction of 50% in excess mortality due to XLH for burosumab compared to SoC.
- Improvement in health-related quality of life for burosumab compared to SoC through a reduction in fatigue, pain, stiffness and improvement in physical functioning as captured by changes in WOMAC scores from baseline, mapped to EQ-5D utility values.
- Improvement in health-related quality of life of caregivers and family members that is equivalent to 20% of the patient utility benefit of burosumab and applied to two family members.

Burosumab increases NHS costs due to its acquisition and administration cost, with some of this cost offset by lower costs associated with morbidity management.

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 13.

Table 13 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate. Health effects on carers is included in the company's base case analysis.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon is lifetime (up to age 100 years).
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate. The systematic review identified one pivotal clinical trial (CL303) and follow-up study (BUR02) for burosumab in the adult XLH population, which is used in the base case analysis.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life (HRQoL) in adults.	The CS is appropriate. HROoL was based on a reduction in fatigue, pain, stiffness and improvement in physical functioning as captured by changes from baseline in WOMAC scores and mapped to EQ-5D using a published utility mapping algorithm and valued using the UK tariff. The mapping algorithm by Wailoo et al. (2014) was used in the base case analysis.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate. WOMAC outcomes from CL303 were combined with WOMAC outcomes from the phase 3b open-label extension study, BUR02. However, post-week 96 data were based on subgroups of patients from these studies.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.

Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The model is a state transition cohort model (see Figure 13 for a schematic of the model and Figure 14 for the structure of the model), which tracks patients on burosumab as they move through the states of (i) Alive, on treatment; (ii) Alive, off treatment; and (iii) Dead. All patients start in the 'Alive, on treatment' state and transition to the 'Alive, off treatment' state based on initial response to treatment, an annual discontinuation rate, and risk of mortality. Patients are assessed for response to treatment according to the proposed stopping criteria for treatment, where only patients achieving a clinically relevant benefit from burosumab remain on long-term treatment. The continuation of treatment is based on a requirement of reaching serum phosphate levels above the lower limit of normal range (LLN) after 24 weeks of treatment and an improvement in WOMAC total score at 12 months after starting treatment (see Section 4.2.6.1). An annual discontinuation rate is also incorporated for burosumab treatment. The 'Alive, off treatment' state represents all patients who are not on burosumab treatment conditional on being alive and is the starting state for patients on SoC.

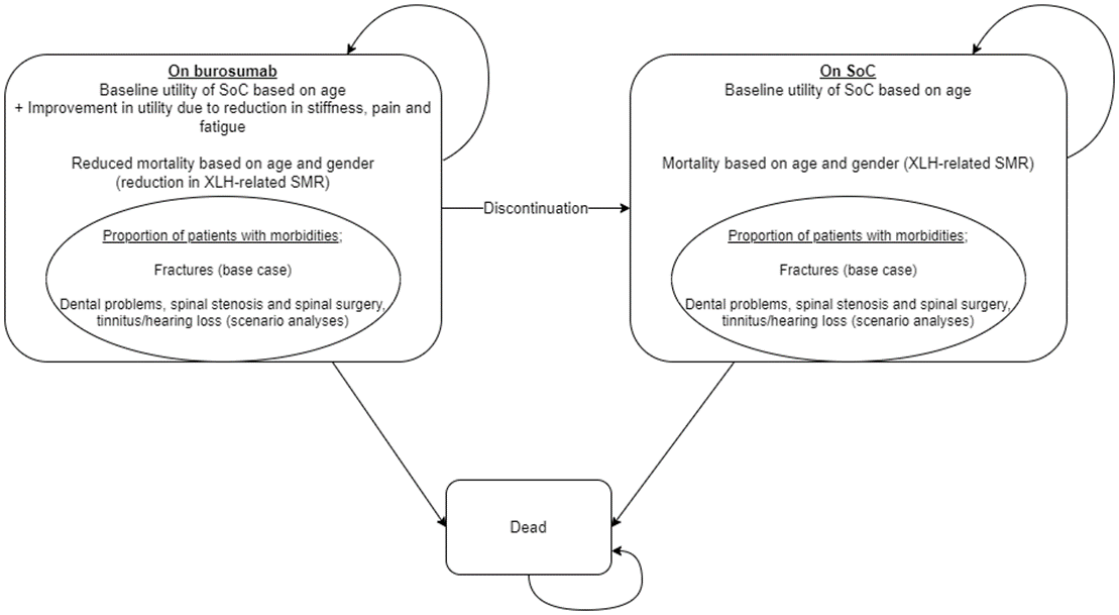
The probabilities of patients experiencing incident morbidities is estimated as a function of age and treatment status. For patients on burosumab treatment, the probability of experiencing a morbidity incident is reduced whilst on treatment. The base case model includes morbidities where treatment with burosumab is likely to reduce the incidence of future events or lead to the resolution of the events. Fractures including upper limb, vertebrae/spinal, foot, tibia/fibula, femur/pelvis, and other fractures are included in the base case, where reduction in the incidence of future events is captured directly through the use of lower fracture rates for burosumab-treated patients, while resolution of existing fractures is captured through quality of life improvements observed in WOMAC from CL303 and BUR02. Other morbidities of dental abscesses, spinal stenosis (and subsequent surgical treatment), and tinnitus/hearing loss are included in a sensitivity analysis. Once a patient experiences a morbidity event, they are assumed to accrue utility decrements associated with the morbidity in each model cycle. Multiple morbidities can occur for each patient in each cycle.

An excess mortality risk due to XLH is estimated by applying a hazard ratio to the age- and sex-specific general population hazard of death based on general population life tables for England. This

is used to represent the survival for patients on SoC over a lifetime horizon (up to age 100). A reduction in this excess mortality risk is assumed for burosumab treatment (see Section 4.2.6.3).

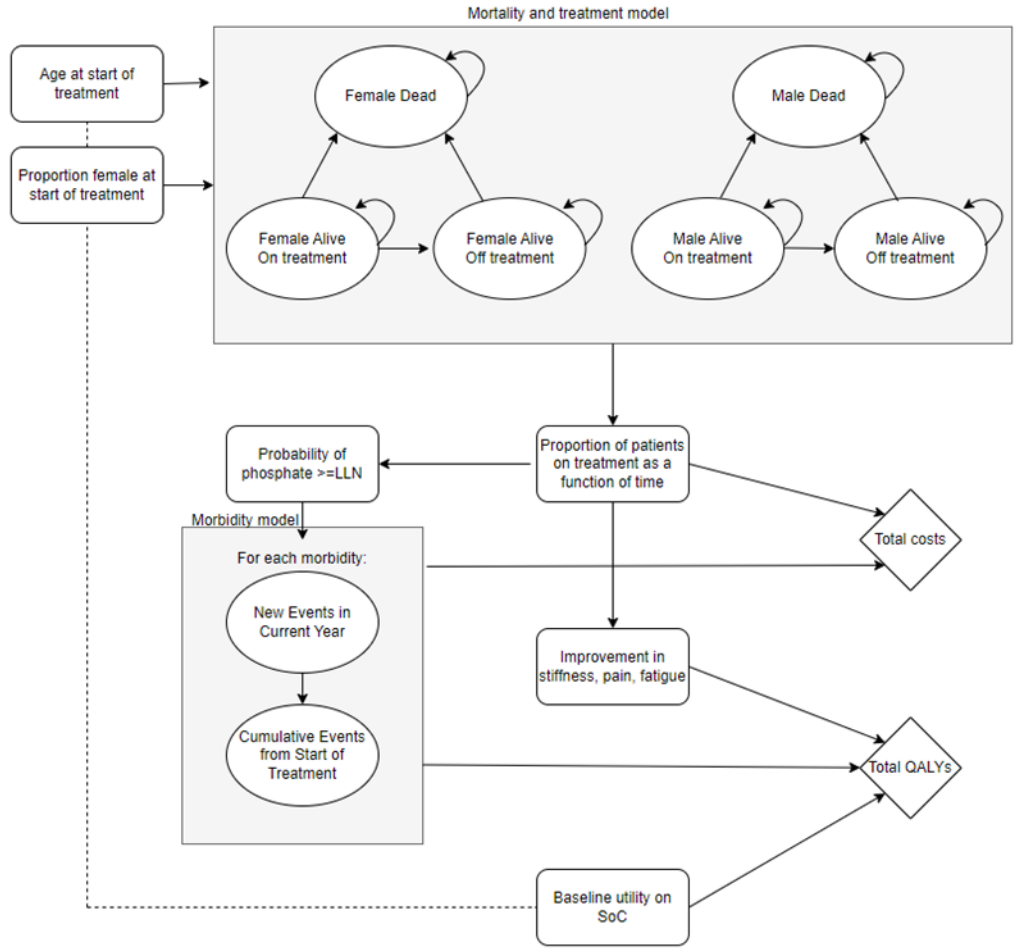
The cycle length used in the model is one year and a half-cycle correction is implemented.

Figure 13 Cost-effectiveness model schematic (reproduced from CS Figure 27, page 116)



Abbreviations: SoC: standard of care; SMR: standardised mortality rate.

Figure 14 Cost-effectiveness model structure (reproduced from CS Figure 28, page 117)



Abbreviations: SoC: standard of care; LLN: lower limit of normal range.

Points for critique

The EAG considers the model structure to be broadly representative of XLH disease characteristics in adults, where treatment with burosumab is expected to improve serum phosphate levels and bone mineralisation and lead to modifiable aspects of impaired skeletal health and provide health-related quality of life improvements through improved physical functioning and reduction in pain and stiffness. However, the impact of treatment on mortality is not known. There are a number of intersectional factors that contribute to an increased risk of mortality in adults with XLH compared to the general population (see Table 4, p29 of CS) but the potential effects of burosumab treatment on this excess mortality is not known. The company assumes that by addressing the root cause of XLH (i.e. normalising phosphate homeostasis) and mitigating the ongoing, multi-system effects of hypophosphataemia that may drive increased mortality, treatment with burosumab will extend life expectancy.

The model structure for overall survival based on an excess mortality hazard due to XLH is independent of the models used to predict the incidence of individual morbidities, which are nested within overall survival. This approach differs from that used in the CADTH model, where a structural link was implemented between the morbidity events and mortality. In the CADTH model patients move between the health states of 'Alive with fractures' and 'Alive without fractures', based on the probability of developing a fracture and the probability of healed fracture, respectively, over time. Only patients in the alive with fractures state were assumed to have an increased mortality risk and only after the age of 50 years, while general population mortality risk was considered for the alive without fractures state. This means that the survival benefit of burosumab treatment in the CADTH model is driven by reducing the risk of incident fractures and increasing the likelihood of healed fractures rather than modelling mortality as an independent process. The EAG considers that both approaches (either modelling a structural link between morbidity and mortality or modelling morbidity and mortality as independent processes) are appropriate but subject to structural uncertainty because of the lack of evidence of mortality benefit from burosumab. The EAG notes that while it may be argued that any estimate of fracture-associated mortality will not account for potential confounders that are causal to both fractures and mortality, or the potential multi-system effects (other than fractures) of hypophosphataemia that may drive increased mortality in this population, the advantage of an explicit structural link between fractures and mortality is that it allows external evidence to be considered on how treatments for fractures impact on mortality. Without any evidence about the effects of burosumab on mortality, there is complete uncertainty about the magnitude of the mortality benefit (see Section 4.2.6.3).

item 1. The structural assumption associated with modelling the incidence of morbidities and mortality as independent events is uncertain.

4.2.2.2 Survival model

The survival model for patients on SoC over a lifetime is based on an excess mortality risk due to XLH compared to the general population hazard of death, and provides the proportion of the XLH population that is female by age based on the starting proportion at age 18 years (65% from CL303). The excess mortality is derived by applying a hazard ratio (HR) from Hawley et al. (2020) [2] to the age- and sex-specific general population hazard of death from life tables for England [2]. The HR from Hawley et al. is based on mortality data of individuals with XLH from the UK Clinical Practice Research Datalink (CPRD) database from 1995 to 2016, with linkage to the Office for National Statistics (ONS) dataset where available. The authors developed an algorithm to grade subjects according to likelihood of having XLH: highly likely, likely, possible, unlikely, or unable to determine. Of the 522 cases initially identified, 122 were used in the analyses: 27 highly likely, 37 likely and 58 possible cases of XLH. Up to four non-XLH controls of same age, gender and GP

practice were matched to each potential XLH case. The HR for overall survival between the likely or highly likely XLH population and the matched cohort was 6.65 (95% CI, 1.44 to 30.72), while the corresponding HR between all at least "possible" XLH patients and the matched cohort was 2.93 (95% CI, 1.24 to 6.91), by censoring patients at time of transfer from their index GP practice. The study also included an analysis in which follow-up was extended until the end of study period (without censoring), which resulted in a HR of 2.88 (95% CI, 1.18 to 7.00) between the likely or highly likely XLH population and the matched cohort. In the CS, the HR of 2.88 was applied to the general population hazard of death from lifetables to inform the survival of patients on SoC for the base case analysis.

The company conducted a confirmatory study based on extending Hawley et al. by applying the same XLH grading algorithm to patients from both the CPRD GOLD and the larger database of CPRD AURUM, linked to secondary care Hospital Episode Statistics (HES) and ONS mortality data and Index of Multiple Deprivation (IMD) data (see Appendix R of CS). Of the 782 cases identified (and eligible for data linkage), 79 were graded as highly likely and likely XLH. Ten non-XLH controls of the same age, gender, IMD and ethnicity were matched to each XLH case. The resulting HR for overall survival between the likely or highly likely XLH population and the matched cohort was 2.33 (95% CI, 1.16 to 4.67), which is approximately a 30% lower risk than the HR of 2.88 (95% CI, 1.18 to 7.00) from Hawley et al.

The impact of burosumab treatment is included as a reduction in the excess mortality risk due to XLH (see Section 4.2.6.3)

Points for critique

Given the lack of published evidence on causes of death or mechanisms that lead to increased mortality in adults with XLH, the EAG considers the source of UK data used to derive the observed excess mortality risk to be appropriate. However, a number of notable limitations were reported in Hawley et al: (i) the potential for misclassification due to the lack of a validated algorithm for grading subjects according to likelihood of XLH; (ii) the lack of agreed UK guidelines for the routine care and management of adults with XLH; and (iii) the potential for relatively severe cases of XLH being favoured for inclusion in their analyses due to incorporating frequency of laboratory testing and treatment with activated vitamin D and phosphate supplements into the case identification process. Despite these limitations, a post-hoc sensitivity analysis using all 522 cases initially identified with their controls produced a HR of 2.87 (95% CI, 2.08 to 3.95), which was consistent with the HR of 2.88 (95% CI, 1.18 to 7.00) for the likely or highly likely XLH population.

The EAG notes that the model uses the HR of 2.88 (95% CI, 1.18 to 7.00) from Hawley et al. for its base case analysis. The EAG is not clear why the company did not use the corresponding HR of 2.33

(95% CI, 1.16 to 4.67) from its confirmatory study based on extending Hawley et al. The company states that their study represents a larger, more robust validation of the findings by Hawley et al. due to over 91% of XLH patients being identified from the larger CPRD AURUM database, while also capturing more death events with greater precision, and using a greater number of non-XLH controls matched to XLH cases (see Appendix R of CS). Therefore, the EAG considers it more appropriate to use the observed excess mortality risk from the company's study, which appears to have been conducted using the same methods and subject to the same limitations as Hawley et al., but includes a larger database and more recent data, with data from CPRD GOLD available from 1995 to June 2022 and CPRD AURUM from 1995 to January 2022.

item 2. The larger sample of data from the CPRD GOLD and AURUM databases provides greater precision to inform the mortality for individuals with XLH.

4.2.2.3 Modelling of morbidities

The model includes morbidities where treatment with burosumab is expected to reduce the incidence of future events or lead to the resolution of the events. The selection of morbidities was based on criteria outlined on page 115 of the CS and validated with three clinical experts with experience of treating adults with XLH in the UK. Fractures of the upper limb, vertebrae/spinal, foot, tibia/fibula, femur/pelvis, and other fractures are included in the base case analysis, while other morbidities are included in a sensitivity analysis.

The annual fracture rates in adults with XLH receiving SoC is based on CL303 data from complete bone scan radiographs, which were taken at trial baseline to detect multiple active fractures in the same bone. The observed total number of fractures at each site location for all patients was used to derive the mean crude annual fracture rate (total number of fractures divided by age) by fracture site (Figure 31, p125 of CS). All fracture events (active fractures only) were modelled as repeat events and assuming a constant rate over time using a negative binomial model, except for upper limb fractures where a Poisson model was used. The predicted annual fracture rate by site is reported in Table 34 of the CS: 0.001 (i.e., equivalent to 10 per 10,000 person years) for upper limb fractures, 0.002 (20 per 10,000 person years) for vertebrae/spinal fractures, 0.01 (100 per 10,000 person years) for foot fracture, 0.04 (400 per 10,000 person years) for tibia/fibula fracture, 0.01 (100 per 10,000 person years) for femur/pelvis fracture, and 0.001 (10 per 10,000 person years) for other fractures.

For burosumab-treated patients, a reduction in the incidence of future events is captured through the use of lower fracture rates compared to those for SoC (see Section 4.2.6.2), while resolution of existing fractures is captured through quality of life improvements observed in WOMAC from CL303 and BUR02 (see Section 4.2.8.3). Mortality associated with fracture-related events is not directly

linked in the model because overall survival in the model implicitly captures deaths associated with fracture events (and other morbidities).

Points for critique

The EAG's clinical advisor considered the selection of morbidities to be broadly appropriate, with fracture risk considered to be most relevant because poor bone mineralisation caused by hypophosphataemia increases the risk of fractures associated with osteomalacia (pseudofractures). The EAG also notes that the European Public Assessment Report (EPAR) for burosumab focuses on the modifiable aspects of the adult disease associated with improvements in serum phosphorus levels and bone mineralisation, which is the skeletal disease and osteomalacia that gives rise to increased risk of fractures and pseudofractures, while other morbidities such as dental problems and hearing loss are not considered modifiable aspects of the disease.

The EAG is unable to validate the data underpinning the models used to estimate the predicted annual fracture rates for SoC because the data are not presented in the CS. Fractures were modelled as repeat events and the choice of model was based on best fit informed by Akaike information criterion (AIC) statistics. The EAG notes that age is not included in the models as a covariate; therefore, the fracture rates for SoC are assumed to remain constant over time. The EAG considers the company's approach to be appropriate and the assumption that fractures associated with osteomalacia are age-independent to be reasonable.

The EAG notes that the company did not present baseline data on fractures from the Global XLH natural history study (CL001), which appears to have been used to predict the incidence of morbidities, including fractures, in the burosumab submission to the SMC, whilst also been used in the CS to inform the incidence of other morbidities in the sensitivity analysis. The EAG considers CL001 to be a relevant source of alternative data to inform the annual incidence rate of fractures because it reflects a larger sample reporting on the epidemiology of XLH, particularly in terms of incidence, prevalence, risk factors, co-morbidity, treatment modalities and mortality.

4.2.3 Population

The patient population in the model is adults (aged ≥18 years) with a confirmed diagnosis of XLH who have chronic hypophosphataemia, symptoms that include a Brief Pain Inventory (BPI) score of ⩾4, and for whom conventional therapy is unsuitable due to ineligibility, intolerance or insufficient efficacy (i.e. failure to normalise phosphate levels, or persistence of symptoms despite treatment). This population aligns with the CL303 population where participants were required to have a worst pain score over the last 7 days of ≥4 on the BPI to be eligible for the trial and most patients (90.3%) had received prior therapy with both oral phosphate and active vitamin D metabolites or analogues, while the remainder had been treated with one of the two conventional therapies. The proposed

population is a subgroup of the licensed indication in adults, which is for the full population of adults with XLH (see Section 1.1 of CS for the rationale for deviating from the final NICE scope).

The baseline characteristics are based on the patient population of CL303, which is used to inform the distribution of starting ages in the model (Table 24, p112 of CS), the proportion of female patients at age 18 years (65%), and the proportion of population by weight band for burosumab dosing (Table 46, p149 of CS). The weight distribution is based only on EU patients from CL303 because the company noted that there were substantial weight differences between patients in different regions of the trial, while the age distribution and proportion of females is based on the full population from CL303. Baseline utility values are also based on data from CL303 (full population).

No separate subgroup populations are considered in the company's base case analysis.

Points for critique

The EAG has three key concerns in relation to the population considered in the CS. The first concern relates to the precise definition of the population that is likely to receive treatment in UK clinical practice. The company has positioned burosumab as a last line therapy in a subpopulation of adults for whom there are no alternative treatment options available, i.e., in those for whom conventional therapy is unsuitable due to ineligibility, intolerance or insufficient efficacy. As a consequence, the company assumes that the comparator of SoC does not include conventional therapy (only symptomatic treatment of morbidities). The EAG considers there to be two separate groups of patients in relation to use of conventional therapies: (i) those who are ineligible or intolerant to conventional therapy; and (ii) those for whom conventional therapy is showing insufficient efficacy. In the latter group, the EAG considers it more appropriate to reflect the fact that some patients may discontinue conventional therapy for a period of time due to insufficient efficacy, but are more likely to restart conventional therapy at a later point in time as symptoms persist. Therefore, in the absence of burosumab treatment (and no other treatment options available), there is likely to be a proportion of adults who will continue to take conventional therapy intermittently over time. This means that there is uncertainty regarding the size of the eligible adult population who may receive burosumab in the NHS and the precise definition of treatment failure with conventional therapy for burosumab to be considered as an alternative treatment option.

The second key concern relates to how treatment decisions will be made for the subgroup of adult patients who have previously experienced burosumab treatment in a paediatric setting. Since NICE has recommended burosumab for treating XLH with radiographic evidence of bone disease in children aged 1 year and over, and in young people with growing bones, there will be a subgroup of patients who are transitioning over from the paediatric to the adult population at age 18, who are either currently receiving burosumab treatment, or have previously received it as a child or

adolescent. For this subgroup of patients there is uncertainty regarding which criteria will be used to determine appropriate treatment based on having previously experienced burosumab, as well as an equity consideration in relation to access to burosumab when a patient reaches age 18 who is currently receiving treatment. The CS does not discuss the generalisability of the cost-effectiveness data or trial evidence to a burosumab-experienced population. In response to EAG points for clarification, the company indicates that the protocol for CL303 permitted prior use of burosumab and 7 patients had been exposed to burosumab previously as adults in an earlier clinical study; however, no data or outcomes specific to this subgroup of patients with prior exposure to burosumab are presented, nor is any data available in a subpopulation who previously received burosumab as a child. The company states that at age 18 years, the patient converts to the adult dose and dosing regimen, as per the marketing authorisation in adults, which results in a lower total dose on average for adults than for children between age 1-17 years; however, the effect on outcomes remains unclear and the implications of a negative recommendation in adults for adolescents receiving burosumab and transitioning to adults at age 18 is not explored.

> ***item 3. There is uncertainty regarding how treatment decisions will be made for the subgroup of adult patients who have previously experienced burosumab treatment (specifically, children receiving burosumab as they transition to adults at age 18 and patients who recommence burosumab as adults following treatment as a child) and the generalisable of the cost-effectiveness evidence to a burosumab-experienced population.***

The third concern relates to how well the patient population of CL303 aligns with the adult population with XLH in UK clinical practice, in terms of baseline population characteristics and baseline utility values used in the model. The EAG considers participants receiving burosumab in the Early Access Programme (EAP) in England to be more representative of the modelled population than the CL303 trial population, which includes [redacted] as of April 2023. Data from participants enrolled in the EAP were not reported in the CS; however, the model provides the age and weight distributions for the EAP population (see Figure 15 and Figure 16 for a comparison of the age and weight distributions, respectively, of the EAP population with the CL303 population). The population of CL303 is younger than EAP, with 76% of trial participants below the age of 50 years compared to 58% of EAP participants, due to a maximum age restriction of 65 years in the trial's inclusion criteria. The weight distribution of EU participants from CL303 (used in the company's base case analysis) is lighter in weight than EAP, with only 28% of trial participants weighing above 75kg compared to 40% of EAP participants. The use of baseline characteristics of the EAP population to represent UK clinical practice was also supported by one of the company's clinical experts, who indicated that the trial population was fitter and had a lighter weight distribution than EAP and, therefore, less representative of patients seen in UK clinical practice (see Appendix Q of CS). The

proportion of female participants from EAP is not reported in the model; however, the EAG notes that the percentage of females graded as likely or highly likely XLH in the UK CPRD data from Hawley et al., is 70%, which is consistent with the value used in the model of 65% at age 18 years from CL303.

The EAG notes that the age and weight distribution for the adult population is likely to change over time with the availability of burosumab. Over the long-term, it may be expected that there is a larger subgroup of XLH adult patients who have previously received burosumab in the paediatric setting and for whom the identification of XLH and management of treatments may be considered more straightforward than for a burosumab-naïve population. Therefore, over time the identification of patients eligible for burosumab as an adult may become easier and the future profile of patients in terms of baseline population characteristics may change.

> ***item 4. Baseline population characteristics of age and weight, and baseline EQ-5D utility values by age, based on the CL303 trial may not match those seen in UK clinical practice and may change over time with more a burosumab-experienced population. The EAG considers the age and weight distribution of EAP participants to be more representative of patients expected to receive burosumab in NHS practice.***

Figure 15 Age distribution of participants in EAP and CL303

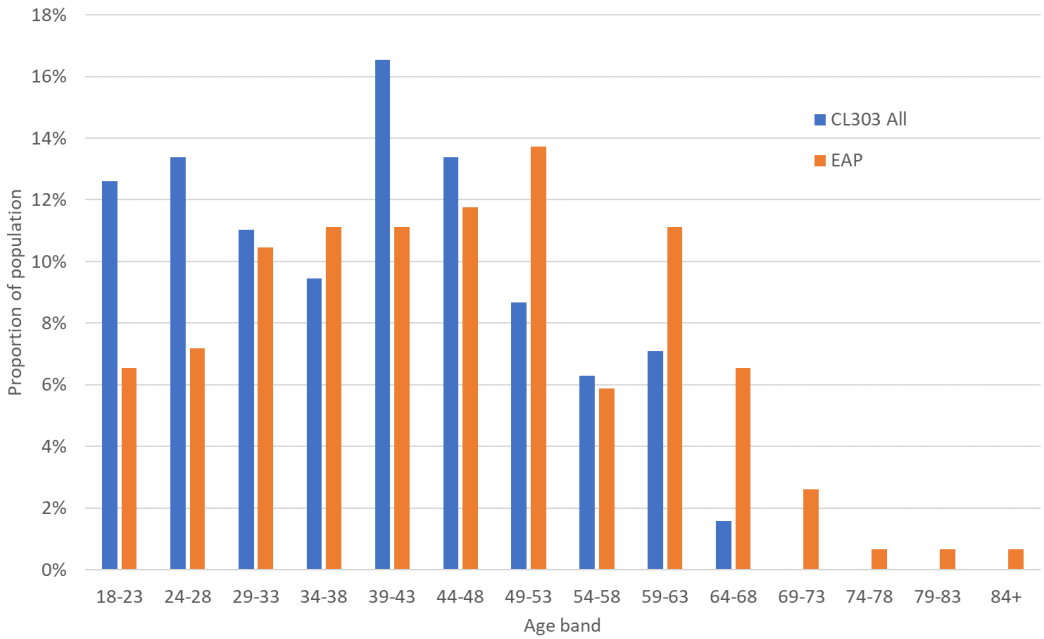
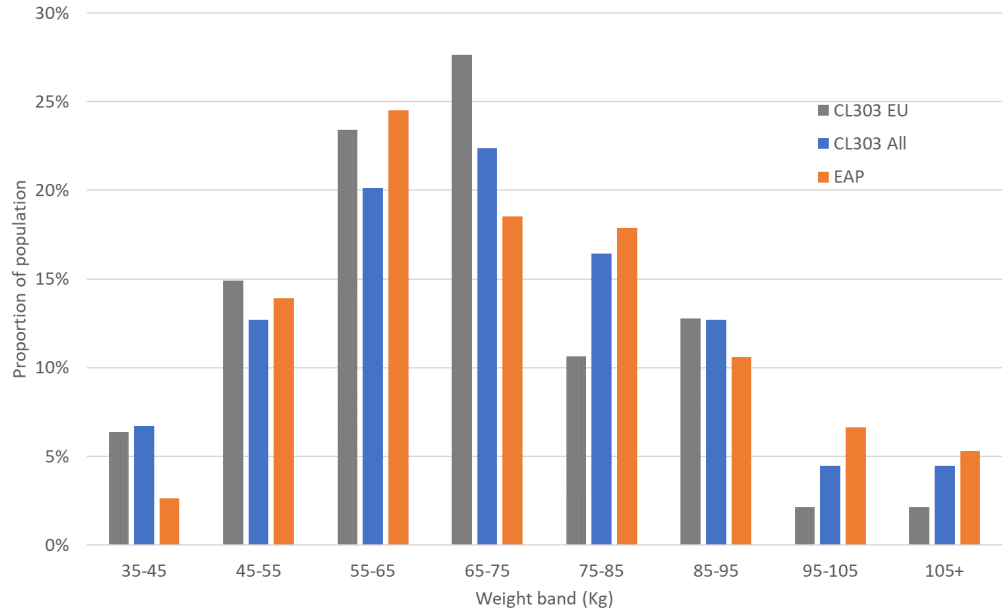


Figure 16 Weight distribution of participants in EAP, CL303 EU and CL303 All



The EAG considers the general approach used by the company to generate age-specific cost-effectiveness results that are aggregated according to the proportion of the population with XLH in each age category to be appropriate for capturing heterogeneity in the XLH adult population (instead of using an average patient age in the model). However, the distribution of starting ages and weights used in the model (and % females) should reflect not only the distributions of the XLH adult population in the UK but also the age, sex and weight distributions used to inform other parameters in the model; for example, the EAG notes that the HR from Hawley et al. used to derive the excess mortality due to XLH is not based on the same age and sex distribution of CL303 participants. The EAG also notes that the submitted cost-effectiveness model is not sufficiently flexible to allow patient weight (used to inform burosumab dosing) to vary over time within each discrete age band at which patients start treatment, i.e., as patients age in the model, their weight is not permitted to change over time as they leave the age band at which they started treatment. In response to EAG points for clarification, the company undertook an analysis assessing the impact of age on weight of patients included in CL303. This showed that age was not a significant predictor of weight.

4.2.4 Intervention and comparator

The intervention is burosumab and the comparator is SoC in the model. Burosumab is implemented as per its marketing authorisation, where the recommended starting dose in adults is 1.0 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, given by intravenous injection every four weeks.

The proposed positioning of burosumab is a last line therapy for adults for whom conventional therapy is unsuitable (vitamin D analogues and phosphate supplementation). Therefore, for the modelled population no other active treatment options are considered available. SoC is defined as usual care without burosumab, representing symptomatic treatment of morbidities only.

Points for critique

The comparator in the CS is defined as symptomatic treatment of morbidities only, in line with the company's proposed positioning of burosumab in symptomatic adults for whom conventional therapy is not suitable due to ineligibility, intolerance or inadequate efficacy. However, as noted above, the EAG considers there to be uncertainty regarding the definition of treatment failure with conventional therapy in patients for whom burosumab would be considered to be an alternative treatment option. The comparator differs from that considered in the submissions to the SMC, CADTH and PBAC, where the comparator was defined as SoC representing a mix of conventional therapy (vitamin D analogues and phosphate supplementation) and/or no treatments (routine symptomatic management). In the previous models, the proportion of the population that was assumed to receive conventional therapy differed across the submissions: 41% of patients on average were assumed to receive conventional therapy in the SMC submission based on the Global natural history study (CL001); 70.1% received oral phosphorus and calcitriol in the PBAC model, which was informed by online survey data from CL001 and expert elicitation; while in the CADTH submission the proportion receiving phosphate, vitamin D and/or calcimimetic as the comparator was not stated. In the previous models, only the costs of conventional therapy were included, while the effects were not considered. In all models, SoC was informed by the placebo arm of CL303 due to the lack of evidence comparing burosumab with conventional therapy and the low-quality evidence for vitamin D analogues and phosphate supplementation that is insufficient for determining clinical benefit in terms of serum phosphate normalisation. Therefore, although conventional therapy was included as part of the comparator in the previous models, it was deemed not to provide an improvement in the rate of serum phosphate normalisation over placebo and the incidence of morbidities was assumed to be equal to untreated XLH patients. In this respect, it is only the definition of SoC and the inclusion of costs associated with conventional therapy that differs between the previous models and the CS.

The EAG notes that the company's approach may be considered conservative because it excludes the costs associated with conventional therapy from the model; however, there remains uncertainty about the clinical benefit associated with conventional therapy in terms of rates of serum phosphate normalisation compared to placebo or burosumab.

4.2.5 Perspective, time horizon and discounting

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon (up to age 100 years), at which point the model predicts that nearly all patients in the cohort have died. A 3.5% annual discount rate is used for both costs and health effects.

Points for critique

The CS adheres to the NICE health technology evaluations manual [39] and the EAG considers the approach used by the company to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

Treatment with burosumab in the company's base case analysis is assumed to affect the (i) levels of serum phosphate (normalising phosphate homeostasis); (ii) incidence of fractures; and (iii) risk of mortality; in addition to improvements in health-related quality of life (see Section 4.2.8). The model includes tapering (build-up and waning) of treatment effects and a treatment continuation/stopping rule. Each of these elements relating to the effectiveness of burosumab and the extrapolation of effects over the long-term are discussed below.

4.2.6.1 Serum phosphate normalisation and criteria for treatment continuation

The probability of serum phosphate normalisation is based on the proportion of participants who achieved mean serum phosphate above the LLN range across midpoint of dose intervals through to week 24 from CL303, which was 94.1% for burosumab and 7.6% for placebo. The model uses the proportion in the placebo arm to represent the normal phosphate levels with SoC because the population of CL303 were not permitted to receive conventional therapy, which aligns with the company's positioning of burosumab when conventional therapy is unsuitable. The 'Alive, on treatment' and 'Alive, off treatment' states of the model represent all patients starting on either burosumab or SoC, respectively, therefore, the probability of serum phosphate normalisation for burosumab after 24 weeks is based on the incremental of burosumab and SoC of 92.4% (=100-7.6%). This is applied in the model at 24 weeks to support the continuation of treatment after year 1 and applied per annum to determine the proportion with a reduction in the incidence of morbidities and reduced mortality risk over the long-term due to increased rates of serum phosphate normalisation associated with burosumab compared to SoC, i.e., the model assumes that serum phosphate normalisation observed at week 24 in CL303 will persist while patients remain on treatment.

Continuation of treatment in the model is based on a requirement of reaching serum phosphate levels above LLN at 24 weeks and an improvement in WOMAC total score at 12 months after starting treatment. An improvement in WOMAC score was observed in 83.1% of participants in CL303 at 48 weeks, which was the closest study visit to one year. Therefore, the model allows for a total of 16.9%

of patients to discontinue treatment in year 1 and only patients achieving a clinically relevant benefit from burosumab remain on long-term treatment. Continuation of treatment in years 2 and beyond is based on an annual discontinuation rate of 3% per annum, which the company justified on the basis of expert opinion and discontinuation rates from the EAP for burosumab.

Points for critique

The target of serum phosphate normalisation in the model is consistent with the primary efficacy endpoint of CL303 and the primary driver of morbidity in adults with XLH. Therefore, the EAG considers the company's criteria based on a requirement of reaching serum phosphate levels above LLN at 24 weeks to be appropriate for assessing the initial response to treatment and modelling the reduction in morbidities and mortality risk due to increased rates of serum phosphate normalisation over time. However, the model also considers a second criteria for assessing initial response to treatment, which is the requirement of an improvement in WOMAC total score at 12 months after starting treatment. The EAG questions whether this second hurdle is necessary and appropriate. Firstly, the EAG notes that WOMAC scores are not commonly used in UK clinical practice to assess response to treatment, or evaluate whether a patient should have access to treatment. Secondly, in the absence of alternative treatments available and the patient has reached the target of serum phosphate normalisation after week 24, it may not seem reasonable to impose an additional hurdle on quality of life because of the potential to experience a reduction in morbidities and mortality with phosphate levels maintained. Thirdly, there may be other advantages to burosumab treatment such as a reduction in opioid use for pain management, even if the required improvement in WOMAC total score is not observed. For example, data on 40 adults receiving burosumab at the University College London Hospitals NHS Foundation Trust (UCLH), where no stopping criteria were imposed, showed that 9 out of 20 patients (45%) who were using opioids at baseline had stopped opioid use at one year and there was no new opioid use. Fourthly, the EAG notes that no stopping criteria were included in either the CL303 trial or the EAP in England.

The proposed stopping criteria for treatment in the model affects the proportion of patients who remain on treatment at the end of year one, where a total of 16.9% of patients discontinue burosumab in year 1 due to not meeting the criteria for treatment continuation. If no stopping rules are imposed, the burosumab discontinuation rate in the first year is 7.35% based on data from CL303, where 5 out of 68 participants in the burosumab arm discontinued treatment between baseline and week 24. [redacted] The proposed stopping criteria also affects the utility values implemented in the model for burosumab after the first year, where the company provides the utility effects for

burosumab based on all patients continuing treatment (i.e., no stopping rules applied) and the effects when stopping criteria are implemented in the first year based on the subset of participants in CL303 who experienced an improvement in WOMAC at week 48 and had serum phosphate levels above LLN at 24 weeks. The resulting long-term utility effects for burosumab are more favourable with stopping criteria applied in the first year than without stopping rules (see Section 4.2.8.2).

The annual discontinuation rate of 3% in years 2 and beyond is based on clinical opinion and supported by the observed annual discontinuation rates from the EAP (Table 25, p114 of CS). The EAP does not include stopping criteria. The long-term discontinuation rate might be expected to be lower for those who responded to treatment in the first year on the basis that this patient population have no other alternative treatment options available. The discontinuation rates in the first and subsequent years differ from those used in the CADTH and PBAC models; in the CADTH model, the discontinuation rate in the first year was based on CL303 and no long-term discontinuation was assumed after year 1 on the basis that expert opinion indicated that most patients would continue with lifelong treatment due to the chronic nature of XLH, while in the PBAC model patients on burosumab were expected to discontinue treatment at a rate of 7% in the first year and 1% every subsequent year thereafter. The EAG considers the impact of the stopping criteria and alternative assumptions for the discontinuation rate on the cost-effectiveness of burosumab in Section 6.

> ***item 5. There is uncertainty about whether the proposed treatment stopping criteria for burosumab would be implemented in clinical practice and the impact on long-term treatment discontinuation rates.***

4.2.6.2 Morbidity benefit

The model assumes that patients on burosumab experience a reduction in morbidities due to increased rates of serum phosphate normalisation compared to SoC. In the base case analysis, patients with normalised serum phosphate levels are assumed to experience fracture incidence rates equivalent to that of the general population, while the annual fracture incidence rates for SoC are based on those predicted from baseline CL303 trial data (Section 4.2.2.3). Therefore, the effect of burosumab on the development of new fractures annually is applied according to the probability of serum phosphate normalisation of 92.4%, while the effect of healing active fractures is captured by WOMAC through improvements in health-related quality of life.

The model assumes that the excess fracture incidence rates due to XLH for SoC are reduced by 100% to that of the general population for burosumab, conditional upon achieving serum phosphate normalisation. The fracture rates in the general population were identified from Curtis et al., (2016) [40], which reports age- and sex-specific fracture incidence rates in the UK over a 24-year period between 1988 and 2012 based on CPRD data for adults ≥18 years. In Curtis et al., fractures were classified

according to the International Classification of Diseases, ninth edition (ICD-9) categories and incidence rates calculated by dividing the number of individuals with the fracture by the total person-years of follow-up. Table 14 shows the fracture incidence rates per 10,000 person years, reported by age, sex and site in Curtis et al., which are used to represent the rates of the general population in the model.

Table 14 Fracture incidence rates per 10,000 person years by age, sex, and site reported in Curtis et al., (2016)

	Age 18-49 years			Age 50+ years		
Fracture type	**Male**	**Female**	**Both**	**Male**	**Female**	**Both**
Tibia/fibula fractures†	7.4	3.5	5.5	4.5	8.3	6.5
Femur/hip fracture*	1.4	0.6	1.0	11.3	32.1	22.4
Foot fracture (foot and ankle) †	21.3	17.9	19.6	13.1	27.8	20.9
Upper limb (radius/ulna) fractures*	11.0	9.1	10.1	8.9	39.7	25.1
Vertebrae/spinal fractures*	1.8	1.3	1.5	4.6	9.4	7.1
Other fractures (ribs, skull, pelvis and patella fractures) †	17.5	6.2	11.9	13.2	17.6	15.6

†Sex-specific incidence rates not implemented in the model;

*Age- and sex-specific incidence rates used in the model for 15 age band categories (18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90+)

Points for critique

The model assumes that with normalised serum phosphate levels the fracture incidence rates are the same as those of the general population based on Curtis et al., (2016) [40] but these rates do not distinguish between hypophosphataemia-driven osteomalacia and fragility fractures from fractures due to trauma experienced by non-affected individuals, or fractures due to osteoporosis usually experienced by the elderly. The EAG also notes that the disutility associated with fractures in the model is based on a range of different sources, irrespective of the cause of fracture; for example, utility multipliers are based on osteoporotic fractures in postmenopausal women and morphometric fracture populations rather than clinical fracture populations.

The company's justification for the incidence of fractures being reduced to that of the general population for those who achieve normalised serum phosphate is based on the observation that no new fractures were reported in patients receiving burosumab in CL303 and BUR02 (see Table 36 of CS). However, the EAG notes that the EMA assessment report for burosumab (EMA/423776/2020[29], page 97 of 151) indicates that six new active fractures/active pseudofractures were reported in the burosumab arm within weeks 0-24, one new fracture within weeks 24-36, and none within weeks 36-48 of CL303. In response to EAG points for clarification, the company accepted that the statement in the CS was incorrect and that some new active fractures and pseudofractures were reported during

CL303 as part of safety outcomes. The EMA also indicated that normalisation of the bone may take months or even years to heal (supported by evidence from CL304 that showed that bone structure was not completely normalised at week 48 in bone biopsies), which could contribute to a continued incidence of new fractures despite burosumab treatment.

The clinical significance of reduced incidence of new fractures with burosumab is unclear because there is no correlation with outcomes in study CL303 or outcomes that are important to patients such as pain. The only data available to support the effects of burosumab on fractures is a post-hoc exploratory analysis of healing of active bone fractures or pseudofracture in CL303. At week 24, 43% (28 out of 65 fractures) of active fractures or pseudofractures had fully healed in the burosumab arm compared with 7.7% (7 out of 91 fractures) in the placebo arm, while 24.6% (16 out of 65 fractures) were partially healed in the burosumab arm but 27.5% (25 out of 91 fractures) were also partially healed in the placebo arm. Therefore, the exploratory outcomes in CL303 show only a trend towards greater healing of active fractures or pseudofractures with burosumab compared with placebo and no evidence to support a reduction in the incidence of new fractures.

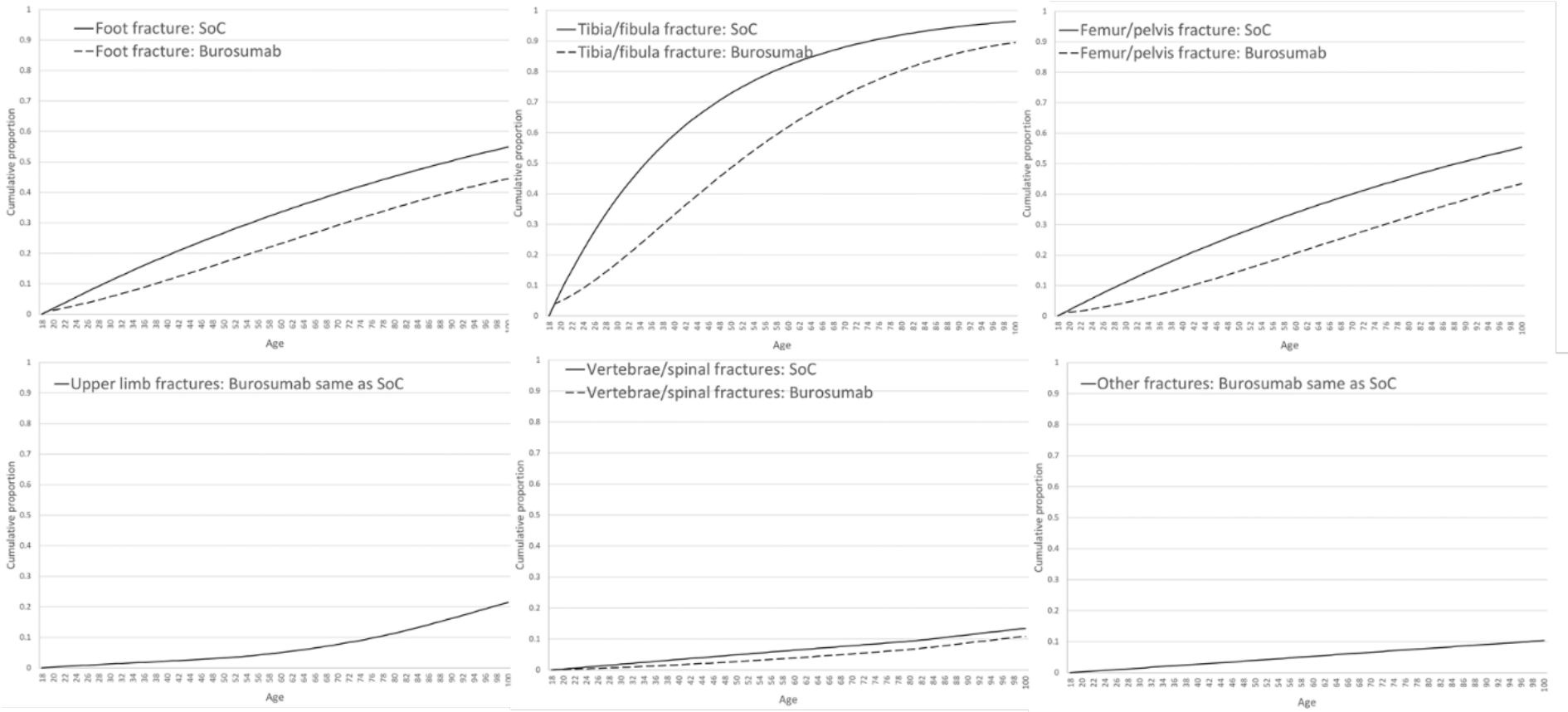
The company assumes a 100% reduction in the excess risk of fractures due to XLH to rates equivalent to that of the general population. The EAG is concerned that this assumption has not been adequately evidenced for the reasons outlined above. While it may be clinically plausible that burosumab would lead to a reduction in fractures with improvement in serum phosphate within normal levels the assumption has not been evidenced and is likely to overestimate the effect of burosumab. In the model, patients can incur one or more fracture events over time based on the annual incidence rate due to XLH for SoC, or the general population rate for burosumab for those with normalised serum phosphate. In terms of the source used to inform the fracture incidence rates for the general population, the EAG is satisfied that Curtis et al., (2016) [39] is a reasonable choice of source but acknowledges that burosumab is targeted at reducing the incidence of hypophosphataemia-driven osteomalacia and fragility fractures rather than fractures experienced by non-affected individuals from Curtis et al. The EAG notes that there were a number of inconsistencies in the way that the data from Curtis et al were implemented in the model by site of fracture (e.g., age and sex-specific incidence rates were implemented for some types of fractures, while for others total incidence rates were used, even when data by sex were available); however, the EAG considers that these inconsistencies are unlikely to have a material impact on the cost-effectiveness results.

Figure 17 shows the resulting cumulative proportion of patients with a history of fractures as a function of age for burosumab versus SoC, by site of fracture. The difference between burosumab and SoC is most apparent for foot fracture, tibia/fibula fracture and femur/pelvis fractures. In Section 6, the EAG considers the impact on the cost-effectiveness of burosumab of alternative assumptions for the reduction in the excess XLH fracture risk.

> ***item 6. The assumption that achievement of serum phosphate within normal levels leads to fracture incidence rates equivalent to those in the general population (i.e., no excess risk due to XLH) has not been evidenced.***

In terms of the source used to inform the fracture incidence rates for the general population, the EAG is satisfied that Curtis et al., (2016) [40] is a reasonable choice of source but acknowledges that burosumab is targeted at reducing the incidence of hypophosphataemia-driven osteomalacia and fragility fractures rather than fractures experienced by non-affected individuals from Curtis et al. The EAG notes that there were a number of inconsistencies in the way that the data from Curtis et al were implemented in the model by site of fracture (e.g., age and sex-specific incidence rates were implemented for some types of fractures, while for others total incidence rates were used, even when data by sex were available); however, the EAG considers that these inconsistencies are unlikely to have a material impact on the cost-effectiveness results.

Figure 17 Cumulative proportion with a history of fractures by age and site of fracture for burosumab and SoC



4.2.6.3 Mortality benefit

No mortality benefit for burosumab was observed within the short trial duration and small population of CL303 and BUR02. However, the company anticipates that by normalising phosphate homeostasis, mitigating the multi-system effects of hypophosphataemia, and reducing opioid use (not examined in the trial), treatment with burosumab will address the drivers of mortality in XLH and extend life expectancy. Therefore, the company assumes a reduction in the excess mortality associated with XLH for those receiving burosumab treatment, although the exact mechanisms and magnitude of benefit is unclear. In the base case analysis, a 50% reduction in the excess mortality risk due to XLH is assumed for burosumab, i.e., the XLH-related excess mortality hazard ratio of 2.88 for SoC compared to the general population is reduced to a hazard ratio of 1.94 for burosumab compared to the general population. The reduction in mortality is applied to patients in the burosumab arm of the model while on treatment, according to the probability of serum phosphate normalisation of 92.4%. As a consequence, the survival model for the population of XLH is a function of age, sex and treatment received.

Points for critique

The EAG's key concern in relation to the mortality benefit with burosumab is the lack of data to support a mortality benefit. Without any evidence about the effects of burosumab on mortality, there is complete uncertainty about the magnitude of the mortality benefit and, in fact, it is even speculative that interventions that reduce fractures will affect mortality in this patient population [36]. The assumption of a 50% reduction in the excess XLH mortality risk for burosumab is arbitrary. Furthermore, because the model does not incorporate a structural link between fractures (or other morbidities) and mortality, it is not possible to explicitly assess the link between achievement of serum phosphate within normal levels to fracture-related events and associated fracture-related mortality.

The approach used by the company differs from the CADTH model, where only patients with fractures were assumed to have an increased mortality risk and only after the age of 50 years. The increased risk of death for patients experiencing fracture after age 50 in the CADTH model was based on evidence from a meta-analysis of the effect of treatments for osteoporosis on mortality, which suggests a 11% reduction in mortality with treatment (relative risk, 0.89; 95% CI, 0.80 –0.99) [41]. Although multi-system effects of hypophosphataemia other than fractures may drive increased mortality in this patient population, the evidence for the effect of treatments for osteoporosis on fracture-related mortality suggests that the mortality benefit is likely to be much lower in magnitude than that used in the company's model. In the absence of any evidence for multi-system effects of hypophosphataemia on mortality the effect of burosumab on mortality remains unknown. In Section 6, the EAG considers the impact of alternative assumptions for mortality benefit on the cost-

effectiveness of burosumab, including: (i) no mortality benefit; (ii) a 11% reduction for fracture-related mortality risk based on Bolland et al (2010) [41]; and (iii) an arbitrary 25% reduction in excess XLH mortality risk to account for additional multi-system effects other than fractures.

item 7. There is no evidence to support a mortality benefit with burosumab.

4.2.6.4 Tapering of treatment effects

A tapering of treatment effect on the incidence of morbidities and mortality is applied in the model in order to reflect the time it takes for the effect of burosumab to be fully developed and wear off after treatment discontinuation. Table 15 summarises the treatment effect build up and waning assumptions for morbidities and mortality. The company assumed that the effect on the incidence of new fractures was immediate on the basis that no new fractures were observed in CL303 (which was later corrected to mean BUR02 in response to EAG points for clarification), while the effect would be lost two years after treatment discontinuation (with 50% effect in year one after end of treatment) on the basis that WOMAC scores returned to similar levels to baseline for those not receiving burosumab during the interim period between CL303 and BUR02 (7 participants with a mean period of 9 months without treatment, range 6-16 months).

The company assumed the effect on mortality was long-term over a lifetime horizon for those receiving treatment, while the effect on mortality after discontinuation of burosumab lasted for two years after end of treatment (75% in year 1 and 50% in year 2) and lost from year 3 after end of treatment.

Table 15 Tapering of burosumab effect on morbidities and mortality (adapted from Tables 30 and 31 of CS).

Time period	Treatment effect assumption on	
	Morbidities	Mortality
Year 1 on treatment	100%	75%
Year 2 and beyond on treatment	100%	100%
One year after end of treatment	50%	75%
Two years after end of treatment	0%	50%

Points for critique

There is limited evidence to support tapering of treatment effect for burosumab. The company assumed that the effect on the incidence of new fractures was immediate because no new fractures were observed in BUR02. However, as discussed previously, six new active fractures/active pseudofractures were reported in the burosumab arm of CL303 within weeks 0-24 and one new fracture within weeks 24-36; therefore, the company's justification for immediate effect on the incidence of fractures is flawed, while no justification is provided for a 50% effect on morbidities in

the year after treatment discontinuation. The tapering effect assumptions on mortality are arbitrary because there is no evidence to support a mortality benefit for burosumab.

The EAG's key concern in relation to the tapering effect assumptions is the inconsistencies between the effects applied on mortality and those applied on morbidities. In particular, the EAG notes that there is an ongoing benefit on mortality two years after treatment discontinuation, while there is no benefit on the incidence of fractures, and there is an immediate effect of treatment on fractures, while the effect is 75% for mortality in year 1. From a conceptual point of view, it would seem more reasonable to have consistency in the tapering effect of burosumab on morbidities and mortality, in the absence of evidence for the contrary.

The EMA indicated that normalisation of the bone may take months or even years to heal, which was supported by evidence from CL304 that showed that bone structure was not completely normalised at week 48 in bone biopsies. Therefore, the EAG does not consider it reasonable to assume an immediate 100% effect of treatment on fractures. The EAG considers 75% in year 1 on treatment to be more reasonable, in line with the mortality effect and evidence from CL303 where 63.1% of active fractures or pseudofractures at baseline had healed in the burosumab arm by week 48.

In Section 6, the EAG considers a scenario where the tapering effect is the same for morbidities and mortality, which is equivalent to 75% in year 1 on treatment, 100% in year 2 and beyond on treatment, 50% in year 1 after end of treatment and 0% from year 2 after end of treatment. The implications on the cost-effectiveness results of switching off the waning effect is also considered.

> ***item 8. There are inconsistencies in the assumptions for the tapering effect of burosumab on morbidities and mortality. The EAG does not consider it reasonable to assume an immediate effect of treatment on the incidence of fractures, or a mortality effect two years after treatment discontinuation in the absence of evidence to support a mortality benefit.***

4.2.7 Adverse events

Adverse events are not considered in the company's model.

Points for critique

The EAG considers it reasonable to exclude the costs and health-related quality of life associated with adverse events from the model because the overall incidence and severity were comparable in the burosumab and placebo arms of CL303, with no serious treatment emergent adverse events (see Table 23, p103 of CS). There were also no discontinuations due to adverse events in CL303.

4.2.8 Health-related quality of life

4.2.8.1 Summary of company's submission

The company conducted a systematic literature review to identify studies reporting health-related quality of life (HRQoL) for adults with XLH (see Appendix H of CS). Sixteen studies were selected for data extraction and an additional study [42] identified after the review search date: three reported EQ-5D-5L index values for a UK population (without burosumab) [43] [44] [42], while thirteen reported SF-36 scores (seven studies) or WOMAC scores (six studies) with the potential for mapping to EQ-5D utility values. One real world evidence study based on the EAP for burosumab in England [28] provided one-year measurements of EQ-5D-5L domain scores in adults initiated with burosumab (see Section 2.6.6.1 of CS); however the change in EQ-5D utility (across the domains) from baseline to one year was not reported in this study. In the absence of EQ-5D utility values for burosumab, the utility values used in the model were derived by mapping from WOMAC scores obtained in CL303 and BUR02 (open-label follow-up study of CL303) to EQ-5D using a published mapping algorithm developed by Wailoo et al. (2014) [45].

The CS considers HRQoL relating to (i) baseline utility in adults with XLH, which is estimated as a function of age based on data from CL303; (ii) incremental utility benefit for burosumab based on combining data from CL303 and BUR02 and extrapolating the effects over time; (iii) disutility associated with morbidities, which is implemented in the model as a utility improvement for burosumab associated with a reduced incidence of fractures in the base case analysis; and (iv) a spillover effect on the utility of caregivers and family members, which is assumed to be 20% of the patient utility benefit of burosumab and applied to two caregivers/family members.

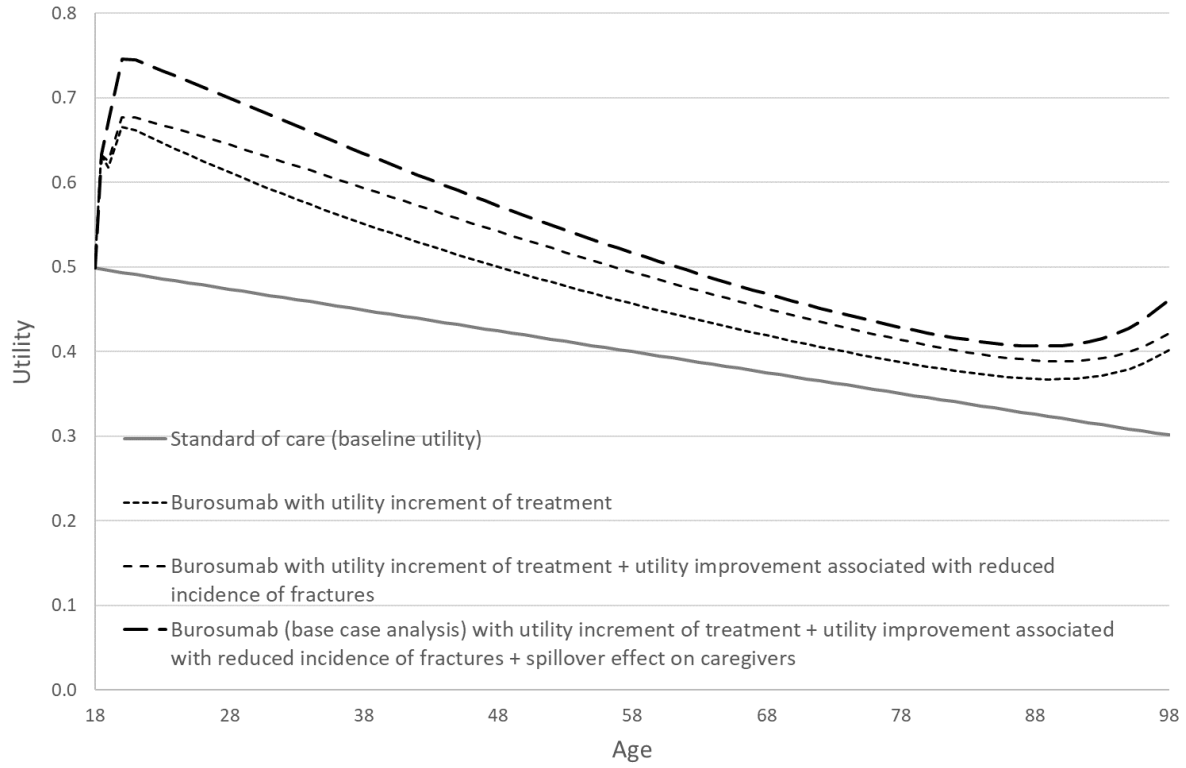
Table 16 summarises the utility values used in the company's base case analysis, while Figure 18 shows the corresponding utility benefit for burosumab compared with SoC as a function of age. The impact of treatment on HRQoL is a key driver of the model results. The differences shown for burosumab compared to SoC are substantially higher in the model than those observed in CL303 based on continued improvement over time, utility improvements associated with a 100% reduction in the incidence of new fractures with burosumab, and a significant increase in utility derived from the spillover effect on caregivers and family members.

Table 16 Utility values used in the company's base case analysis (CS Table 45 p147-148)

Item	Mean input value (SE)	Sources
Baseline utility (coefficients of a linear regression model)		
Intercept	0.5428 (0.0639)	Estimated from a linear regression model applied on pre-treatment EQ-5D utilities (mapped from WOMAC scores) using data from CL303 trial.
Age	-0.0025 (0.0015)	

Utility increments for burosumab applied to baseline utility		
Year 1	0.1468 (0.011)	Estimated from asymptotic models using EQ-5D utilities (mapped from WOMAC scores) in CL303 and BUR02 trials over 168 weeks (with treatment stopping rules applied). These incremental values are not adjusted for the change in utility observed in the placebo arm of CL303.
Year 2	0.2112 (0.015)	
Year 3+	0.2150 (0.018)	
Utility multipliers associated with fracture events		
All lower limb/hip fractures *first year* (Tibia/fibula, femur/pelvis and foot)	0.700 (0.010)	Based on values used in NICE TA204 (Denosumab for the prevention of osteoporotic fractures in postmenopausal women).
All lower limb/hip fractures *subsequent years* (Tibia/fibula, femur/pelvis and foot)	0.800 (0.013)	
Vertebrae/spinal fractures *first year*	0.910 (0.013)	
Vertebrae/spinal fractures *subsequent years*	0.990 (0.005)	
Upper limb fractures *first year*	0.934 (0.011)	
Upper limb fractures *subsequent years*	1.000 (0.008)	
Other fractures *first year*	0.934 (0.011)	
Other fractures *subsequent years*	1.000 (0.008)	
Spillover effect on caregivers and family members		
Year 1	0.0587	Assumed to be 20% of the utility benefit for burosumab and applied to two caregivers/family members.
Year 2	0.0845	
Year 3	0.0860	
Abbreviation: EQ-5D: EuroQol health-related quality of life questionnaire; NICE: National Institute for Health and Care Excellence; SE: standard error; SoC: standard of care; TA: Technical Appraisal; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index		

Figure 18 Modelled utility for SoC and burosumab as a function of age.



4.2.8.2 Baseline utility values

The baseline utility value for SoC and burosumab in the model is estimated as a function of age based on pre-treatment WOMAC scores from CL303 (across both treatment arms) and mapped to EQ-5D utility values using the algorithm developed by Wailoo et al. (2014) [45]. A linear regression model was fitted to the mapped utility values, with age as an independent variable in order to predict baseline utility as a function of age (Table 16 shows the regression parameters used in the model). The predicted average baseline utility is low (value of 0.498 for age 18 years), with a modest, non-statistically significant reduction with age (value of 0.444 for age 40 years, which was the average age of participants in CL303). The company also presents baseline utility values based on data from CL001 (see Table 38, p134 of CS), which are slightly higher than those of CL303 (e.g., values of 0.567 and 0.541 for age 18 and 40 years, respectively).

Points for critique

In the NICE reference case, utility values produced by the preference-based instrument of EQ-5D is the preferred measure of HRQoL in adults [39]. When EQ-5D data is not available, the data can be estimated by mapping from other HRQoL measures to EQ-5D, but this is considered a departure from the NICE reference case. EQ-5D data was not collected in CL303; therefore, WOMAC scores from the pivotal trial were mapped to EQ-5D. The mapping function chosen by the company was based on a literature search to identify suitable mapping algorithms, although details about the searching methods are not presented in the CS. Of the four algorithms identified[46, 45, 47, 48], the EAG considers

the algorithm developed by Wailoo et al. to be the most appropriate based on the findings of Kiadaliri et al. (2016) [49], which assessed the external validity of the available algorithms to estimate EQ-5D-3L from the WOMAC, and found that the mixture model by Wailoo et al. reflected the distribution of EQ-5D-3L data more accurately than the ordinary least squares models by Barton et al. and Xie et al. [49]. Kiadaliri et al. [49] showed that all the models were prone to systematic bias, where the algorithms significantly overpredicted the observed scores for severe health states and underpredicted for mild health states. However, the EAG notes that the algorithms were validated among a sample of Swedish mid-age and older people with knee pain and knee osteoarthritis and only 20% of possible EQ-5D-3L health states were observed in the study sample; thereby potentially limiting the generalizability of the findings to other patient populations such as XLH. The company did attempt to validate the mapping approach by comparing EQ-5D utility values mapped from WOMAC scores using the algorithm by Wailoo et al. (2014) [45] with those mapped from SF-36 scores, using a published algorithm by Rowen et al. (2019) [50], based on data collected in CL001. The data showed a strong correlation between the two mapping algorithms (Pearson correlation coefficient of 0.82). The EAG considers that the selection and validation of mapping algorithm is appropriate; however, a sensitivity analysis exploring the variation in outputs using alternative mapping algorithms would be useful to assess the implications of the choice of algorithm, in line with the recommendations in the NICE health technology evaluations manual [39].

The EAG notes that two of the studies[42, 43] that reported EQ-5D utility values in XLH adults in the UK were not considered in the CS as a source of baseline data (a third study by Jandhyala 2022 [44] reported change in mean score over one year in a sample of 10 UK patients but average scores were not reported). Both these studies used cross-sectional data from an ongoing UK-based multi-centre prospective cohort study, RUDY (Rare and Undiagnosed Diseases Study), which is a web-based registry and patient-driven platform designed to improve understanding of rare musculoskeletal diseases, including XLH. In Forestier-Zhang et al., (2016) [43], a sample of 24 participants with XLH (mean age of 46.3 years and 79% female) completed the EQ-5D-5L questionnaire and the corresponding mean utility value generated using the England value set of Devlin et al., (2018) [51] was 0.648 (SD 0.290). In Cole et al., (2023) [42], a larger sample from RUDY of 48 participants with XLH was considered (median age of 46 years and 77% female) and the corresponding mean utility value was 0.651 (SD 0.270) for the EQ-5D-5L questionnaire, while the corresponding mean utility value was 0.554 (SD 0.300) for the EQ-5D-3L index score (crosswalk from EQ-5D-5L), which is the value set preferred in the NICE health technology evaluations manual [39].

The mapped utility values from CL303 are lower than the mean EQ-5D-3L utility value reported in Cole et al. (2023) [42], which may suggest that participants in CL303 were more symptomatic than those expected to be seen in UK clinical practice. However, in the absence of utility values for a UK

population as a function of age, the EAG considers the baseline utility values from CL303 to be a reasonable choice. The baseline utility values used in the model are the same for SoC and burosumab and, therefore, should not affect the incremental difference in total QALYs between the treatments. However, the EAG notes that the baseline utility value does affect the QALYs associated with morbidities because the disutilities associated with morbidities are estimated in the model by applying utility multipliers for a morbidity event as a proportion of the baseline utility (see Section 4.2.8.4 below). This means that the higher the baseline utility value, the higher the disutility associated with morbidity events, which is less favourable to SoC compared with burosumab because the model assumes a 100% reduction in the incidence of morbidities for burosumab.

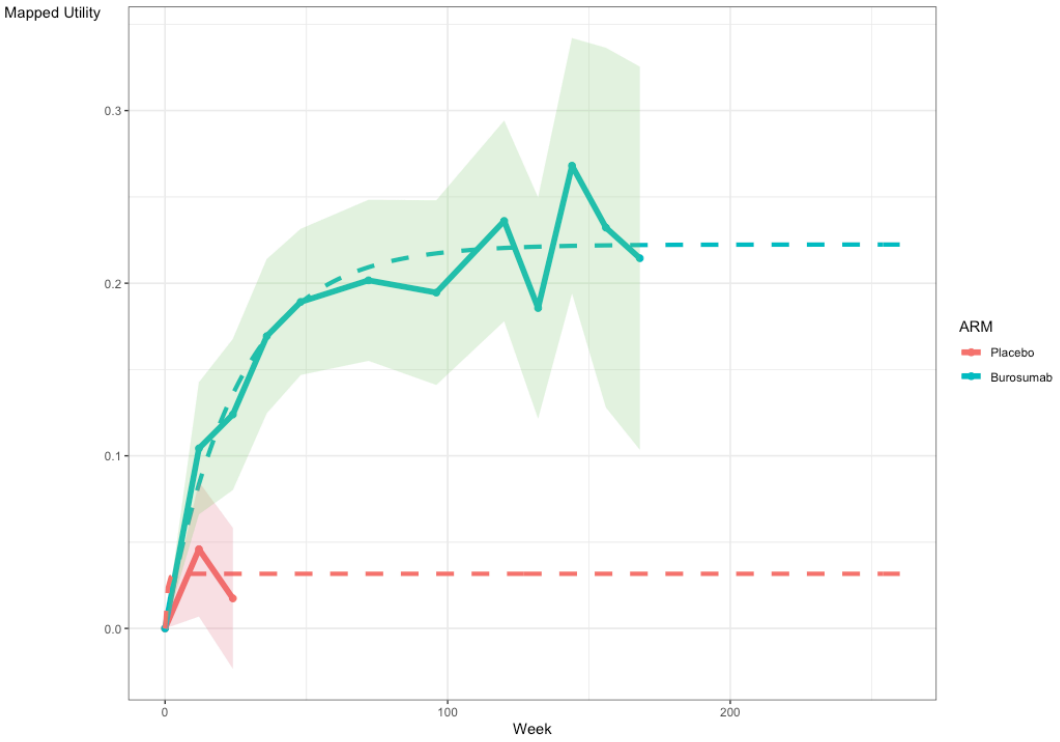
4.2.8.3 Incremental utility gain for burosumab and extrapolation of effect over time

The effect of burosumab treatment on utility is based on WOMAC data from CL303 and BUR02. In the model, patients on burosumab gain an improvement in utility for the duration that they remain on treatment, whilst those who discontinue treatment receive 50% of the utility gain in the year after end of treatment (i.e., a waning effect on utility gain of 50% for one year after end of treatment). In CL303, a statistically significant difference in change from baseline between burosumab and placebo was observed in the WOMAC subscale scores of stiffness and physical function at week 24. However, after week 24, only open label and uncontrolled data are available from CL303; from weeks 24 to 48, participants entered an open label treatment continuation period, during which they all received burosumab, while after that there were two open-label treatment extension periods, the first from week 48 to 96 and the second in the US only from week 96 to 149. After week 96, participants from CL303 in the EU had the option to enter the open-label study of BUR02, along with EU participants from CL304, for up to a further 48 weeks (Figure 11, p64 of CS). To provide additional data on the effect of burosumab treatment on WOMAC outcomes, open label and uncontrolled data from CL303, US patients only from CL303 and BUR02 were combined (see Table 39, p136 of CS for number of adults with WOMAC data at each follow-up period). WOMAC outcomes from the combined trials were mapped to EQ-5D utility values (using the algorithm of Wailoo et al. [45]) to provide mean change from baseline utility up to week 168 for burosumab and up to week 24 for placebo (see Figure 37, p137 of CS).

In order to extrapolate the change from baseline utility over time, the company fitted a non-linear asymptotic model to each arm independently to predict change in utility as a function of time. The resulting model fits are shown in Figure 19. The incremental utility gain for burosumab relative to SoC is implemented in the model as a mean change from baseline in years 1 to year 3, after which the utility gain is assumed to remain constant at the year 3 value over time. The company provides utility increments for burosumab for both placebo-adjusted and non-placebo-adjusted utility values, with the latter being selected for the base case analysis. The term ‘non-placebo-adjusted’ refers to the change

from baseline utility for burosumab without deduction of the extrapolated change from baseline observed in the placebo arm of CL303. The resulting mean increments in utility for burosumab in the base case analysis are 0.147 for year 1 on treatment, 0.211 for year 2 on treatment and 0.215 for year 3 and beyond on treatment, while no increment in utility is applied for SoC. The company also presents mean utility increments for burosumab when no treatment stopping criteria are applied in the first year, which decreases the mean utility increments in year 2 (0.193) and years 3 and beyond (0.207).

Figure 19 Asymptotic model fit for change from baseline in mapped utility values for burosumab and placebo (reproduced from Figure 39, p142 of CS)



Weeks	0	12	24	36	48	72	96	120	132	144	156	168
Tx Obs	55	55	55	54	55	50	49	42	11	23	10	10
Placebo Obs	65	65	65	0	0	0	0	0	0	0	0	0

Points for critique

The EAG has a number of concerns relating to the estimate of utility gain for burosumab relative to SoC and the extrapolation of incremental utility over time. First, as highlighted in Section 3.2.3, the EAG notes that there were some imbalances in baseline characteristics between the arms of CL303, including greater pain intensity and a higher score in the WOMAC physical function subscale in the burosumab arm compared to the placebo arm, indicating a potentially greater symptom burden in the burosumab arm at baseline, which could impact on the statistical significance of the mean change from baseline in WOMAC scores between the two arms at week 24. Moreover, as discussed in

Section 3.2.4, although the mean change from baseline in WOMAC stiffness and physical function at week 24 was statistically significantly greater in the burosumab arm compared to placebo, it is not clear if the mean difference is clinically meaningful given that the point estimates are below the XLH-specific minimal clinically important difference (MCID) of 10 points for WOMAC stiffness and 8 points for WOMAC physical function.

The second key concern is that after 24 weeks, only open label and single arm data for less than 3 years of treatment are available to support burosumab benefits in relation to symptoms in the long-term with continuous treatment. The lack of comparative data after 24 weeks is a concern in itself, but the EAG's major concern is that the data informing the change from baseline in WOMAC scores for burosumab after week 96, which marks the end of the treatment continuation period of CL303, is based on different patient populations that differ in terms of baseline characteristics and WOMAC scores. For example, at week 120, only WOMAC data from US participants is available from CL303, while from week 132, WOMAC data from only EU participants is available from BUR02 and at week 144 WOMAC data is combined from both BUR02 and US participants in CL303. It is clear that there are differences between the populations because the weight distribution of EU participants in CL303 is lighter than the weight distribution of all participants in CL303, which has implications for the drug acquisition costs of burosumab. In addition, the attrition rates observed after week 96 means that the results beyond this point may not be reliable. The EAG has reason to believe that the use of WOMAC scores from different populations are affecting outcomes because there is a noticeable spike in the change from baseline in mapped utility values from week 96 to week 120 when only data from US participants in CL303 are included (see Figure 19). After week 120, the data becomes increasingly uncertain due to the very low number of observations providing data in subsequent periods (only a total of 10 participants provide data in weeks 156 and 168).

The company uses an asymptotic model to extrapolate the utility benefit of burosumab beyond the observed periods of the CL303 and BUR02 trials, while other models, including linear and polynomial models, were considered inappropriate by the company because the predicted utility values were clinically implausible when extrapolated beyond the observed period (see Appendix T of CS). The EAG considers the company's approach to the extrapolation of utility values to be reasonable but notes that the model was fitted to each arm independently due to the limited data available for the placebo arm, which means that the relative difference between burosumab and placebo is not considered in the predicted mean change from baseline for burosumab. However, the EAG's key concern relates to the selection of data (or data cut-off point) that is used to inform the asymptotic model. As noted above, there is a spike in the mapped utility change from baseline for burosumab between weeks 96 and 120 when the population used to provide WOMAC data changes at the end of the treatment continuation period of CL303. This is particularly noteworthy because the

data between week 48 and 96 seems to suggest that the utility change from baseline reaches a plateau at just below a value of 0.2. However, by incorporating post-week 96 data from different patient populations and very small samples, more variability is introduced in the asymptotic model, with the predicted utility change from baseline producing a much larger estimate than the observed utility change between weeks 72 and 96. This suggests that the asymptotic model is heavily influenced by the post-week 96 data, which is much more uncertain than the pre-week 96 data. The EAG considers the data up to week 96 from the treatment continuation period of CL303 to be the only reliable trial data to inform the asymptotic model fit to WOMAC mapped utility change from baseline. The EAG considers participants receiving burosumab in the EAP in England to be more representative of the modelled population than the CL303 trial population; therefore, a comparison of the change in EQ-5D utility values from baseline to one year (and beyond) in EAP with the mapped WOMAC utility data from CL303 would provide an important reference to assess the benefits of burosumab over the short-term.

item 9. The EAG considers the WOMAC data up to week 96 from the treatment continuation period of CL303 to be the only reliable source (in the absence of data from the EAP for burosumab in England) to inform the mapped utility change from baseline for burosumab.

The asymptotic model shows that the utility gain reaches a plateau at around 3 years, after which the utility gain is assumed to remain constant over time. Therefore, the company assumes that the relative benefit of burosumab compared to SoC observed in the short-term trials (24 weeks blinded placebo-control or 168 weeks in total with open-label single-arm extension data) can be extrapolated to a lifetime horizon. The EAG considers the long-term utility benefit of burosumab to be highly uncertain and notes that the cost-effectiveness of burosumab compared with SoC is very sensitive to the mean incremental change in utility from baseline for burosumab because the benefits are extrapolated over a long period with continuous treatment.

item 10. There is uncertainty about the lifelong benefit of burosumab. After 24 weeks, only open label and single arm data for less than 3 years of treatment are available to support burosumab benefits in relation to symptoms in the long-term with continuous treatment.

A third concern relates to the differences that the EAG notes between the estimates of utility change from baseline for burosumab presented in Figure 37 of the CS (without the asymptotic model fit) and Figure 39 (with the asymptotic model fit, also reproduced in Figure 19). For example, the EAG notes that the mean change from baseline utility for burosumab at week 96 in Figure 37 of CS is approximately 0.15, whereas the corresponding value is just under 0.2 in Figure 39 of CS. Furthermore, the EAG notes that at week 24, the area of uncertainty (represented by the standard

error) for the mean change from baseline in mapped utility values for burosumab and placebo overlap in Figure 37 of CS, whereas after employing the asymptotic model fit (and using bootstrapping to estimate the standard error) the area of uncertainty for the two arms becomes distinct with no overlap suggesting that there is no uncertainty between burosumab and SoC in terms of mean change from baseline in mapped utility at week 24. These inconsistencies between the data presented in Figures 37 and 39 of CS are not explored in the CS. The EAG suspects that the differences may be due to a different subset of patients included, where Figure 37 of CS may include all patients from CL303 and Figure 39 of CS may only include patients who achieved an improvement in WOMAC at week 48 and had serum phosphate above the lower level of normal range at week 24, i.e., with the company's proposed stopping criteria applied. However, the EAG notes that the differences in utility values for burosumab between Figures 37 and 39 of CS are much more striking (larger in magnitude) than those reported with and without the stopping criteria applied for years 2 and 3+ in Table 41 of the CS; for example, the mean change from baseline for burosumab with stopping criteria applied is 0.211 and 0.215 in years 2 and 3+, respectively, whereas the corresponding values are 0.193 and 0.207 without stopping criteria applied. These differences are relatively small (0.018 for year 2 and 0.008 for year 3+) compared to the difference in magnitude of approximately 0.04 in utility change from baseline for burosumab at week 96 in Figures 37 and 39 of CS.

> ***item 11. The EAG notes a number of inconsistencies in the predicted utility estimates for burosumab reported in the company submission, which the EAG is unable to explore without access to the utility data.***

A fourth concern relates to whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed in the 24-week period of CL303. The extrapolated WOMAC mapped utility change from baseline in the placebo arm corresponds to a mean improvement in utility of approximately 0.03 over the long-term (see red dashed line in Figure 19). The company uses the non-placebo-adjusted utility values in the model, which means that the placebo effect observed in the controlled period of the CL303 trial is not deducted from the mean change from baseline utility for burosumab. The company justifies this approach based on an exploratory finding of Kamenicky et al. (2023), which showed that WOMAC scores from those interrupting burosumab treatment between the 96-week CL303 study and the 48-week open-label extension of BUR02 returned to similar levels to baseline after a 6 to 16-month treatment gap. However, the EAG notes that the total number of participants without burosumab in this interim period was considerably small (7 participants only) and the mean difference in WOMAC total and subscale scores between those who received compassionate burosumab treatment (23 participants) and those without burosumab (7 participants) during the interim period was statistically non-significant in the WOMAC total score and subscale scores, except for stiffness. Furthermore, treatment during the interim period was not

recorded, so it is not known whether participants received conventional therapy during the interval. Therefore, the EAG considers the exploratory findings from Kamenicky et al. (2023) [23] to provide limited evidence to support the argument for the use of non-placebo adjusted utility values in the model, specifically noting that Kamenicky et al. [23] only provides an indication of a return to 'similar' levels of baseline scores but how similar the WOMAC scores in the interim period translate to the small placebo effect of 0.03 is unknown. The EAG considers a scenario in Section 6 with the utility gain for burosumab compared to baseline utility adjusted for the placebo effect observed in CL303.

item 12. There is uncertainty about whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed in the 24-week period of CL303.

For patients who discontinue treatment with burosumab, the model assumes a waning effect on utility gain of 50% for a period of one year after the end of treatment. The EAG notes that this assumption is arbitrary. In the study by Kamenicky et al (2023) [23], a post-hoc exploratory analysis exploring outcomes in participants who discontinued burosumab treatment between the 96-week CL303 study and the 48-week open-label extension of BUR02 (a total of 7 participants) indicated that the benefits of burosumab on improvements in WOMAC stiffness and physical function scores and BPI-SF worst pain scores returned to a similar level to baseline; however, the time to return to baseline is not reported. The EAG notes that out of these 7 participants, four restarted burosumab within 8 months of discontinuation and the other three participants within 13 to 16 months, which suggests that the return to baseline utility is likely to be within one year of treatment discontinuation. In the absence of evidence to inform the time to return to baseline utility, the EAG considers a scenario in Section 6 with the utility waning effect turned off in order to assess the implications on the cost-effectiveness of burosumab.

item 13. There is uncertainty about the timing and magnitude of the waning effect on utility gain from baseline when patients discontinue burosumab treatment.

4.2.8.4 Disutility associated with morbidities

Utility multipliers are assigned to morbidities in the model. In the base case analysis, each type of fracture is assumed to independently reduce the age- and treatment-specific utility values. The impact of new fractures on utilities is categorised as either acute or chronic. Acute disutilities are applied in the year in which the event occurs, while chronic disutilities are applied over the remainder of the patient's lifetime. The disutilities are derived from reference case utility multipliers reported in NICE TA204 (denosumab for the prevention of osteoporotic fractures in postmenopausal women) [52], which were based on Peasgood et al. (2009) [53] for all lower limb/hip fractures, Cockerill et al. (2004) [54] for vertebrae/spinal fractures in a prevalent morphometric fracture population, and Borgström et al.

(2006) [55] and Ström et al. (2008) [56] for wrist fractures used for upper limb fractures and other fractures in the model (see Table 43, p145 of CS).

The disutility associated with living a year with each fracture is estimated as a proportion of the baseline utility:

Annual incident fracture rate*(1- utility multiplier for fracture)*baseline utility value

No disutility is applied to SoC on the basis that the impact of fractures on HRQoL is already incorporated in the baseline utility value. Therefore, only the net improvement in utility associated with the reduction in incident fractures for treatment is applied to burosumab, i.e., a utility increment for burosumab is estimated based on the difference between the age- and treatment-specific utility with and without the multiplier.

Points for critique

The CS does not provide details on the targeted literature search used to identify utility multipliers for morbidities, which are based on values reported for fractures in NICE TA204 [52]. In TA204, the committee concluded that the source of data, informed by a systematic literature review, and approach to modelling disutility for osteoporotic fractures was acceptable. However, the EAG notes that for use in the company's model none of these sources are specific to hypophosphataemia-driven osteomalacia and fragility fractures and some are based on morphometric fracture populations. The EAG also notes that there are some inconsistencies between the approach used in the CS and NICE TA204; for example, in the CS the utility multiplier for tibia/fibula fractures, femur/pelvis fractures and foot fractures is based on the value of 0.7 (first year) for all lower limb/hip fractures from Peasgood et al. (2009) [53], whereas in TA204 the utility multiplier of 0.93, derived from wrist fractures from Ström et al. (2008) [56], was used for other fracture types, including pelvis, femur, rib, clavicle, sternum, scapula, tibia and fibula. The EAG considers the company's choice of source for informing tibia/fibula, femur/pelvis and foot fractures from Peasgood et al. (2009) [53] to be more appropriate than Ström et al. (2008) [56], but notes that the utility multipliers used in the model are uncertain. The value of these multipliers is expected to have a large effect on the cost-effectiveness of burosumab because the model assumes a 100% reduction in the excess risk of fractures due to XLH for those with normalised serum phosphate on burosumab, which leads to a significant difference in the cumulative proportion with a history of tibia/fibula, femur/pelvis and foot fractures by age for burosumab compared with SoC, where the utility multipliers are applied.

The EAG notes that some of the fractures (tibia/fibula, femur/pelvis, foot, and vertebrae/spinal fractures) accrue a lifetime utility decrement. The EAG has a concern that this may overestimate the disutility associated with fractures. First, it does not reflect the likelihood of fracture healing over

time, which could lead to improvements in HRQoL rather than assuming a constant lifetime disutility after the event (post-year 1). Second, because mortality and morbidities are modelled independently, the duration of lifetime disutility associated with fracture events is not adjusting for fracture-specific mortality. Third, the disutilities associated with fractures in addition to the treatment-specific utilities may represent some double counting of morbidity effects because the treatment-specific utility values based on WOMAC scores are extrapolated over a lifetime.

The EAG also notes that the magnitude of the disutility associated with fractures is dependent on the baseline utility value because the disutilities are implemented in the model as a proportionate effect on the baseline utility. This means that any change to the baseline utility affects the magnitude of the disutilities, e.g., a higher baseline utility value implies a higher disutility associated with fractures. Therefore, even though the baseline utility is the same for burosumab and SoC, a higher value would favour burosumab because it would result in higher disutilities associated with fractures for SoC.

> ***item 14. There is uncertainty about the magnitude and duration of the disutilities associated with morbidities and the assumption of independent effects when multiple events can occur over a lifetime horizon.***

4.2.8.5 Impact of burosumab treatment on caregivers and family members

The company assumes that when patients are on burosumab treatment, caregivers and family members experience a positive effect on HRQoL, described in the CS as a spillover effect. This effect is assumed to be equal to 20% of the patient utility benefit of burosumab and applied to two caregivers/family members. The assumption was based on a HRQoL research study undertaken by the company (see Appendix S of CS) using the EQ-5D-5L and the Work Productivity and Activity Impairment Questionnaire with informal carers or family members of adults diagnosed with XLH in the UK (a total of 19 participants providing informal care). The mean difference in observed versus expected EQ-5D utilities was -0.184 (95% CI: -0.339 to -0.029), when compared with age-linked UK general population utility data. The company states that 20% of the long-term patient utility benefit associated with burosumab treatment (i.e., 0.215 in year 3 and beyond) and applied to two caregivers/family members results in a utility improvement for caregivers/family members of 0.086, which the company states is conservative because it is below the impact of caring for an adult with XLH based on the company's research study. The company also undertook a targeted literature review exploring the burden and spillover effects on carers and family members of adults with musculoskeletal conditions and found conflicting results, with quantitative research studies indicating minimal spillover effects while qualitative studies reveal significant impacts [57].

Points for critique

The EAG has a concern that the spillover effect may be overestimated by including an effect on two informal caregivers/family members rather than one caregiver/family member for adults with XLH, where two may seem more reasonable for a child with XLH than for an adult. The EAG notes that in the company's HRQoL research study, the majority of participants providing care or support for an adult with XLH were a partner or spouse (40%), while 36% were a parent of the individual with XLH, 8% a sibling, 8% a grandparent, 4% a child and 4% an in-law. The impact on more than one carer is unknown as participation in the study by more than one carer or family member was in only four XLH patients, while five carers or family members reported being connected to more than one adult patient with XLH. The EAG also considers that the way in which burosumab is administered (mainly self-administration) supports patients to be independent and is less likely to impose an additional burden on family members.

The EAG notes that three participants in the company's HRQoL research study had an XLH diagnosis themselves. The mean difference in observed versus expected EQ-5D utilities of -0.184 (95% CI: -0.339 to -0.029) is across the total sample of participants (N=19). When mean differences for participants with (N=3) and without XLH (N=16) are considered the corresponding values are -0.737 (95% CI: -1.401 to -0.073) and -0.081 (95% CI: -0.190 to 0.029), respectively. Therefore, when carers with XLH are excluded from the analysis the difference in utility is no longer statistically significant and lower in magnitude than for the total sample of participants (i.e., a loss of 0.081 vs. 0.184). The EAG does not consider it appropriate to include carers with XLH in the analysis because the spillover effect is added to the patient utility benefit with burosumab in the model, which is likely to include some double counting of treatment benefits, particularly given that the most frequent current treatment reported for care recipients was burosumab (36%) in the company's research study (although treatment for carers with XLH is not reported separately).

In summary, the EAG considers there to be uncertainty about the magnitude of burosumab treatment benefit on caregivers and family members and the number of carers/family members affected.

> ***item 15. There is uncertainty about the magnitude of burosumab treatment benefit on caregivers and family members who support adults with XLH and the number of carers/family members affected.***

4.2.9 Resource use and costs

4.2.9.1 Summary of company's submission

The company's base case analysis includes resource use and costs relating to: (i) drug acquisition and administration costs for burosumab; (ii) treatment management costs; and (iii) morbidity costs associated with fractures. Most costs for non-drug resource use were sourced from the National Schedule of Reference Costs 2020-2021 [58] and the Personal Social Services Research Unit (PSSRU)

2021 report [59]. Costs were inflated to 2020/21 prices using the Health Services Index obtained from the PSSRU report [59] where appropriate and discounted at an annual rate of 3.5%.

Table 17 summarises the costs included in the company's base case analysis.

Table 17 Costs used in the company's base case analysis

Item	Model input	Source
Drug acquisition costs per year		
Burosumab	[redacted]	Calculated based on the dosing of Burosumab for adults: 1 mg/kg of body weight, rounded to the nearest 10 mg, with a maximum dose of 90 mg [4] Burosumab is given every 28 days by subcutaneous injection. The mean patient weight (67.234 kg), which is used to calculate costs, is derived using weights recorded from EU participants (N=47) in CL303, using the proportion of population by weight band (see CS Table 46, p149). Dose reductions are recommended in the SmPC if serum phosphate is above the upper limit of normal range. The model applies a permanent dose reduction by 50% to 0.5 mg/kg in 5.97% of all patients (based on 8 out of 134 participants in CL303 with dose reduction). The list price of a 20mg vial solution of burosumab is £5,984.00. The model uses the confidential PAS discount ([redacted]) from the Highly Specialised Technology guidance 8 (HST8) for burosumab use in the paediatric population (confidential price is [redacted] per a 20mg vial).
SoC	£0	Treatment options for adults with XLH are limited. No other active treatment options are modelled in the absence of burosumab.
Drug administration costs per year		
Burosumab	£199.33	The model assumes 95% of patients self-administer, with nurse-led training funded by the company. The 5% of patients administered by a hospital nurse are assumed to require 20 minutes of nurse time. Given the 28-day administration cycles, patients receive burosumab 13 times a year. PSSRU 2021 [59] cost (2/6 of hourly (20 mins) nurse cost x 13 times a year as 4-weekly injections)
Treatment management costs per year		
Burosumab	First year: £ 328.87 Sequent years: £ 286.35	Calculated based on draft clinical practice recommendations for the UK [15] and clinical opinion (see CS, Appendix Q). The disease management unit costs are based on NHS Reference costs 2020/21 [58] and PSSRU 2021 [59], presented in CS Table 50, p152.
SoC	£286.35	
Morbidity costs per year		
Burosumab **SoC**	Total: £14,917.77 Foot fracture: £2,427.65 Tibia/Fibula fracture: £3,631.66 Femur/Pelvis fracture: £3,551.47 Vertebrae/spinal fractures: £767.03	Calculated based on fracture unit costs, fracture resource use, hospital admission (short or long stay) and post-fracture care in different fracture sites. Fractures unit costs are from PSSRU 2021 [59] and 2020-2021 NHS reference costs [58].

	Upper limb fractures: £2,386.82 Other fractures: £2,153.15	Proportion of hospital admissions based on TA204 [52], Bouee et al 2006 [60], and clinical expert opinion (see CS Table 52). Post fracture care unit costs are from PSSRU 2021 [59] with the frequency of post fracture care assumed (see CS Table 54, p155). The costs are weighted by the proportion managed by GP, hospital day case, and hospital admission with no procedure or requiring surgical procedure (see CS Table 51, p153).

Abbreviations: SoC: standard of care; PN: prurigo nodularis; PAS: patient access scheme.

4.2.9.2 Burosumab acquisition and administration costs

The recommended dose for burosumab in adults is 1 mg/kg of body weight, rounded to the nearest 10 mg, with a maximum dose of 90 mg [4]. The smallest available vial is 10 mg so there is no vial wastage. Pricing is linear; therefore, all vials cost the same per mg. Dose reductions are recommended in the SmPC if serum phosphate is above the upper limit of normal range. Burosumab is administered subcutaneously every 28 days.

The mean patient weight is based on the weight distribution of EU participants (N=47) from CL303 (see Figure 16). A dose reduction for 5.97% of patients is included in the model based on 8 out of 134 participants in CL303 having reduced dose across the placebo-controlled treatment and open-label extension periods. For these patients, the dose was reduced permanently by 50% to 0.5 mg/kg in the trial. Based on the proportion of patients within each weight band and with dose reduction, the average calculated dose per cycle is 65.23 mg, which equates to an average dose of 851 mg per year or 42.54 vials of 20 mg.

The list price of a 20mg vial solution of burosumab is £5,984. [redacted]. Therefore, the average burosumab drug acquisition cost per patient per year in the model is estimated to be [redacted].

[redacted]

[redacted]

The administration cost of burosumab assumes that the majority of patients (95%) can self-administer, with nurse-led training funded by the company. The model assumes that 5% of patients require burosumab to be administered by a hospital nurse and requires 20 minutes of nurse time. Given the 28-day administration cycles patients receive burosumab 13 times a year, which equates to an administration cost of £199.33 per year.

Points for critique

The average dose of burosumab is dependent on patient weight. The weight distribution used in the model is based on CL303 EU participants (N=47), whose mean weight is 67.2kg, which equates to an average dose of 851mg per year at a cost of [redacted]. As discussed previously, the EAG considers the participants in the EAP in England to be more representative of UK clinical practice. The mean weight of participants in the EAP ([redacted]) is 70.3kg, which equates to an average dose of 889mg per year at a cost of [redacted], which is used in the EAG's base case analysis in Section 6. The EAG also considers there to be uncertainty in the proportion of patients requiring dose reduction and the duration of dose reduction. In the model the dose reduction appears to be based on all participants in CL303, while the weight distribution is based only on EU participants. The CS does not report the dose reduction for participants in the EAP.

The EAG notes that the company's model is not sufficiently flexible to allow patient weight to vary over time within each discrete age band at which patients start treatment; for example, as patients age in the model their weight is not permitted to change over time as they leave the age band at which they started treatment. Adults with XLH tend to have multiple co-morbidities and a higher prevalence of obesity compared with the general population. Therefore, it may be expected that the weight of adults with XLH changes with age over time more than in the general population. However, age was not shown to be a statistically significant predictor of weight in CL303 participants (see company's response to EAG points for clarification, question B1).

The base case analysis assumes that 95% of patients self-administer burosumab treatment, with only 5% of patients requiring administration by a hospital nurse and only requiring 20 minutes of nurse time. The EAG considers that the administration costs for burosumab may be underestimated because

patients are likely to require an increased number of outpatient visits during the initial titration period, e.g., during the first 3 months of starting treatment. In the model, only additional treatment management costs for burosumab are included in the first year in relation to practice nurse time for taking blood samples and lab measurement of serum phosphate, but additional practice nurse time is likely to be required for administration of the costly drug (for a minimum of the first few doses) and subsequent dose reductions.

> ***item 16. The drug administration costs of burosumab may be underestimated if less than 95% of patients self-administer, patients require an increased number of outpatient visits during the initial titration period and/or greater than 20 minutes of nurse time is required for administration.***

4.2.9.3 Treatment management costs

Management costs for XLH vary by treatment in the model and are stratified by first year on treatment and subsequent years. The treatment management costs include resource use associated with practice nurse time for taking blood samples for serum phosphate measurement, lab measurement of serum phosphate, kidney ultrasonography, and clinic visit with accompanying biochemistry (see Tables 49 and 50, p151 of the CS), which were based on draft clinical practice recommendations for the UK and expert opinion. The corresponding treatment management costs for burosumab are £333.85 in the first year and £286.35 in subsequent years, while for SoC the cost is £286.35 per annum.

Points for critique

The EAG considers the treatment management costs to be reasonable but, as noted above, the EAG considers that all patients on burosumab may require an increased number of clinic visits during the initial titration period and more regular serum phosphate monitoring for assessment of response compared with SoC. However, the EAG notes that the treatment management costs are relatively small compared to the drug acquisition costs of burosumab and therefore unlikely to have a material impact on the cost-effectiveness of burosumab.

4.2.9.4 Morbidity costs associated with fractures

The morbidity costs included in the company's base case analysis are those associated with fractures. These include the proportion of management costs in different care settings by site of fracture, i.e., the percentage managed by a GP, percentage treated as a hospital day case, and percentage of hospital admissions with and without a surgical procedure (Tables 51 and 52, p153 of CS), which was based on NICE TA204 [52] and informed by Bouee et al. (2006) [60]. A weighted average of the proportion of patients treated in the different settings is used in the model to inform the resource use associated with each type of fracture.

Fractures unit costs are based on those from PSSRU 2021 [59] and 2020-2021 NHS reference costs [58]. It was assumed that, for patients managed by a GP, an hour would be required to treat a fracture. The associated PSSRU unit cost used was 'General practitioner – unit costs per hour of patient contact, with qualification costs', which was £255 [59]. All other unit fracture costs were associated with a hospital visit. For SoC, the CS states that the weighted average unit cost for fractures excludes lowest complexity and comorbidity (CC) scores in NHS reference costs because the smaller, typically fragile and deformed skeletons of XLH patients are very complex to treat or operate and slow to heal. For burosumab, the CS states that the weighted average unit cost includes all CC category scores because the remineralised bones of burosumab treated patients are expected to be thicker and stronger and similar to the general population. However, the EAG notes that in the model the unit costs of fractures by site of fracture do not differ between burosumab and SoC and matches those of SoC (i.e., excludes lowest CC category scores in NHS reference costs). Post-fracture care is included in the model as a follow-up visit with GP and physiotherapy costs (Table 54, p155 of CS).

Points for critique

The EAG considers the fracture unit costs by site of fracture to be reasonable. The EAG notes that the company did not use differential unit costs for fractures by treatment in the base case analysis, as stated in the CS. The EAG is unclear whether this inconsistency is due to an error in the implementation of costs in the model or a misrepresentation of the reporting of modelled costs in the CS. The EAG considers it appropriate to use the same unit costs for fractures for burosumab and SoC, in line with the approach used in the company's base case analysis. However, the EAG does not consider there to be sufficient justification to exclude the lowest CC category scores from the weighted average unit cost of fractures. The impact of including all CC category scores on the cost-effectiveness of burosumab is minimal, with a decrease in the total costs of burosumab and SoC and a marginal increase in the ICER (EAG scenario not shown).

The EAG also notes that the model does not include surgical procedure costs for vertebrae/spinal fractures in the base case analysis. The EAG believes that the company have excluded these costs to avoid double counting in the scenario analysis that considers other morbidities because in the scenario analysis the costs of spinal surgery is treated as a separate event; however, in the base case analysis, it means that these costs are excluded. Inclusion of these costs is unlikely to have a material impact on the ICER because the [redacted].

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

All analyses presented in the CS [redacted]. A summary of the inputs and variables used in the company's base case analysis is presented in Table 60, p160 of the CS and the assumptions used in the model are summarised in Table 61, p163 of the CS.

Table 18 shows the company's base case probabilistic and deterministic cost-effectiveness results. The probabilistic ICER for burosumab relative to SoC is [redacted], while the deterministic ICER is [redacted]. The cost effectiveness plane is presented in Figure 40, p167 of the CS.

Table 18 Company's base case results (reproduced from Tables 62 and 64 of the CS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Probabilistic							
SoC	£9,514	18.92	7.83				
Burosumab	[redacted]	19.40	[redacted]	[redacted]	0.48	[redacted]	[redacted]
Deterministic							
SoC	£9,489	18.90	7.83				
Burosumab	[redacted]	19.42	[redacted]	[redacted]	0.52	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

Points for critique

[redacted]

To aid understanding of the key drivers of the cost-effectiveness results, Table 19 and Table 20 provide a summary of the disaggregated costs and QALYs, respectively. The additional costs of burosumab compared to SoC are predominantly driven by the drug acquisition costs of burosumab, with some of this cost offset by reduced morbidity costs associated with lower rate of fractures. The QALY gain for burosumab is driven by the gains in HRQoL associated with burosumab treatment because no other active treatment option is available in this patient population in the absence of burosumab.

Table 19 Summary of the disaggregated costs in the company's deterministic base case results

Item	Cost of Burosumab (£)	Cost of SoC (£)	Incremental costs (£)	% of total incremental costs
Burosumab acquisition cost	[redacted]		[redacted]	[redacted]
Drug administration cost	£5,719	£5,413	£306	[redacted]
Morbidity cost (fracture)	£2,135	£4,076	-£1,941	[redacted]
Total	[redacted]	£9,489	[redacted]	100.0%

Abbreviations: SoC, standard of care.

Table 20 Summary of the disaggregated QALYs in the company's deterministic base case results

Item	QALYs of Burosumab	QALYs of SoC	Incremental QALYs	% of total incremental QALYs
Burosumab treatment	[redacted]	0.00	[redacted]	[redacted]
Spill over to family members	[redacted]	0.00	[redacted]	[redacted]
Morbidities and baseline XLH impact	[redacted]	7.83	[redacted]	[redacted]
Total	[redacted]	7.83	[redacted]	100.0%

Abbreviations: QALYs, quality-adjusted life years; SoC, standard of care.

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company conducted univariate deterministic sensitivity analysis (DSA) on a wide range of model inputs and plotted the twenty most influential parameters on a tornado plot (Figure 42, p170 of the CS). In the absence of confidence intervals or published ranges, upper and lower bounds tested in the DSA were calculated assuming a standard error of 0.1 (see Appendix U, CS for ranges applied). These results indicate that the most influential parameters on the ICER at a £30,000/QALY threshold is the utility values for burosumab for year 3 and beyond whilst on treatment, which increased the ICER to [redacted].

The CS reports sixteen scenario analyses with the deterministic results summarised in Table 21. The ICER is most affected when the utility impact on caregivers and family members is excluded from the base case analysis, which increases the ICER to [redacted]. Varying the degree of reduction in morbidities also affected the ICER, leading to an increase in value of [redacted].

No subgroup analyses were conducted by the company.

Table 21 Results of company's scenario analysis (reproduced from Table 68, p171 of the CS)

Parameter	Base case	Scenario	Incremental Cost (£)	Incremental QALY	ICER (£/QALY)
Base Case			[redacted]	[redacted]	[redacted]
Time horizon	Lifetime	20 years	[redacted]	[redacted]	[redacted]

Annual discount rate (costs and health outputs)	3.50%	6.0%	[redacted]	[redacted]	[redacted]
		5.0%	[redacted]	[redacted]	[redacted]
		1.50%	[redacted]	[redacted]	[redacted]
		0.0%	[redacted]	[redacted]	[redacted]
Age distribution	CL303	CL001	[redacted]	[redacted]	[redacted]
Weight distribution	CL303 EU	CL303 All patients	[redacted]	[redacted]	[redacted]
Mortality	Use Hawley at least likely, 50% reduction in mortality for patients treated with burosumab	Use Hawley at least possibly, 50% reduction in mortality for patients treated with burosumab	[redacted]	[redacted]	[redacted]
		Use Hawley at least likely, 0% reduction in mortality for patients treated with burosumab	[redacted]	[redacted]	[redacted]
Spill-over burden	On	Off	[redacted]	[redacted]	[redacted]
morbidities included in model		Include spinal stenosis, spinal surgery, dental abscess,	[redacted]	[redacted]	[redacted]
Mortality taper	On	Off	[redacted]	[redacted]	[redacted]
Morbidity taper	On	Off	[redacted]	[redacted]	[redacted]
Utility taper	On	Off	[redacted]	[redacted]	[redacted]
Treatment continuation rules	Stopping rule applied	No stopping rule	[redacted]	[redacted]	[redacted]
Degree of reduction in morbidities due to serum phosphate normalisation	100%	0%	[redacted]	[redacted]	[redacted]

Abbreviations: EU: European union; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company undertook both clinical and technical validation of the model. Expert clinical input was sought to validate the model concept, the inputs and methods used, including the model structure, the modelled assumptions, and UK-specific resource utilisation (see Appendices P and Q of the CS).

For technical validation, the CS states that a comprehensive and rigorous quality check was performed once programming was complete; a model validator not involved in the original programming

checked the calculation and reference formulas, and an additional team member checked the values of numbers supplied as model inputs.

Points for critique

The EAG considers the company's validation procedure to be reasonable. However, the EAG reviewed the company model in detail and identified three errors in total. Two errors are in the calculation of fracture rates: (i) In the "event" worksheet, fracture rate per annum for SoC is assumed to be the maximum of the rate from CL303 and the general population rate, but column R (other fractures) was not picking up the maximum value; (ii) In the "event" worksheet, fracture rate for general population was picking up the survival for SoC instead of the survival for the general population. The third error occurred in both the burosumab trace and SoC trace, where the upper limb fractures in subsequent years was picking up vertebra/spinal fractures and vice versa. The EAG corrected these errors in the company's base case analysis, which had little effect on the ICER results, decreasing the ICER by £64/QALY to [redacted] (Table 22).

Table 22 EAG corrected company base case deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Deterministic							
SoC	[redacted]	18.90	7.83				
Burosumab	[redacted]	19.42	[redacted]	[redacted]	0.52	[redacted]	[redacted]

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

A summary of the main issues identified and critiqued in Section 4, along with the scenario where the EAG addresses each issue in its additional analyses, is shown in Table 23. The EAG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where possible, the EAG explored alternative assumptions and model inputs in scenario analyses to the company's corrected base-case analysis (EAG Scenarios 1-21). The EAG's base case consists of the set of assumptions and model inputs that the EAG considers to be more appropriate for assessing the cost-effectiveness of burosumab relative to SoC. Where the EAG is unable to provide a judgement in the absence of evidence (e.g., mortality benefit associated with burosumab), the EAG have presented results of alternative scenarios to the EAG base case. Thorough descriptions of the EAG scenario analyses are presented in Section 6.1.1, while the impact on the cost-effectiveness results is presented in Section 6.2. The effect of making changes simultaneously on elements that are considered to form part of the EAG's preferred base case assumptions and alternative scenarios to the EAG base case are presented in Section 6.3.

Table 23 Summary of the main issues identified by the EAG in Section 4 and EAG scenarios

Critique item and description The EAG considers that:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		EAG Scenarios	EAG Base-case		
1	***The structural assumption associated with modelling the incidence of morbidities and mortality as independent events is uncertain.***	No	No	Yes	Unclear
2	***The larger sample of data from the CPRD GOLD and AURUM databases provides greater precision to inform the mortality for individuals with XLH.***	Sc. 4	Yes	No	No
3	***There is uncertainty regarding how treatment decisions will be made for the subgroup of adult patients who have previously experienced burosumab treatment (specifically, children receiving burosumab as they transition to adults at age 18 and patients who recommence burosumab as adults following treatment as a child) and the generalisable of the cost-effectiveness evidence to a burosumab-experienced population.***	No	No	Yes	Unclear
4	***Baseline population characteristics of age and weight, and baseline EQ-5D utility values by age, based on the CL303 trial may not match those seen in UK clinical practice and may change over time with more a burosumab-experienced population. The EAG considers the age and weight distribution of EAP participants to be more representative of patients expected to receive burosumab in NHS practice.***	Sc. 1-3	Yes	Yes	Yes
5	***There is uncertainty about whether the proposed treatment stopping criteria for burosumab would be implemented in clinical practice and the impact on long-term treatment discontinuation rates.***	Sc. 5-6	No	Yes	Unclear
6	***The assumption that achievement of serum phosphate within normal levels leads to fracture incidence rates equivalent to those in the general population (i.e., no excess risk due to XLH) has not been evidenced.***	Sc. 7-8	Yes	Yes	Yes
7	***There is no evidence to support a mortality benefit with burosumab.***	Sc. 9-11	Yes	Yes	Yes
8	***There are inconsistencies in the assumptions for the tapering effect of burosumab on morbidities and mortality. The EAG does not consider it reasonable to assume an immediate effect of treatment on the incidence of fractures, or a mortality effect two years after treatment discontinuation in the absence of evidence to support a mortality benefit.***	Sc. 12-14	Yes	Yes	No
9	***The EAG considers the WOMAC data up to week 96 from the treatment continuation period of CL303 to be the only reliable source (in the absence of data from the EAP for burosumab in England) to inform the mapped utility change from baseline for burosumab.***	Sc. 15	Yes	Yes	Yes
10	***There is uncertainty about the lifelong benefit of burosumab. After 24 weeks, only open label and single arm data for less than 3 years of treatment are available to support burosumab benefits in relation to symptoms in the long-term with continuous treatment.***	No	No	Yes	Unclear

Critique item and description The EAG considers that:		Dealt with in the EAG Scenarios	EAG Base-case	Area of remaining uncertainty	Significant impact on ICER
11	***The EAG notes a number of inconsistencies in the predicted utility estimates for burosumab reported in the company submission, which the EAG is unable to explore without access to the utility data.***	No	No	Yes	Unclear
12	***There is uncertainty about whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed in the 24-week period of CL303.***	Sc. 16-17	Yes	Yes	Yes
13	***There is uncertainty about the timing and magnitude of the waning effect on utility gain from baseline when patients discontinue burosumab treatment.***	Sc. 18	No	Yes	No
14	***There is uncertainty about the magnitude and duration of the disutilities associated with morbidities and the assumption of independent effects when multiple events can occur over a lifetime horizon.***	Sc. 19	Yes	Yes	Yes
15	***There is uncertainty about the magnitude of burosumab treatment benefit on caregivers or family members who support adults with XLH and the number of carers.***	Sc. 20-21	Yes	Yes	Yes
16	***The drug administration costs of burosumab may be underestimated if less than 95% of patients self-administer, patients require an increased number of outpatient visits during the initial titration period and/or greater than 20 minutes of nurse time is required for administration.***	No	No	Yes	Unclear

6.1.1 Issues explored by the EAG in additional analyses

6.1.1.1 Scenarios 1-3: Age and weight distribution of adults with XLH

As discussed in Section 4.2.3, the EAG considers participants receiving burosumab in the EAP in England to be more representative of the adult population with XLH in UK clinical practice than the CL303 trial population, which includes [redacted] as of April 2023. The population of CL303 is younger than the EAP, with 76% of trial participants below the age of 50 years compared to 58% in the EAP. The weight distribution of EU participants from CL303, which is used in the company's base case analysis, is lighter than the EAP (and including all participants in CL303), with only 28% of trial participants weighing above 75kg compared to 40% in the EAP.

Scenario 1 first assesses the cost-effectiveness of burosumab relative to SoC using the weight distribution from all participants in CL303 rather than the weight distribution from EU participants only. This is to ensure consistency with the age distribution used in the company's base case analysis, which is based on all CL303 participants. Scenario 2 assesses the implications on the cost-effectiveness of burosumab relative to SoC when the weight distribution is changed to that of participants in the EAP. Finally, Scenario 3 assesses the cost-effectiveness of burosumab relative to SoC using both the age and weight distribution of the EAP population, which the EAG considers to be representative of the adult population with XLH in UK clinical practice.

6.1.1.2 Scenario 4: Mortality for adults with XLH

As discussed in Section 4.2.2.2, the EAG considers the larger sample of data from the CPRD GOLD and AURUM databases to provide greater precision for the estimation of mortality in individuals with XLH. The company's base case uses the hazard ratio of 2.88 (95% CI, 1.18 to 7.00) from Hawley et al. to derive the excess mortality risk due to XLH compared to the general population hazard of death. However, a study based on extending Hawley et al. by applying the same XLH grading algorithm to patients from both the CPRD GOLD and the larger database of CPRD AURUM, linked to secondary care HES and ONS mortality (and IMD) data resulted in a HR of 2.33 (95% CI, 1.16 to 4.67), which is approximately a 30% lower risk than the HR of 2.88 from Hawley et al. The company states that this study represents a larger, more robust validation of the findings by Hawley et al. due to over 91% of XLH patients being identified from the larger CPRD AURUM database, while also capturing more death events with greater precision. Therefore, the EAG considers it more appropriate to use the larger database and more recent data, with data from CPRD GOLD available from 1995 to June 2022 and CPRD AURUM from 1995 to January 2022.

Scenario 4 assesses the cost-effectiveness of burosumab relative to SoC when the excess mortality risk in adults with XLH is based on a HR of 2.33 compared to the general population hazard of death.

6.1.1.3 Scenarios 5-6: Treatment stopping criteria for burosumab and alternative discontinuation rates

As discussed in Section 4.2.6.1, continuation of treatment in the model is based on a requirement of reaching serum phosphate levels above LLN at 24 weeks and an improvement in WOMAC total score at 12 months after starting treatment, while an annual treatment discontinuation rate of 3% is used in years 2 onwards. The EAG considers the first criteria on reaching serum phosphate levels above LLN to be appropriate, but questions whether the second hurdle of requiring improvements in WOMAC is necessary and appropriate given the absence of alternative treatments for this patient population, the fact that WOMAC is not commonly used in UK clinical practice, and there may be other benefits to treatment with burosumab such as a reduction in opioid use. The EAG notes that no stopping criteria were applied in either the CL303 trial or the EAP in England.

The proposed stopping criteria for treatment affects the proportion of patients who remain on treatment at the end of year one and the utility values for patients treated with burosumab after the first year. Scenario 5 assesses the implications on the cost-effectiveness of burosumab relative to SoC when no stopping criteria are included (note that the model was not sufficiently flexible to permit the first criteria on reaching serum phosphate levels, whilst switching off the second criteria on WOMAC improvements).

The annual discontinuation rate of 3% from year 2 onwards is informed by the EAP, where no stopping criteria is applied. The EAG believes that this rate is likely to be reflecting initial loss of efficacy with burosumab, which is already captured in the company's proposed stopping criteria in year 1. The EAG considers a Scenario 6 where the discontinuation rate is 7.35% in the first year based on CL303 (without stopping criteria) and no discontinuation from year 2 onwards.

6.1.1.4 Scenarios 7-8: Burosumab reduction in fracture incidence rates

As discussed in Section 4.2.6.2, the EAG considers there to be considerable uncertainty about the reduction in excess risk of incident fractures with burosumab treatment. The company assumes a 100% reduction in fracture incident rates to those equivalent to the general population. Whilst the EAG believes that it may be clinically plausible that burosumab would lead to a reduction in fractures with improvement in serum phosphate within normal levels the assumption of a 100% reduction is likely to overestimate the effect of burosumab.

Scenarios 7 and 8 assess the cost-effectiveness of burosumab relative to SoC when a 75% and 50% reduction in the incidence of fractures is assumed, respectively.

6.1.1.5 Scenarios 9-11: Burosumab effect on mortality

As discussed in Section 4.2.6.3, no mortality benefit for burosumab was observed within CL303 or BUR02. However, the company anticipates that by normalising phosphate homeostasis and mitigating

the multi-system effects of hypophosphataemia, treatment with burosumab will reduce mortality. The company's base case assumes a 50% reduction in the excess XLH mortality risk with burosumab. The EAG considers that without any evidence of the effects of burosumab on mortality, it is speculative that a mortality benefit exists and the magnitude of any potential benefit is completely uncertain.

Scenario 9 assesses the implications for the cost-effectiveness of burosumab relative to SoC when no mortality benefit is assumed. Scenario 10 assesses the implications when an 11% reduction in mortality is assumed for burosumab relative to SoC, based on evidence from a meta-analysis of the effect of treatments for osteoporosis on fracture-related mortality risk, while Scenario 11 considers the implications of assuming a 25% reduction in excess XLH mortality risk to account for additional multi-system effects other than fractures.

6.1.1.6 Scenarios 12-14: Tapering effect of burosumab on morbidities and mortality

As discussed in Section 4.2.6.4, the EAG noted inconsistencies between the tapering effect of burosumab on mortality and morbidities, with an ongoing benefit on mortality two years after treatment discontinuation whilst no ongoing benefit on the incidence of fractures after treatment discontinuation, and an immediate effect of treatment on fractures (100% reduction in incidence rates) whilst the effect on mortality is 75% in the first year. The EAG considers it more reasonable to have consistency in the tapering effect on morbidities and mortality, in the absence of evidence of the contrary. However, the EAG also notes that no evidence has been presented to support a treatment tapering effect.

Scenarios 12 and 13 assess the implications for the cost-effectiveness of burosumab relative to SoC when no tapering effects are applied on morbidity and mortality, respectively. Scenario 14 assesses the implications when the same tapering effect on mortality and morbidity is assumed, i.e., 75% effect in year 1 on treatment, 100% effect in year 2+ on treatment, 50% effect in year 1 after end of treatment and 0% from year 2 and beyond after end of treatment.

6.1.1.7 Scenario 15: Burosumab utility change from baseline based on WOMAC data up to week 96 from the treatment continuation period of CL303

As discussed in Section 4.2.8.3 the EAG has a key concern that after 24 weeks, only open label and single arm data for less than 3 years of treatment are available to support burosumab benefits in relation to symptoms in the long-term with continuous treatment. The lack of comparative data after 24 weeks is a concern in itself, but the EAG's major concern is that the data informing the change from baseline in WOMAC scores for burosumab after week 96, which marks the end of the treatment continuation period of CL303, is based on different patient populations that differ in terms of baseline characteristics and WOMAC scores. The EAG has reason to believe that the use of WOMAC scores post-week 96 is affecting outcomes because there is a noticeable spike in the change from baseline in

mapped utility values from week 96 to week 120 when only data from US participants in CL303 are included. After week 120, the data also becomes increasingly uncertain due to the very low number of observations providing data in subsequent periods (only a total of 10 participants). The company's asymptotic model fit that is used to extrapolate the utility benefit of burosumab beyond the observed periods appears to be heavily influenced by the post-week 96 data. The EAG considers the data up to week 96 from the treatment continuation period of CL303 to be the only reliable source (in the absence of data from the EAP for burosumab in England) to inform the asymptotic model fit to WOMAC mapped utility change from baseline.

In Scenario 15, the EAG assesses the implications for the cost-effectiveness of burosumab relative to SoC when post-week 96 data are excluded from the asymptotic model fit to WOMAC mapped utility change from baseline. The corresponding utility value used in Scenario 15 is 0.2 in year 2 onwards, while the company's base case value is 0.211 in year 2 and 0.215 in year 3 onwards.

6.1.1.8 Scenarios 16-18: Placebo-adjusted utility values and tapering effect on utility

As discussed in Section 4.2.8.3, there is uncertainty about whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed in the 24-week period of CL303, where the WOMAC mapped utility change from baseline in the placebo arm corresponds to an improvement in utility of approximately 0.03. The company uses the non-placebo-adjusted utility values in their base case analysis. Scenario 16 assesses the implications for the cost-effectiveness of burosumab relative to SoC when the utility gain for burosumab compared to baseline utility is placebo-adjusted. The utility values for patients treated with burosumab from year 2 onwards is also affected by the proposed stopping criteria used in the company's base case analysis. Therefore, Scenario 17 assesses the implications for the cost-effectiveness of burosumab when no stopping criteria are applied (Scenario 5) and the utility values are placebo-adjusted.

The company's base case also assumes a waning effect on utility gain of 50% for a period of one year after treatment discontinuation. In the absence of evidence to inform the timing and magnitude of the waning effect on utility gain, Scenario 18 assesses the implications for the cost-effectiveness of burosumab when the utility waning effect is switched off, i.e., patients return to their baseline utility level immediately after discontinuing burosumab treatment.

6.1.1.9 Scenario 19: Disutility for incident fractures for first year only

As discussed in Section 4.2.8.4, there is uncertainty about the magnitude and duration of the disutility associated with incident fractures and the assumption of independent effects when multiple events may occur over a lifetime horizon. These disutilities are applied in addition to the treatment-specific utilities, which may represent some double counting of morbidity effects because the treatment-specific utility values based on WOMAC scores are extrapolated over a lifetime.

Scenario 19 assesses the implications for the cost-effectiveness of burosumab relative to SoC when the disutility for incident fractures is applied in the first year of the event only.

6.1.1.10 Scenarios 20-21: Utility benefit on caregivers and family members

As discussed in Section 4.2.8.5, there is uncertainty about the magnitude of burosumab treatment benefit on caregivers and family members who support adults with XLH and the number of caregivers/family members affected. The company's base case assumes a spillover benefit on caregivers and family members equal to 20% of the patient utility benefit of burosumab and applied to two caregivers/family members. The EAG has a concern that the spillover effect may be overestimated by including an effect on two informal caregivers and family members rather than one for adults with XLH, where two may be reasonable for a child but less so for an adult, particularly noting that burosumab is administered (mainly self-administration) in a way that supports patients to be independent and less likely to impose additional burden on family members. The EAG also notes that there is no evidence to support a 20% patient utility benefit on caregivers and family members; in the company's HRQoL research study that was used to compare EQ-5D utility values of informal carers and family members of adults with XLH with age-matched general population utility values, only a small loss in utility was identified (0.081), when carers with XLH themselves were excluded from the analysis.

In Scenario 20, the EAG assesses the implications for the cost-effectiveness of burosumab relative to SoC when the utility benefit is included for one caregiver/family member only (equal to 20% of the patient utility benefit), while Scenario 21 assesses the implications when no utility benefit on caregivers/family members is included in the analysis.

6.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

Table 24 shows the results of the EAG scenarios. The EAG scenarios with the largest impact on the company's base case ICER are: (i) Scenarios 21 and 20 with no utility benefit included for caregivers and family members (ICER change from company's base case = [redacted]) and utility benefit for one caregiver/family member only (ICER change = [redacted]), respectively; (ii) Scenarios 16 and 17 with placebo-adjusted utility values (ICER change = [redacted] and [redacted] with and without stopping criteria, respectively); (iii) Scenario 19 with disutility for incident fractures included for one year only (ICER change = [redacted]); (iv) Scenarios 8 and 7 with a 50% and 75% reduction in the incidence of fractures (ICER change = [redacted] and [redacted], respectively); (v) Scenario 15 with burosumab's utility change from baseline based on extrapolating WOMAC data up to week 96 from CL303 (ICER change = [redacted]); (vi) Scenarios 9, 10 and 11 with 0%, 11% and 25% reduction in excess XLH mortality with burosumab (ICER change = [redacted], [redacted], and [redacted], respectively); (vii) Scenarios 2

and 3 with age and weight distribution based on participants in the EAP (ICER change = [redacted] for age and weight distribution and [redacted] for weight distribution only); (viii) Scenario 1 with weight distribution based on all participants in CL303 for consistency with the age distribution used in the company's base case (ICER change = [redacted]); and (ix) Scenario 5 with no stopping criteria applied (ICER change = [redacted]).

The scenarios with a smaller relative impact compared to the ones listed above are those related to: (i) treatment tapering effect, where the ICER changes from the company's base case by [redacted] for no utility tapering (Scenario 18), [redacted] for the same tapering effect on morbidity and mortality (Scenario 14), [redacted] for no tapering effect on morbidity (Scenario 12) and [redacted] for no tapering effect on mortality (Scenario 13); (ii) Scenario 4 with excess XLH mortality risk based on the larger CPRD AURUM database (ICER change = [redacted]); and (iii) Scenario 6 with burosumab's discontinuation rate reduced to 7.35% in the first year and no discontinuation from year 2 onwards (ICER falls by [redacted] because when the stopping criteria are removed in the first year, a lower discontinuation rate results in proportionally greater QALY benefits).

Table 24 Cost-effectiveness results of the EAG scenario analyses

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's corrected base-case results	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
1	Weight distribution of CL303 All	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
2	Weight distribution of EAP	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
3	Age and weight distribution of EAP	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,504	6.86	-	-	-
4	Excess mortality risk due to XLH (HR = 2.33 vs. general population)	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,808	8.06	-	-	-
5	No treatment stopping criteria	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
6	Annual treatment discontinuation rate of 7.35% in first year and no discontinuation from year 2 and beyond	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
7	75% reduction in the incidence of fractures with burosumab	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
8	50% reduction in the incidence of fractures with burosumab	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
9	No reduction in mortality with burosumab	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
10	11% reduction in mortality with burosumab (mortality relative risk = 0.89)	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
11	25% reduction in mortality with burosumab	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		SoC	£9,493	7.83	-	-	-
12	No treatment tapering effect on morbidity	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
13	No treatment tapering effect on mortality	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
14	Same tapering effect on mortality and morbidity (75% in year 1 on treatment, 100% in year 2+ on treatment, 50% in year 1 after end of treatment and 0% from year 2+ after end of treatment)	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
15	Burosumab utility change from baseline based on extrapolating WOMAC data up to week 96 from CL303	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
16	Placebo-adjusted utility values	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
17	No treatment stopping criteria with placebo-adjusted utility values	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
18	No treatment tapering effect on utility	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
19	Disutility associated with incident fractures for the first year only	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
20	Utility benefit for 1 caregiver/family member only	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
21	No utility benefit on caregivers/family members	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-

6.3 EAG's preferred assumptions

The EAG's preferred assumptions include the following changes from the company's base case:

- Age and weight distribution of participants in burosumab's EAP, which the EAG considers to be more representative of the adult population with XLH in UK clinical practice than the CL303 population – Scenario 3;
- Excess mortality risk due to XLH based on the larger CPRD AURUM database with a HR of 2.33 (95% CI, 1.16 to 4.67) compared to the general population, which is approximately a 30% lower risk than the HR of 2.88 from Hawley et al. – Scenario 4;
- Same tapering effect on mortality and morbidity (75% in year 1 on treatment, 100% in year 2+ on treatment, 50% in year 1 after treatment discontinuation and 0% from year 2+ after treatment discontinuation) – Scenario 14;
- Burosumab utility change from baseline based on extrapolating WOMAC data up to week 96 from CL303, i.e., excluding post-week 96 data from BUR02 – Scenario 15;
- Utility benefit for 1 caregiver/family member only – Scenario 20.

Table 25 shows the cumulative impact of the EAG's preferred assumptions on the ICER.

The selection of changes made to the EAG base case is based on the available evidence; however, a number of important uncertainties remain. To address the remaining uncertainties, the EAG presents a number of scenarios on the EAG base case. These include alternative assumptions to the company's base case relating to:

- A reduction in the incidence of fractures with burosumab of 75% in Scenario 7 and 50% in Scenario 8, compared to the company's assumption of 100% reduction equal to that of the general population;
- Mortality benefit associated with burosumab of 0% in Scenarios 9 (no evidence is available to support a mortality benefit), 11% in Scenario 10 (based on evidence of the effect of treatments for osteoporosis on fracture-related mortality risk), and 25% in Scenario 11 (to account for additional multi-system effects other than fractures), compared to the company's assumption of 50%;
- Utility benefits for burosumab based on adjusting the utility change from baseline for the placebo effect observed in CL303 in Scenario 16 and applying a disutility for incident fractures in the first year of the event only in Scenario 19, compared to the company's assumption of non-placebo-adjusted utility values and lifetime disutility associated with each fracture event.

Table 26 shows the impact of the alternative assumptions on the EAG base case. The uncertainty in the morbidity benefit of burosumab on reduction in incidence of fractures means that the EAG base case ICER could increase by [redacted] for a 75% reduction, or [redacted] for a 50% reduction, compared to the most optimistic value of 100% reduction included in the EAG base case in the absence of evidence to inform this reduction. The uncertainty in the mortality benefit associated with burosumab means that the EAG base case ICER could increase by [redacted] for a 25% reduction in excess XLH mortality risk, [redacted] for a 11% reduction, or [redacted] for no excess mortality reduction, compared to the more optimistic value of 50% reduction in excess mortality risk used in the EAG base case, in line with the company's base case in the absence of evidence to inform this risk. The uncertainty in the utility benefits for burosumab means that the EAG base case ICER could increase by a further [redacted] if placebo-adjusted utility values are used in the model and the disutility associated with incident fractures occurs in the first year of the event only.

Table 25 Cumulative cost-effectiveness results for the EAG's preferred assumptions

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's corrected base-case results	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£9,493	7.83	-	-	-
3	Age and weight distribution from the EAP	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,504	6.86	-	-	-
3+4	+ Excess XLH mortality risk	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
3+4+14	+ Same tapering effect on mortality and morbidity	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
3+4+14+15	+ Utility data up to week 96 extrapolated	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
3+4+14+15 +20	+ Utility benefit for 1 caregiver/family member only	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-

Table 26 Cost-effectiveness results for alternative assumptions on the EAG's base case

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	EAG base case (3+4+14+15+20)	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
Morbidity benefit with burosumab (100% reduction in the incidence of fractures in base case)							
7	75% reduction in the incidence of fractures	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
8	50% reduction in the incidence of fractures	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
Mortality benefit with burosumab (50% reduction in mortality in the base case)							
9	No reduction in mortality	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
10	11% reduction in mortality	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
11	25% reduction in mortality	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-
Utility benefit with burosumab (non-placebo-adjusted utility values and disutility for incident fractures in subsequent years in the base case)							
16+19	Placebo-adjusted utility values + disutility for incident fractures in first year only	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		SoC	£8,841	7.10	-	-	-

6.4 Conclusions of the cost effectiveness section

The company submitted a decision model to assess the cost-effectiveness of burosumab for the treatment of adults (≥18 years of age) with a diagnosis of XLH compared to SoC (defined as symptomatic treatment of morbidities only). The patient population aligns with the population in the pivotal CL303 trial, where participants were required to have a worst pain score over the last 7 days of ≥4 on the BPI and for whom conventional therapy is unsuitable due to ineligibility, intolerance or insufficient efficacy (i.e. failure to normalise phosphate levels, or persistence of symptoms despite treatment), which is a subgroup of the licensed indication in adults for the full population with XLH. However, the EAG has two key uncertainties in relation to the patient population included in the cost-effectiveness assessment. The first is that there is likely to be a proportion of adults who will continue to take conventional therapy intermittently over time, which creates uncertainty about the size of the eligible adult population who may receive burosumab in the NHS and the precise definition of treatment failure with conventional therapy for burosumab to be considered as an alternative treatment option. The second key concern relates to how treatment decisions will be made for the subgroup of adult patients who have previously experienced burosumab treatment (specifically, children receiving burosumab as they transition to adults at age 18 and patients who recommence burosumab as adults following treatment as a child) and the generalisable of the cost-effectiveness evidence to a burosumab-experienced population. The EAG also considers that the baseline population characteristics of age and weight, and baseline EQ-5D utility values by age, based on the CL303 trial may not match those seen in UK clinical practice and may change over time with more a burosumab-experienced population. The EAG considers participants enrolled in burosumab's EAP to be more representative of patients expected to receive burosumab in NHS practice.

The model structure used to assess cost-effectiveness is broadly representative of XLH disease characteristics in adults, where treatment with burosumab is expected to improve serum phosphate levels and bone mineralisation and lead to modifiable aspects of impaired skeletal health and provide HRQoL improvements through improved physical functioning and reduction in pain and stiffness. However, the impact of treatment on mortality is not known. The company assumes that by addressing the root cause of XLH and mitigating the multi-system effects of hypophosphataemia that may drive increased mortality, treatment with burosumab will reduce the excess mortality risk due to XLH by 50%. Without evidence to support the effects of burosumab on mortality, there remains uncertainty about the magnitude of the mortality benefit. The company's model does not incorporate a structural link between fractures and mortality, therefore, it has not been possible to explicitly translate the improvements in serum phosphate levels and fracture-related events into effects on fracture-related mortality. The evidence for the effect of treatments for osteoporosis on fracture-related mortality suggests that the mortality benefit is likely to be much lower in magnitude than that

used in the company's model. Without evidence to support a mortality benefit it is also speculative that interventions that reduce fractures will affect mortality in this patient population. This remains a key uncertainty for the cost-effectiveness of burosumab.

The reduction in the incidence of fracture events is captured directly through the use of lower fracture rates for burosumab-treated patients (rates equal to those of the general population for patients with normalised serum phosphate levels), while resolution of existing fractures is captured through quality of life improvements observed in the pivotal trial CL303 and extension study BUR02. The company's assumption of 100% reduction in the excess risk of fractures due to XLH to rates equivalent to that of the general population is not adequately supported. Six new fractures were reported in the burosumab arm within weeks 0-24 and one new fracture within weeks 24-36 of CL303. The EMA also indicated that normalisation of the bone may take months or even years to heal, which could contribute to a continued incidence of new fractures despite burosumab treatment. Furthermore, the clinical significance of reduced incidence of fractures is unclear because correlation with outcomes from the pivotal trial or those important to patients (e.g., symptomatic burden of pain) has not been presented. The EAG notes that the exploratory outcomes in CL303 show only a trend towards greater healing of active fractures or pseudofractures with burosumab compared with placebo and no evidence is available to support a reduction in the incidence of new fractures.

Continuation of treatment in the model is based on a requirement of reaching serum phosphate levels above LLN at 24 weeks and an improvement in WOMAC total score at 12 months after starting treatment. The EAG considers that the first criteria on reaching normalised serum phosphate levels to be appropriate, but considers the second hurdle of requiring improvements in WOMAC to be potentially unnecessary due to the absence of alternative treatments for this patient population, the fact that WOMAC is not commonly used in UK clinical practice, and other treatment benefits such as a reduction in opioid use may mean that patients remain on treatment long-term.

The health-related quality of life benefits associated with burosumab are highly uncertain. The effect of burosumab on utility is based on mapping data on WOMAC change from baseline to EQ-5D from CL303 and BUR02 and extrapolating the effect over time. The use of open label, single arm data for less than 3 years of treatment to support the benefits of burosumab in relation to symptoms in the long-term with continuous treatment is uncertain. The EAG is concerned that the extrapolation of utility values into the long-term is heavily influenced by post-week 96 data from BUR02, which is much more uncertain based on low patient numbers (and from different patient populations) than the pre-week 96 data from CL303. The company did not adjust the burosumab utility values for the placebo effect observed in the 24-week period of CL303, which has a large impact on the cost-effectiveness results because any small changes in the utility values are extrapolated over a long

period of time. The utility values for patients treated with burosumab from year 2 onwards is also affected by the company's proposed stopping criteria in year 1.

There is uncertainty about the magnitude of burosumab benefit on caregivers and family members who support adults with XLH and the number of caregivers. The company assumes a spillover benefit on caregivers/family members equal to 20% of the patient utility benefit of burosumab and applied to two caregivers/family members. The EAG considers that this spillover effect is likely to be overestimated given that burosumab is administered in a way that supports patients to be independent and less likely to impose additional burden on family members.

The modelled assumptions with the largest impact on the ICER are those relating to: (i) utility benefit of burosumab on caregivers/family members (ICER increases from [redacted] to [redacted] for no benefit and to [redacted] for one caregiver/family member only); (ii) placebo-adjusted utility values (ICER increases from [redacted] to [redacted] with stopping criteria and to [redacted] without stopping criteria); (iii) disutility for incident fractures included for one year only (ICER increases from [redacted] to [redacted]); (iv) percentage reduction in the incidence of fractures (ICER increases from [redacted] to [redacted] and [redacted] for 50% and 75%, respectively); (v) utility change from baseline based on extrapolating WOMAC data up to week 96 of CL303 (ICER increases from [redacted] to [redacted]); (vi) percentage reduction in excess XLH mortality risk with burosumab (ICER increases from [redacted] to [redacted], [redacted] and [redacted] for 0%, 11% and 25%, respectively); (vii) age and weight distribution based on participants in the EAP (ICER increases from [redacted] to [redacted]); and (vii) no stopping criteria applied in the first year (ICER increases from [redacted] to [redacted]).

The EAG's preferred assumptions include the following changes from the company's base case: (i) age and weight distribution of participants in burosumab's EAP; (ii) excess mortality risk due to XLH based on CPRD AURUM database with a HR of 2.33 (95% CI, 1.16 to 4.67) compared to the general population; (iii) same tapering effect on mortality and morbidity; (iv) burosumab's utility change from baseline based on extrapolating WOMAC data up to week 96 from CL303; and (v) utility benefit for one caregiver/family member only. The resulting ICER increases from [redacted] to [redacted] However, a number of important uncertainties remain relating to: (i) percentage reduction in the incidence of fractures with burosumab; (ii) mortality benefit associated with burosumab; and (iii) utility benefits for burosumab based on adjusting the utility change from baseline for the placebo effect observed in CL303 and applying a disutility for incident fractures in the first year of the event only compared to the company's assumption of non-placebo-adjusted utility values and disutility associated with each new fracture event accrued cumulatively, all of which would further increase the EAG's base case ICER.

7 SEVERITY MODIFIER

The CS states that with undiscounted QALYs, XLH patients meet the absolute shortfall criteria for a 1.7 severity weighting, while with discounting patients reaching adulthood may meet the criteria for a 1.2 severity weighting depending on the data source used to estimate general population utilities. Therefore, the company believes that severity of XLH should be taken into account.

For the comparison of QALYs on SoC with those of the general population, two alternative sources were used to estimate QALYs in the general population: (i) the web-based QALY shortfall calculator provided by Schneider et al., (2021) [61] using the reference case settings (https://shiny.york.ac.uk/shortfall/); and (ii) general population utilities informed by the equation provided in Ara and Brazier (2010) [62] applied to mortality from ONS national life tables for 2017-19. Two starting ages of 18 and 40 years are considered in the CS and the gender distribution is based on 65% females from CL303.

Table 57 of the CS provides a summary of the QALY shortfall analysis without discounting, while Table 27 below provides a summary with discounting at 3.5% per annum. When discounting is applied, XLH patients age 18 years meet the NICE absolute QALY shortfall criteria for a 1.2 multiplier with general population utilities informed by Ara and Brazier (2010) [62], but when the alternative source based on the reference case settings in the QALY shortfall calculator are used (Alava et al., 2022 [63]) the shortfall criteria are not met. At the average age of participants enrolled in CL303, i.e., 40 years, the shortfall criteria for severity weighting does not hold.

Table 27 Company's QALY shortfall analysis with discounting (reproduced from Table 58 of CS)

Start age	Calculation	Expected total QALYs for the general population	Total QALYs patients with XLH	Absolute QALY shortfall	Proport-ional QALY shortfall	QALY severity weight
18	Alava et al., 2022	22.92	10.99	11.93	0.52	x1.0
	Ara&Brazier 2010	23.47	11.02	**12.46**	0.53	**x1.2**
40	Alava et al., 2022	18.63	7.94	10.70	0.57	x1.0
	Ara&Brazier 2010	19.28	7.98	11.31	059	x1.0

Points for critique

The EAG notes that the NICE health technology evaluations manual states that absolute and proportional shortfall calculations should include discounting at the reference case rate. Therefore, the EAG considers the discounted QALYs to be the only appropriate analysis to consider a QALY

severity weight. Under the company's discounted QALY shortfall analysis, the absolute QALY shortfall criteria is only met for XLH patients age 18 years and using general population utility values from Ara and Brazier (2010) [62]. The EAG notes that the decision problem addressed in the CS is for all adults (aged ≥18 years) with a confirmed diagnosis of XLH and is not a subpopulation aged 18 years only (or average age 18 years), which is addressed in the company's shortfall analysis. The cost-effectiveness results presented in the CS takes account of the distribution of ages at which patients may start treatment, which is based on the distribution of participant ages in CL303 (see Figure 15 in Section 4.2.3). Therefore, the EAG considers it only appropriate to also consider the distribution of ages in the QALY shortfall analysis. Table 28 and Table 29 show EAG additional analyses for the QALY shortfall for the distribution of ages in CL303 using the company's base case assumptions for general population utility values informed by Alava et al., (2022) [63] and Ara and Brazier (2010) [62], respectively. Using the reference case settings (Alava et al., 2022) [63] in the QALY shortfall calculator for the expected total QALYs in the general population and the total QALYs for XLH patients from the SoC arm of the model, the QALY shortfall criteria are not met at any starting age (Table 28). When the alternative (historic) source of utility values for the general population (Ara and Brazier, 2010) [62] are used, the absolute QALY shortfall criteria are only met for starting ages below 27 years, which accounts for 26% of the CL303 population (Table 29).

In Section 6.3, the EAG presents their preferred set of assumptions that differ from the company's base case assumptions. Amongst these, the EAG indicates a preference for the age distribution of participants in burosumab's EAP in England to be more representative of the adult population with XLH who would be treated with burosumab in the NHS than the CL303 population, and an excess mortality risk due to XLH for SoC based on the CPRD AURUM database with a HR of 2.33 (95% CI, 1.16 to 4.67) compared to the general population than the HR of 2.88 from Hawley et al. These two EAG alternative assumptions have implications for the total QALYs for XLH patients on SoC and, therefore, impact the QALY shortfall analysis. Table 30 shows EAG additional analyses for the QALY shortfall for the distribution of ages in EAP using the EAG's base case assumptions for general population utility values informed by Ara and Brazier (2010) [62]. The absolute QALY shortfall criteria are only met for starting ages between 18 and 24 years (mid-point 21 years in Table 30), which accounts for 7% of the EAP population, and using the older source of utility values for the general population estimates of Ara and Brazier (2010) [62]. The EAG notes that the QALY shortfall criteria are not met for any starting age using the reference case settings in the QALY shortfall calculator of Schneider et al., (2021) [61]. The EAG concludes that the most appropriate QALY weight for severity is 1.0.

Table 28 QALY shortfall analysis using the company's base case assumptions for general population utility values informed by Alava et al., (2022) for a range of starting ages based on age distribution in CL303

Start age	Proportion in CL303	Expected total QALYs for the general population	Total QALYs patients with XLH	Absolute QALY shortfall	Proportional QALY shortfall	QALY severity weight
21	13%	22.50	10.62	11.881	0.53	x1.0
27	13%	21.47	9.84	11.635	0.54	x1.0
32	11%	20.49	9.14	11.354	0.55	x1.0
37	9%	19.39	8.40	10.992	0.57	x1.0
42	17%	18.16	7.62	10.537	0.58	x1.0
47	13%	16.82	6.82	10.002	0.59	x1.0
52	9%	15.35	5.99	9.359	0.61	x1.0
57	6%	13.75	5.14	8.610	0.63	x1.0
62	7%	12.06	4.29	7.771	0.64	x1.0
67	2%	10.28	3.46	6.816	0.66	x1.0

Table 29 QALY shortfall analysis using the company's base case assumptions for general population utility values informed by Ara and Brazier (2010) for a range of starting ages based on age distribution in CL303

Start age	Proportion in CL303	Expected total QALYs for the general population	Total QALYs patients with XLH	Absolute QALY shortfall	Proportional QALY shortfall	QALY severity weight
21	13%	23.006	10.619	**12.387**	0.54	**x1.2**
27	13%	21.949	9.835	**12.114**	0.55	**x1.2**
32	11%	20.946	9.136	11.809	0.56	x1.0
37	9%	19.820	8.398	11.422	0.58	x1.0
42	17%	18.729	7.623	11.106	0.59	x1.0
47	13%	17.345	6.818	10.527	0.61	x1.0
52	9%	15.794	5.991	9.803	0.62	x1.0
57	6%	14.331	5.140	9.191	0.64	x1.0
62	7%	12.427	4.289	8.138	0.65	x1.0
67	2%	10.660	3.464	7.196	0.68	x1.0

Table 30 QALY shortfall analysis using the EAG base case assumptions for general population utility values informed by Ara and Brazier (2010) for a range of starting ages based on age distribution in EAP

Start age	**Proportion in EAP**	**Expected total QALYs for the general population**	**Total QALYs patients with XLH**	**Absolute QALY shortfall**	**Proportional QALY shortfall**	**QALY severity weight**
21	7%	23.006	10.773	**12.234**	0.53	**x1.2**
27	7%	21.949	10.013	11.936	0.54	x1.0
32	10%	20.946	9.336	11.609	0.55	x1.0
37	11%	19.820	8.620	11.200	0.57	x1.0
42	11%	18.729	7.866	10.863	0.58	x1.0
47	12%	17.345	7.080	10.265	0.59	x1.0
52	14%	15.794	6.266	9.528	0.60	x1.0
57	6%	14.331	5.423	8.908	0.62	x1.0
62	11%	12.427	4.571	7.856	0.63	x1.0
67	7%	10.660	3.733	6.927	0.65	x1.0
72	3%	8.744	2.908	5.837	0.67	x1.0
77	1%	7.130	2.142	4.989	0.70	x1.0
82	1%	5.446	1.481	3.965	0.73	x1.0
87	1%	3.693	0.959	2.734	0.74	x1.0

8 REFERENCES

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APPENDICES

APPENDIX 1

This appendix presents a descriptive summary of WOMAC, BPI and BFI scales and a critique of the company's evidence for their reliability and validity in adult XLH presented in the CS.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC is a self-administered questionnaire widely used in the evaluation of hip and knee osteoarthritis. It has a recall period of 48 hours, and consists of 24 items, divided into 3 subscales: Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright; Stiffness (2 items): after first waking and later in the day; and Physical Function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties. Questions are scored on a scale of 0-4, corresponding to: None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4). Scores for each subscale are summed up, with a possible range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function. A total WOMAC score can be derived from the sum of the scores of all three subscales.

Brief Pain Inventory Short Questionnaire (BPI-SF)

The BPI-SF is a self-reported, short pain-specific questionnaire. It was initially developed to assess pain severity in cancer patients. The BPI evaluates the condition of all pain over the past 24 hours. It consists of 15 items, and measures two dimensions: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). In the CL303 trial, two questions from the BPI-SF about the use of pain medications and relief from pain medications were not administered, although use of pain medications were captured separately. Pain location (item 2) was also not captured. Worst pain score of 1-4 indicates mild pain, 5-6 indicates moderate pain, and 7-10 severe pain.

Although the BPI is designed to evaluate all pain, rather than pain specific to XLH, the source of the pain was accounted for by the investigator at screening, and the patients with absence of any skeletal pain likely attributed to XLH/osteomalacia were not considered for eligibility. Unlike at screening, it does not appear that the source of the pain was accounted for at baseline and follow-up measurements.

BFI

The BFI is a self-reported questionnaire with 9 items related to fatigue over the last 24 hours. Originally designed for assessing the severity of fatigue experienced by cancer patients due to their

condition and treatment, the questionnaire includes two dimensions: fatigue severity, and the interference of fatigue on daily life (activity, mood, walking ability, work, relations with others, and enjoyment of life). BFI Global Fatigue score is calculated by averaging scores from the 9 items. Global scores range from 0 to 10, with higher score indicating worse fatigue severity and interference.

Validation studies of patient reported outcomes

The company submission stated that all three scales are validated for use in XLH, and minimal clinically important differences (MCID) in XLH-specific change were presented in Document B, Table 13. The company referenced three studies to support this statement, including two conference abstracts and one conference poster.[30-32] A summary of their results is presented in Table 31.

The WOMAC, BPI-SF and BFI were not designed to measure outcomes in adults with XLH. Given that these scales inform the results of CL303, the decision to formally validate these scales for this population was appropriate. However, the results from the validation studies were presented after the protocol for CL303 was registered, and were co-authored by employees of Kyowa Kirin and Ultragenyx. The fact that the results of these studies were only presented as conference abstracts or posters means that the reporting of their methods and results is very limited, making their evaluation difficult. The validation of the three PROs scales were derived from the CL303 trial population, which differ from the UK EAP population (see Section 3.2.3). Reported results suggested there was moderate to strong convergent validity (correlation of scale scores with scores on assessments that are conceptually linked) between scales. To some extent, this is not surprising given the overlap between a number of items across scales (e.g. WOMAC and BPI Pain items) although PBI-SF and BFI were weakly correlated with the 6MWT, and WOMAC Stiffness score had a weak correlation with BFI and other external measures (no further details). Where reported, test-retest validity appeared broadly acceptable, except for the WOMAC Stiffness items. Methods for deriving CIMD were not reported, and it does not appear that systematic bias (systematic discrepancy between assessment scales scores and self-perceived improvement in health status) was measured. Given the concerns and limitations listed above, the validity and reliability of the results of the PROs validation studies presented by the company is largely uncertain.

Table 31 Validation of measurement scales used in CL303

	Skrinar 2019[32]	**Skrinar 2019**[31]	**Nixon 2020**.[30]
Tool	BPI-SF	WOMAC	BFI
Original purpose	To assess pain severity in cancer patients	To evaluate severity of knee and hip osteoarthritis	To assess severity of fatigue due to cancer and its treatments

Study objectives	Initial evaluation of item/scale properties, reliability, validity & sensitivity to change. Establish CIMD thresholds	item/scale properties, reliability, validity & sensitivity to change. Establish CIMD thresholds	item/scale properties, reliability, validity & sensitivity to change. Establish CIMD thresholds
Population	CL303 patients, pooled across arms. Duration NR	CL303 patients, pooled across arms. Duration NR.	CL303 patients, pooled across arms. Up to 96 weeks
Item response distributions[1]	"Well distributed". No further details.	>20% marginally present in 5/24 items. No ceiling effect. Floor effect NR.	"mostly well distributed". No floor or ceiling effects (>10%)
Item-scale correlations[2]	0.61 to 0.81	0.59-0.80. "All items correlated highest with their intended scale."	0.85–0.92 for Fatigue Interference and 0.72–0.90 for Global Fatigue. Fatigue severity NR.
Convergent validity[3]	"Moderate" Stronger for PGI-S than 6MWT	Moderate to strong correlation with external measures for all domains and total score, but weaker for Stiffness.	Moderate correlations with BPI Worst Pain , Pain Interference, WOMAC Pain, Physical Function and Total Score. Weak correlation with 6MWT and WOMAC stiffness.
Discrimination between groups at baseline (known groups validity)[4]	"Can discriminate" for "pain medication use, use of walking device, pain severity, walking ability"	Moderate to strong	Unclear -results could not be interpreted.
Internal consistency reliability[5]	Cronbach α=0.917	Physical function: α=0.954 Pain: α=0.798 Total score: α=0.959 Stiffness: not tested	α=0.926 to 0.936
Re-test reliability[6]	High with PGI-I used to define stability	Good with PGI-I to define stability Less favourable for Stiffness	0.677 to 0.859 against PGI-I 0.433 to 0.783 against 6MWT
Responsiveness[7]	"Strong support" that the scale can detect changes over time	"Good" (no other details)	Small to large standardized effect sizes
CIMD[8]	Worst pain: 1.72 Pain interference: 1.0	Physical Function: 8-10 Stiffness: 10-15 Pain: 11 Total score: 10	Worst Fatigue: -1.5 Fatigue Intererence: -1.2 Global Fatigue: -1.2
Conclusions	Analyses support the reliability, validity and responsiveness of BPI-SF in adult XLH	Results supported the use of WOMAC to evaluate treatment interventions in adult XLH	Analyses support the reliability, validity and responsiveness of BFI in adult XLH

1. Identify skewed distribution and any responses that are over-favored, including floor and ceiling effects; 2. evaluates the extent to which each individual item correlates with the domain score it contributes to; 3. evaluates correlations of scale scores with scores on assessments that are conceptually linked; 4. evaluates the extent to which the scale discriminates between groups that are expected to be different; 5. determines the extent to which individual items within the scale (e.g. Fatigue Interference and Global Fatigue domains) measure the same construct (i.e. homogeneity of the scale); 6. reflects the ability of the scale to give reproducible results when administered twice over a given period to a population with stable disease; 7. determines whether observed improvements (or reductions) in scores correspond to

improvements (or worsening) in external criteria related to that construct; 8. distribution- and anchor-based approaches are used to estimate clinically meaningful change (i.e. minimal clinically important difference; MCID) in the domains of interest.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Burosumab for treating X-linked hypophosphataemia in adults

ID3822

Factual accuracy check of EAG report

23 August 2023

File name	Version	Contains confidential information	Date
ID3822 EAG report factual accuracy responses_23Aug2023_marked CIC		**CIC redacted**	**23 August 2023**

Contents

EAG report factual accuracy check

The Company thanks the EAG for their report. This document contains the findings of the Company's factual accuracy check of the report, together with the requested accuracy-related changes.

**** IMPORTANT: It appears that the EAG did not receive the Company responses to their clarification questions, which the Company uploaded to NICE on 23 June 2023. This is a serious concern as the Company submitted detailed responses, which should be taken into account. The Company asks that the EAG revise their report taking the clarification responses into account, in addition to the factual accuracy responses provided below. We have not repeated the CQ responses in the current document.**

1. Executive summary

EAG report location	EAG report statement	Company remarks	Requested change	EAG response
Section 1 p. 11	The EAG notes that it submitted points for clarification on the company submission to NICE, but no response to these	The company prepared responses and uploaded them to NICE on 23 June 2023.	Please contact NICE to obtain the Company responses to the EAG's clarification questions. Please remove the statement and revise the report where necessary to	The EAG only received the company's response to points for clarification (PFC) on 11 September 2023 along with the company's factual accuracy checks (FACs). The EAG's updated report focuses on addressing the company's

	clarification points was received		take the responses into account.	FACs set out in this document, and revises the report in light of the clarifications received where this clearly impacts factual accuracy. A note on when responses were received has been added to the EAG report (Section 1, paragraph 3).
Issue 2, p.15	The population for which the submission is positioned conflicts with the current entry criteria for the burosumab EAP in England And The EAG considers there to be uncertainty about the	Although the wording of the inclusion criteria for the submission population differs from the EAP inclusion criteria, in practice the two populations are comparable. Almost all (97%; Kyowa Kirin, data on file) of EAP patients were entered on the grounds of debilitating XLH-related symptoms (typically pain, stiffness and fatigue; NB	Please consider amending based on the fact that the EAP population gives a clear indication of the number of patients who will receive burosumab on the NHS in England.	We have amended Issue 2 acknowledging that the company's positioning broadly aligns with the EAP population. The second part of issue 2 regarding the precise definition of treatment failure and uncertainty regarding the size of the eligible population who may receive burosumab in the NHS is not factually inaccurate. Keen 2021 estimates that approximately

	precise definition of treatment failure with conventional phosphate therapy for burosumab to be considered as an alternative treatment option, which leads to uncertainty regarding the size of the eligible adult population who may receive burosumab in the NHS.	physicians could choose more than one of the eligibility options). There was no specific requirement for a particular pain score, but in practice adults with XLH who are highly symptomatic suffer with a constellation of symptoms that includes pain. Further, burosumab is expected to be offered to adults in line with European and draft UK clinical recommendations, which all state that burosumab should be offered only if conventional therapy is not appropriate or not effective.[1–3] The abstract by Keen 2021[4] documents that only 47.8% of adult XLH patients known to the treating centres were enrolled in the EAP, and estimates that approximately		152 patients (49.8%) out of a total of 305 adults with XLH in England may be eligible for burosumab based on the EAP inclusion criteria; however, Keen 2021 also acknowledges that the XLH population in England ranges from 291 to 578 adults and uncertainty remains on the number of patients affected by debilitating symptoms and clinical complications. The EAG has amended issue 2 to refer to the estimates of eligible population for burosumab in England from Keen 2021.

		152 of 305 adult patients in England would be eligible for burosumab. This indicates that patients were enrolled selectively, and that burosumab will not be offered to all adult patients. The EAP represents the number of patients likely to be offered burosumab in the NHS.		
Issue 3, p. 16	There is uncertainty regarding how treatment decisions will be made for the subgroup of adult patients who have previously experienced burosumab treatment (specifically, children receiving burosumab as they transition to adults at age 18 and patients who recommence burosumab as adults	The current submission is in adults aged 18+. Patients who have received burosumab below this age will have to satisfy the same eligibility criteria as other adults in order to access burosumab as adults. Eligibility for these patients will therefore be decided on an individual basis.	Please amend	Table amended accordingly.

	following treatment as a child)			
Issue 4. Page 15	The EAG has concerns with baseline imbalances in characteristics between study arms in the CL303 trial. Compared with the placebo arm, participants in the burosumab arm were older, and had consistently worse pain, stiffness and function scores at baseline overall.	We note that the EAG has (page 56) has peformed statistical tests of baseline imbalance for 10 variables and noted that there was a statistically significant difference for one variable. However, based on the observation that "most outcomes were worse at baseline in the burosumab arm" they concluded that the differences between treatment arms "highly unlikely to happen by chance alone." We would like to point that given the various outcomes are likely to be correlated, it is by no means unlikely that a number of differences would run in the same direction if, by chance, the patients in the burosumab arm were on average, more severe. We	Please amend report accordingly	This is not a factual inaccuracy. We note that it is not possible to completely rule out differences between the trial arms being due to chance, but we consider that the difference is substantial enough to merit committee discussion. We note that the 24-week trial analyses that compared change from baseline between burosumab and placebo did not adjust appropriately for baseline imbalances because the assumption that these imbalances are not predictive of the trial outcomes was not met. A note on the necessary lack of adjustment for baseline

		also note Stephen Senn's commentary that the value of testing for baseline balance in trials is of questionable utility.[5] The pre-specified 24 week trial analyses (that were accepted for regulatory purposes) compared change from baseline between burosumab and placebo. This adjusts for baseline imbalance. The ad hoc analyses of 24 week data conducted by the EAG (reported on page 43) does not account for the observed baseline imbalance (as per the prespecified trial analyses). This would appear, post-hoc, to bias the analysis against burosumab as the patients in this arm had more severe outcomes at baseline.		imbalances in the EAG analyses was added p43. The EAG additional analyses (Figure 11) were intended to correct for possible regression to the mean or other biases caused by burosumab patients having worse scores at baseline. Not adjusting for baseline scores is precisely the point of these analyses.

		Both analyses account for any placebo responses or regression to the mean effects in that they are comparative and any placebo responses or regression to the mean effects will occur in both arms.		
Issue 10 Page 21	A distinction between types of fracture (active or non-active bone fractures and pseudofractures) is required to assess the implications for treatment management and effects on health-related quality of life.	The model only explicitly includes active fractures, while the impact of pseudofractures was only taken into account through quality of life.	Please amend statement to reflect the distinction between types of fractures that the evaluation makes.	This statement has now been deleted based on the company's response to EAG points for clarification. Section 4.2.2.3 has also been amended.
Issue 12 Page 22	The EAG considers the WOMAC data up to week 96 from the treatment continuation period of CL303 to be the only	Given the limited trial data available for this rare disease, we believe it is important to make best use of this valuable data. To this end we believe the BUR02	Please amend report accordingly	This is not a factual inaccuracy. The company and EAG have alternative views, with justification for both views provided in the EAR for committee deliberations.

	reliable source (in the absence of data from the EAP for burosumab in England) to inform the asymptotic model fit to WOMAC mapped utility change from baseline.	long term follow-up data for patients enrolled from the CL-303 should be included in the analysis.		
Issue 13 Placebo-adjusted utility values (Page 22)	There is uncertainty about whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed in the 24-week period of CL303, where the WOMAC mapped utility change from baseline in the placebo arm corresponds to an improvement in utility	Placebo arm utilities showed an initial improvement at 12 weeks, followed by a return to near baseline levels at 24 weeks, suggesting that any placebo effect on utility is short-lived. WOMAC outcomes following burosumab interruption reported in Kamenicky (2023)[6] show that patients returned to baseline WOMAC scores following withdrawal of treatment. This suggests that there is minimal regression to the mean. If there were	Please amend report accordingly	This is not a factual inaccuracy. The EAG considers there to be uncertainty about whether the placebo adjusted or non-placebo adjusted utility values are more appropriate for estimating the utility gain associated with burosumab from CL303.

	of approximately 0.03.	significant regression to the mean, there would be a residual treatment effect following Tx interruption. Given that placebo treatment is not available, we believe the non-placebo adjusted values should be used.		
Issue 14 Page 22	The EAG considers it unlikely that the disutility associated with each new fracture event is accrued cumulatively and therefore the disutility associated with fractures may be overestimated in the company's base case.	There seems to be a misunderstanding of how the disutility of new fractures is calculated (see also comments made on section 4.2.8.4). The model tracks the cumulative proportion of patients with fractures, i.e. patients with a history of fracture will not accrue additional disutility with a repeat event.	Please amend report accordingly	The report has been amended accordingly.
Issue 15. Utility benefit on caregivers	The company's base case assumes a spillover benefit on caregivers equal to 20% of the patient	The company's base case takes into account impact on family members and caregivers, not just caregivers.	Please amend report accordingly	The EAG's use of the word 'caregivers' referred to caregivers and family members. We have amended the report throughout to be

or family members	utility benefit of burosumab and applied to two caregivers. The EAG has a concern that the spillover effect may be overestimated by including an effect on two caregivers, where two may be reasonable for a child but less so for an adult, particularly noting that burosumab is administered in a way that supports patients to be independent and less likely to impose additional burden on family members.	We agree that "burosumab is administered in a way that supports patients to be independent and less likely to impose additional burden on family members" and believe it is important that this benefit is included in the analysis. With respect to number of family members impacted by a patient's burosumab treatment, this is hard to estimate, but we note that XLH is a genetic disease and has a lifelong and multigenerational impact that extends across the family, including non-affected siblings and partners (CS Section 1.3.5.6, p. 36). It has been described as affecting people's "whole bodies, whole lives, and whole families" (CS p. 31).[7]		clear that it is caregivers and family members.

2. Introduction and background

EAG report location	EAG report statement	Company remarks	Requested change	NOTES
2.2.4, p. 29	There is currently no evidence that improving biochemical outcomes improves patient outcomes.	It is not accurate to say that there is no evidence of this. Hypophosphataemia is the root cause of the clinical manifestations of XLH (see Company Submission p.25-28, Table 3). Phosphate is a key component of bone mineralisation and also plays an essential role in metabolic processes and tissue structure and function throughout life (CS Section 1.3.1.3, p. 21-22).[1,8–10] The adverse effects of low phosphate are wide-ranging, and amelioration of some of the acute and ongoing effects when phosphate is normalised is to be expected. Improving biochemical outcomes (principally serum phosphate) is the principle behind all XLH-targeted	Please remove the sentence.	The sentence has been removed.

		pharmacological treatment. Clinical guidelines recommend that symptomatic adult patients should be offered treatment to raise serum phosphate, in order to improve their outcomes.[1–3] Study CL303 provides placebo-controlled and open label evidence of improved patient outcomes in the form of improved symptoms and functioning after phosphate normalisation with burosumab, and an increase in fracture healing. The benefits to patients were accepted by the EMA in its approval of burosumab in adults. Discussing the patient-reported benefits of burosumab, the EPAR states that: "… patients' experiences of symptom and activity improvement, as reported in patient interviews and feedback, support the view that the effects are meaningful to patients. The totality of these data and the consistency of effect among the assessments demonstrate that, despite the long-term complications and symptoms experienced by adults with XLH,		

		burosumab improves symptoms and function that are clinically meaningful to patients."[11] In patients with a gap in treatment between participation in CL303 and BUR02 (n=7), an exploratory analysis found that the benefits of burosumab on biochemical outcomes, PROs and ambulatory function may be lost when treatment is interrupted but recover over time when treatment is reinstated.[6] The clinical guideline by Haffner et al. states that "Conventional treatment with active vitamin D and oral phosphate improves pain, osteomalacia and oral health."[1] This clinical consensus further contradicts the assertion that there is no evidence of any benefit from improving biochemical outcomes, albeit that the efficacy of conventional treatment is limited by its delivery, poor tolerability and risk of adverse effects and has not been systematically assessed.		

		Furthermore, the EAG's final paragraph on p.29 accepts that normalising phosphate levels is expected to improve symptoms, physical functioning and HRQoL (… restore phosphate homeostasis, thereby normalising serum phosphate levels and improving symptoms, physical functioning and HRQoL for adults with highly symptomatic XLH).		
2.2.4.1, p. 31	The company preferred BPI score of ≥4 (worst pain in last 7 days) reflective of 'persistent and debilitating symptoms' is a very low pain threshold that is not commonly used in NHS practice	The use of BPI worst pain ≥4 is in line with the trial inclusion criteria. Clinical consultation with 2 clinicians about the suitability of the submission population did not result in any feedback that this was an unsuitable threshold (Appendix Q).	Please add that this threshold reflects the trial inclusion criteria.	Not a factual inaccuracy. The fact that this threshold reflects the trial inclusion criteria is not disputed.
2.2.4.1, p. 31	It is unclear whether the children with XLH who have been on burosumab	Transition from paediatric burosumab: the current submission is in adults aged 18+. Patients who have received burosumab below this age will have to	Please change to: "Patients aged 18+ who have received burosumab as children will have to	This information was added. We remain concerned that response to

	(where it is already approved, HST82) … would be eligible for burosumab based on the company's preferred positioning.	satisfy the same eligibility criteria as other adults in order to access burosumab as adults. Eligibility for these patients will therefore be decided on an individual basis.	satisfy the same eligibility criteria as other adults in order to access burosumab. Eligibility for these patients will therefore be decided on an individual basis."	burosumab treatment in childhood might affect the ability for patients to continue treatment into adulthood once they reach 18 years of age.
2..2.4.1, p. 30; and 2.3.1, p. 35	[The CS population is not reflected in] … clinical advice to the EAG that stated that burosumab has a better adverse effect profile compared to conventional treatment and therefore likely to be offered as a first-line treatment.	As noted in the Company Submission (document B, p. 39-42), clinical guidelines – including draft clinical practice recommendations from NHS clinicians[2] – state that burosumab should be considered if conventional therapy is not beneficial, not tolerated, or has resulted in complications[1–3] Burosumab is expected to be offered in England in line with clinical guidelines, which position conventional treatment as the first option.	Please add: "However, clinical guidelines – including draft clinical practice recommendations from NHS clinicians[2] – state that burosumab should be considered if conventional therapy is not beneficial, not tolerated, or has resulted in complications.[1–3] The company submission population is aligned with these guidelines".	Section 2.3.1 was edited accordingly.
2.3.3, p. 35	Clinical advice to the EAG suggests that WOMAC and BPI scales are not	Eligibility for study CL303 was based on the BPI 'Worst pain' score, and <u>not</u> the full BPI-SF questionnaire. The 'Worst pain' score is a single question	Please add: "However, the whole BPI-SF will not be required. Draft practice guidelines from UK	A sentence on VAS as an alternative to

	routinely used in the NHS to assess patients with XLH therefore selection criteria that recommend the use of BPI scales to be eligible for burosumab will be challenging to apply within the NHS.	assessed on a 1-10 numeric rating scale (see CS document B Table 13), and is therefore very simple to administer. In their draft clinical practice recommendations for the management of XLH in adults in the NHS, Mohsin et al. recommend "Assessment of severe and average pain over the last seven days that the clinician considers is attributable to XLH using VAS 0-10".[2] This is closely analogous to the BPI 'Worst pain' evaluation. In their checklist for follow-up of adult XLH patients (Mohsin p. 21), the BPI-SF pain severity scale is an option for assessing patients' pain at each visit. A single question asking patients to rate their worst pain in the last 7 days using a 0-10 VAS or numeric scale is all that is required to assess worst pain in the same way as the BPI-SF, and clinical experts consulted by the Company advised that this would be simple to incorporate into practice (CS Appendix Q). Furthermore, it is not unreasonable that there should be a	clinicians recommend 'Assessment of severe and average pain over the last seven days that the clinician considers is attributable to XLH using VAS 0-10'.[2] This is closely analogous to the BPI 'Worst pain' evaluation, and the Company has received clinical advice that this will be easy to incorporate in a routine assessment."	BPI was added to Section 2.3.4.

		thorough assessment of eligibility for a more costly new treatment in a rare disease.		

3. Clinical effectiveness

EAG report location	EAG report statement	Company remarks	Requested change	NOTES
Section 3, p. 43		There is a pagination error in the EAG report starting at Section 3. Pagination jumps from 36 to 43 and all subsequent page numbers are 43.		Corrected, thank you.
3.1.1	Further details were sought from the company in the EAG points for clarification (PFCs), which the EAG have not received within the timelines of the EAR delivery.	The additional information requested was provided as part of the EAG clarification responses, which the Company provided to NICE on 23 June but which did not reach the EAG.	Please contact NICE to obtain the Company responses to the EAG's clarification questions. Please amend the statement and revise the report where necessary to take the responses into account.	This sentence has been deleted. Revisions to Table 4 in section 3.1.1 have been made to take account of the company clarification response.
3.2.2.1	Participants were required to have a	Please note that the average BPI score was calculated from 8 scores	Please add: "However, the average BPI score	The EAG's understanding is that

	Brief Pain Inventory Short Form (BPI-SF) worst pain score ≥4 in the last 24 hours attributed to XLH/osteomalacia. The limited recall period of the BPI questionnaire (24 hours) means that it is not aimed at measuring chronic pain symptoms.	(pain diaries from the 7 days prior to the visit and the score at the visit), except for the randomization stratification, which was based on 7 scores (pain diaries from the prior 7 days).[12] (See CS document B, p. 58). This means that the pain scoring was more robust and representative than relying on one single 24-hour assessment period.	was calculated from 8 scores (pain diaries from the 7 days prior to the visit and the score at the visit), except for the randomization stratification, which was based on 7 scores (pain diaries from the prior 7 days).[12]"	average BPI scores were not used to assess eligibility. The trial CSR, section 8.6.2.3.1 states: "The short-form BPI is a self-reported, pain-specific questionnaire with a recall period of 24 hours." And "BPI Worst Pain was administered at SV1 to assess eligibility"
3.2.2.1	The EAG requested a comment from the company on the applicability of the CL303 trial selection criteria to NHS practice, and are currently awaiting a response.	The additional information requested was provided as part of the EAG clarification responses, which the Company provided to NICE on 23 June but which did not reach the EAG.	Please contact NICE to obtain the Company responses to the EAG's clarification questions. Please amend the statement and revise the report where necessary to take the responses into account.	We have amended the text in Section 3.2.2.1.

3.2.1	The EAP RWD includes [redacted] (as of April 2023) who have received burosumab in England.	The information is marked AIC in the EAG report but should be CIC. It is important to note that the EAP was not set up to collect RWD. The data we have used to inform the submission from the full EAP is based on the limited and confidential information collected through the application forms. The RWD collection has been set up retrospectively and is ongoing. All 5 UK sites are signed up to the RWD collection so all 136 adults are eligible, but opt-out provisions mean it may not include all (yet to be confirmed). Independently to this, UCLH have written up some of their experience and presented it at a conference,[13] and we have used this in the submission."	Please change the marking to CIC Change wording to 'The EAP includes [redacted] (as of April 2023) who have received burosumab in England, although opt-out options mean that not all may be included in the RWD analyses'.	This has been corrected.
3.2.3	Further details, including separate baseline characteristics and subgroup data for	The additional information requested was provided as part of the EAG clarification responses, which the Company provided to NICE on 23	Please contact NICE to obtain the Company responses to the EAG's clarification questions.	The section has been amended accordingly for both issues.

	subjects with and without standard therapy prior to the washout period, and for subjects with prior burosumab exposure, were requested as a PFC. The EAG are currently awaiting a response. And the EAG asked for the company to confirm whether all participants were on optimized and stable pain management at baseline as PFC, and are currently awaiting a response.	June but which did not reach the EAG.	Please amend the statement and revise the report where necessary to take the responses into account.	
3.2.7	40 out of the [redacted] participants	The information is marked AIC in the EAG report but should be CIC.	Please change the marking to CIC	Amended.
3.5	Additional work on clinical effectiveness	The analyses are based on unpublished data from the CSRs, and have been undertaken ad hoc. They	Please mark the results AIC	AIC marks added

	undertaken by the EAG	should not be placed in the public domain.		
3.6.2	There was no evidence that subjects treated with burosumab had clinically significant improvements in physical functioning compared with placebo at 24 weeks. There was no evidence that burosumab was more effective than placebo at reducing pain and fatigue.	It is incorrect to state that there is no evidence that that burosumab was more effective than placebo at reducing pain and fatigue and did not show clinically significant improvements in physical functioning compared to placebo at 24 weeks. All three endpoints showed improvement at 24 weeks although differences were not statistically significant at $p<0.05$ for all endpoints. As noted in Briot et al. (2021)[14] physical function, pain, and fatigue scores continued to increase improve beyond 24 weeks We would suggest caution in drawing conclusions regarding a lack of clinically significant effects based on estimates MICDs. In this study MICDs were estimated based on a differences of 0.5 SDs in the outcomes and responses defined as ranging from “a little better” to “very	Please amend report accordingly	The paragraph has been edited.

		much better" on the PGI or >=3 point improvements in relevant BPI or SF-36 scales. As such, although these estimates are labelled as minimally important clinical differences, they do not represent a threshold at which an effects become important to individuals. Rather they represent thresholds above which we can be confident a group average effect is important. In addition, the combination of effects, as reflected in utility estimates, are likely to be important to patients		

4. Cost effectiveness

EAG report location	EAG report statement	Company remarks	Requested change	EAG comment

Section 4.1	It appears that EconLit was searched, but no search strategy was reported.	The search strategy was provided in response to EAG clarification questions, question C4.	Removal of statement.	This statement has been deleted.
4.2.2.3.	The EAG has a concern that the company's model does not make a distinction between active or non-active bone fractures and pseudofractures. The predicted annual fracture rates by site in the model are based on baseline CL303 radiograph data for all fractures, whether active, non-active or pseudofracture.	As provided in response to question B11 of the clarification questions, the economic model explicitly focuses on active fractures only. The impact of burosumab on active pseudofractures and the healing of fractures at baseline was included in the model through capturing the impact on WOMAC scores, and therefore only included as part of the quality of life improvement associated with burosumab treatment, not as part of the modelled fracture events.	Please contact NICE to obtain the Company responses to the EAG's clarification questions. Please amend the statement and revise the report where necessary to take the responses into account.	This concern has now been removed based on the company's response to EAG points for clarification
4.2.3	The EAG also notes that the submitted cost-effectiveness model is not sufficiently flexible to allow patient weight (used to inform burosumab dosing) to vary over time	While the statement is factually correct, additional data was provided in response to the clarification questions that there is no trend in patients' weight with age, therefore this flexibility is not needed		This concern has now been removed based on the company's response to EAG points for clarification

	within each discrete age band at which patients start treatment, i.e., as patients age in the model, their weight is not permitted to change over time as they leave the age band at which they started treatment.			
4.2.4	Item 6. There is uncertainty about the relative effectiveness of conventional therapy with burosumab or placebo in terms of rates of serum phosphate normalisation.	The EAG acknowledges the irrelevance of conventional therapy for the proposed positioning of burosumab, and even states that the company's approach may be considered conservative compared to the approaches used in the evaluations from SMC, CADTH and PBAC.	Please either remove this section or add explanation that conventional therapy is not considered as a treatment alternative for this population.	Item 6 is now deleted as a concern.
4.2.6.1	…in the absence of alternative treatments available and the patient has reached the target of serum phosphate normalisation after week 24, it may not seem	The longer-term assessment is in line with the available clinical guidelines and is meant to assess the long-term impact of bone remineralisation after increases in serum phosphate levels (which the first criteria addresses).	Please amend the statement and refer to clinical guidelines recommending assessment after a longer time period.	This sentence needs to be read in the context of the previous sentences. The EAG's concern is the requirement of an improvement in

	reasonable to impose an additional hurdle because of the potential to experience a reduction in morbidities and mortality with phosphate levels maintained.			WOMAC total score at 12 months when serum phosphate normalisation has been achieved. The EAG has no concern with the recommendation of an assessment after a longer period. WOMAC scores are not commonly used in UK clinical practice to assess response to treatment. The EAG has amended the sentence for increased clarity.
4.2.6.1	The reasons for treatment discontinuation in the EAP are not presented in the CS, but the EAP does not include stopping criteria. Therefore, it would be expected that the annual discontinuation rate of 3%	The reasons for discontinuation from the EAP were requested (question B14) and provided at the clarification questions stage, showing that the large majority of cases (15 of 16 discontinuation) discontinued due to reasons other than loss of efficacy.	Please update section based on information provided, rather than based on expectation.	This section has been updated based on the company's response to EAG points for clarification.

	from the EAP is also reflecting initial loss of efficacy with burosumab, which is already captured in the company's proposed stopping criteria in year 1.			
4.2.6.2	The EAG's key concern in relation to modelling the effects of burosumab on fracture incidence rates is that no distinction between types of fracture (active or non-active bone fractures and pseudofractures) are considered in the model,	Please note, all fractures are active when they first occur. As provided in response to question B11 of the clarification questions, the economic model includes incident fractures only.		This concern has now been removed based on the company's response to EAG points for clarification.
4.2.6.2	However, the EAG notes that the EMA assessment report for burosumab (EMA/423776/202028, page 97 of 151) indicates that six new fractures were reported in the burosumab arm within weeks 0-24 , one new	The figures quoted include pseudofractures too. As noted above, pseudofractures were not explicitly modelled, only captured through improvements in WOMAC scores. Tapering of utilities in the first two years of treatment allow for occurrence of new	Please remove pseudofractures from quoted figures.	The text is amended to indicate that the statement from the EMA is referring to active fractures or active pseudofractures; the EMA report does not appear to quote the

	fracture within weeks 24-36, and none within weeks 36-48 of CL303	pseudofractures in the first two years of treatment.		figures separately for active fractures and active pseudofractures.
4.2.6.4	However, as discussed previously, six new fractures were reported in the burosumab arm within weeks 0-24 and one new fracture within weeks 24-36; therefore, the company's justification for immediate effect on the incidence of fractures is flawed,	Same comment as above, the figures quoted include pseudofractures too.	Please remove pseudofractures from quoted figures.	Amended as per above.
4.2.8.1.	… and (iv) a spillover effect on the utility of caregivers and family members, which is assumed to be 20% of the patient utility benefit of burosumab and applied to two caregivers.	The company's base case includes family members and caregivers, not just caregivers.	Please amend statement.	The EAG have amended the report throughout to be clear that it is caregivers and family members.

4.2.8.3	Moreover, BUR02 included EU participants from both CL303 and CL304, which may differ in terms of baseline characteristics and WOMAC scores, with participants in CL304 required to have no prior treatment for at least 2 years	CL304 patients were not included in the BUR02 WOMAC analysis.	Please amend sentence to reflect correct patient population.	This sentence is deleted based on the company's response to EAG points for clarification.
4.2.8.3	The EAG considers the data up to week 96 from the treatment continuation period of CL303 to be the only reliable trial data to inform the asymptotic model fit to WOMAC mapped utility change from baseline.	Given the limited trial data available for this rare disease, we believe it is important to make best use of this valuable data. To this end we believe the BUR02 long term follow-up data for patients enrolled from the CL-303 should be included in the analysis	Please amend section accordingly.	This is not a factual inaccuracy. The company and EAG share alternative views, with justification for both views provided in the EAR for committee deliberations.
4.2.8.4.	Second, the annual excess incidence rate for fractures due to XLH is based on modelling fracture events as repeat events, which means that	The model tracks the cumulative proportion of patients with fractures, i.e. patients with a history of fracture will not accrue additional disutility with a repeat event.	Correction needed to reflect model calculations.	The EAG have amended the report accordingly.

	patients could have the event multiple times and accrue an additional lifetime disutility with each new event.			
4.2.9.2	Therefore, it may be expected that the weight of adults with XLH changes with age over time more than in the general population	Additional data was provided data in response to the clarification questions that there is no trend in patients' weight with age.	Please amend statement based on data provided rather than on expectation.	The EAG has amended this statement based on the company's response to EAG points for clarification.

5. References

1. Haffner, D. *et al.* Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol* **15**, 435–455 (2019).
2. Mohsin Z, Bubbear J, Gardiner O, & Javaid MK. *Clinical practice recommendations for the management of X-linked hypophosphataemia in adults*.
3. Trombetti, A. *et al.* Interdisciplinary management of FGF23-related phosphate wasting syndromes: a Consensus Statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia. *Nat Rev Endocrinol* (2022) doi:10.1038/s41574-022-00662-x.
4. Keen R, Bubbear J, & Clunie G. Estimated prevalence of adults with XLH in England based on burosumab early access experience from five sites. in (2021).
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7. Hamilton, A. A. *et al.* Whole Body, Whole Life, Whole Family: Patients' Perspectives on X-Linked Hypophosphatemia. *J. Endocr. Soc.* **6**, bvac086 (2022).
8. Beck-Nielsen, S. S. *et al.* FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J Rare Dis* **14**, 58 (2019).
9. Penido, M. G. M. G. & Alon, U. S. Phosphate homeostasis and its role in bone health. *Pediatr. Nephrol.* **27**, 2039–2048 (2012).

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11. European Medicines Agency. *Assessment report. CRYSVITA*. https://www.ema.europa.eu/en/documents/variation-report/crysvita-h-c-4275-ii-010-g-epar-assessment-report-variation_en.pdf (2020).
12. Insogna, K. L. *et al.* 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 Min. Res* **33**, 1383–1393 (2018).
13. Krishna G, Cuarentas A, Murphy E, Lachman R, & Javaid MH. Improvement in patient outcomes following initiation of burosumab in adults with XLH: a single centre experience. in (2023).
14. Briot, K. *et al.* Burosumab treatment in adults with X-linked hypophosphataemia: 96-week patient-reported outcomes and ambulatory function from a randomised phase 3 trial and open-label extension. *RMD Open* **7**, (2021).

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **06 October 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	Edit Remák
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Kyowa Kirin Limited
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 5: Evidence for efficacy on pain, physical functioning and fatigue	No	The EAR states that: "After accounting for possible regression to the mean and placebo effects, the EAG found no clear evidence of a difference between burosumab and placebo for most patient-reported outcomes (pain, physical functioning and fatigue); most differences between burosumab and placebo appeared not to be clinically meaningful, and were generally not statistically significant". **Summary of response** The company does not accept that the difference in PRO improvements between placebo and burosumab should be dismissed as 'not clinically meaningful'. • This statement seems to be based on comparisons with the company's estimates of MCID thresholds. However, these do not represent a threshold at which changes become meaningful for individual patients, and do not take into account combined effects on multiple endpoints, so should not be used to categorise group differences as not clinically meaningful. • The EMA judged that the totality of data and consistency of effect demonstrated that burosumab produces improvements in symptoms and function that are clinically meaningful to patients.[1]

		• The placebo effect is accounted for in the primary trial analyses, as they compare change from baseline between arms. Regression to the mean cannot be ruled out but, if it did occur, it would occur to some extent in both treatment arms. Neither the placebo effect nor regression to the mean is likely to have had a major effect on the placebo-controlled efficacy analyses. • The CL303 study found statistically significant improvements from baseline, compared with placebo, in various PRO scores at week 24. Statistically significant improvements over baseline were maintained at 48 and 96 weeks (see below for details). **Statistically significant improvements were seen in the CL303 trial** • Participants treated with burosumab had significant improvements in stiffness, pain, fatigue and physical functioning. [2,3] o At Week 24, participants had statistically significant improvements from baseline in WOMAC stiffness, BPI worst pain (average and greatest), BPI pain interference, and BFI worst fatigue (average and greatest), compared with placebo.[2] o At Week 48, statistically significant improvements from baseline were maintained for all WOMAC and BPI-SF scores.[3] o At Week 96, statistically significant improvements from baseline were maintained for all patient-reported outcome measures.[3] **Regression to the mean and placebo response** The EAG performed statistical tests of baseline imbalance for 10 variables and states that "Compared with the placebo arm, participants in the burosumab arm appeared to be older, with consistently worse pain, stiffness and function scores at baseline overall. The proportion of unhealed pseudofractures was higher in the placebo arm."

		However, based on the observation that "most outcomes were worse at baseline in the burosumab arm" they concluded that the differences between treatment arms "highly unlikely to happen by chance alone." It is important to highlight that, given the various outcomes are likely to be correlated, it is by no means unlikely that a number of differences would run in the same direction if, by chance, the patients in the burosumab arm were on average, more severe. We also note Stephen Senn's commentary that the value of testing for baseline balance in trials is of questionable utility.[4] We would like to reiterate that: • The pre-specified 24 week trial analyses (that were accepted for regulatory purposes) compared change from baseline between burosumab and placebo. This adjusts for baseline imbalance. • The *ad hoc* analyses of 24 week data conducted by the EAG does not account for the observed baseline imbalance (as per the prespecified trial analyses). This would appear, post-hoc, to bias the analysis against burosumab, as the patients in this arm had more severe outcomes at baseline. • Both analyses account for any placebo responses or regression to the mean effects in that they are comparative and any placebo responses or regression to the mean effects will occur in both arms. **Validity of using MCIDs to designate whether group mean PRO differences are clinically meaningful** These MCID thresholds were based on "distribution and anchor" population-based approaches, using differences of 0.5 SDs in the outcomes and responses defined as ranging from "a little better" to "very much better" on the PGI or >=3 point improvements in relevant BPI or SF-36 scales.[3,5–7] Therefore they do not represent a threshold at which changes become meaningful for individual patients. Indeed such a threshold is likely to vary between individuals. In addition, the MCID thresholds consider endpoints in isolation and do not account for the combined

		effect of impacts across multiple endpoints for individual patients. MCIDs may represent a threshold above which we are confident that a population level effect is definitely meaningful, but they are unlikely to represent a threshold at which effects become meaningful for individual patients. The mapping of improvements in PRO scores to utilities has the advantage that they provide a meaningful metric that accounts for effects across multiple endpoints and do not rely on a potentially arbitrary threshold. Dismissing PRO improvements as not meaningful to (individual) patients is difficult to justify. **EMA acceptance of meaningful HRQoL benefits with burosumab** The benefits to patients were accepted by the EMA in its approval of burosumab in adults. Discussing the patient-reported benefits of burosumab, the EPAR states that: "… *patients' experiences of symptom and activity improvement, as reported in patient interviews and feedback, support the view that the effects are meaningful to patients.* ***The totality of these data and the consistency of effect among the assessments demonstrate that, despite the long-term complications and symptoms experienced by adults with XLH, burosumab improves symptoms and function that are clinically meaningful to patients***."[1]
Issue 8: Excess mortality for individuals with XLH	Yes	**New published evidence on mortality in XLH** We would like to draw the EAG's attention to a new study providing additional evidence of increased mortality risk in chronic idiopathic hypophosphataemia, of which XLH is a major cause. The paper (Kim et al. 2023[8]) was published in August 2023, independently of Kyowa Kirin; it is supplied with this document and summarised below. The adjusted hazard ratio for mortality vs matched controls was 3.26 (95% CI, 1.83–5.81). Diagnoses of hypophosphataemia between 2003 and 2018 were evaluated in the Korean Health Insurance Review and Assessment claims database. A total of 154 patients (76 male, 78 female) with non-secondary and non-renal

		hypophosphatemia were identified and compared with age-, sex-, and index-year matched controls (n = 1,540). Patients are described as having chronic idiopathic hypophosphataemia. The authors report being unable to distinguish between XLH and tumour-induced osteomalacia (TIO) as the cause (both are driven by excess FGF 23). However, they found a large peak in age of diagnosis at 1-4 years, which is suggestive of XLH. Further, the authors note that TIO is an ultra-rare condition with a reported incidence much lower than XLH. Hypophosphataemic patients had a higher risk of mortality than controls (adjusted hazard ratio [aHR] 3.26; 95% CI, 1.83–5.81). They also had a higher risk of any complication (aHR 2.17; 95% CI 1.67–2.69) including cardiovascular outcomes, chronic kidney disease, hyperparathyroidism, osteoporotic fractures, periodontitis, and depression. Risk of hospitalisation was also increased (aHR, 2.49; 95% CI, 1.97–3.16).
Issue 12: Utility change from baseline and extrapolation over time	No	The EAG's suggested scenario (scenario 15) assesses the impact on cost-effectiveness when post-week 96 data are excluded from the asymptotic model fit to WOMAC mapped utility change from baseline. The corresponding utility value used in Scenario 15 is 0.2 in year 2 onwards, while the company's base case value is 0.211 in year 2 and 0.215 in year 3 onwards. The EAG's concern over use of the post 96-week data from study BUR02 in the company base case is that it is based on different patient populations that differ in terms of baseline characteristics and WOMAC scores. **Response** We believe it is appropriate and valuable to make use of the long-term data post 96 weeks, and that the BUR02 long term follow-up data for patients enrolled from CL303 should be included in the analysis. This is because of the limited trial data available for this rare disease, the value of having long-term data beyond week 96,

		and the evidence (below) that the populations did not differ significantly in key respects and that systematic bias is unlikely • BUR02 was made up of European participants from CL303 after completion of the 96-week study period; of note, patients who did not complete CL303 were also eligible after a protocol amendment. Kamenicky et al. compared baseline characteristics between the BUR02 population and the CL303 population and found no significant differences in age, sex or BPI-SF worst pain scores (see Company clarification response p.26 for table).[9] • 13 European patients who began CL303 did not enrol in BUR02. Disposition is set out in detail in Company CQ response A15. The introduction of some bias owing to the missing patients cannot be ruled out, but response A15 indicates that there was no systematic bias.
Issue 13: Placebo-adjusted utility values and application of stopping criteria	No	**Placebo-adjustment** The EAG states that: "There is uncertainty about whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed in the 24-week period of CL303, where the WOMAC mapped utility change from baseline in the placebo arm corresponds to an improvement in utility of approximately 0.03. The company uses the non-placebo-adjusted utility values in their base case analysis. EAG scenario 16 uses a placebo-adjusted value for the utility gain with burosumab". ***Response*** The Company believes that placebo adjustment of the utility gain for burosumab is not required. Our reasoning is as follows: • Placebo arm utilities showed an initial improvement at 12 weeks, followed by a return to near baseline levels at 24 weeks, suggesting that any placebo effect on utility is short-lived. • WOMAC outcomes following burosumab interruption between finishing study CL303 and starting study BUR02 (reported in Kamenicky [2023])[9]

		show that patients returned to baseline WOMAC scores following withdrawal of treatment. This suggests that there is minimal regression to the mean. If there were significant regression to the mean, there would be a residual treatment effect following Tx interruption. **Application of stopping rule** The EAG states that: "Utility values for patients treated with burosumab from year 2 onwards is also affected by the proposed stopping criteria in the first year. EAG Scenario 17 assesses the impact when no stopping criteria are applied and the utility values are placebo-adjusted". ***Response*** As argued in clarification response B13, the Company believes that the use of a stopping rule for burosumab treatment is appropriate. • The stopping rules were derived after multiple consultations with clinical experts (see CS Appendices P and Q). Given the mode of delivery (repeated injections) and cost of treatment, clinical advice was that it would be unreasonable to continue therapy in patients who do not experience some perceived clinical benefit of treatment, over and above normalisation of serum phosphate. o The draft document on recommended management of XLH in adults in the NHS (Mohsin et al.[10]; see Company Submission p. 41-42) recommends that burosumab therapy should be reviewed annually. Stopping burosumab after 12 months should be considered if average pain over the last week has not improved AND there has not been a reduction in analgesic use from baseline. This demonstrates clinical support for stopping burosumab if patients are not experiencing clinical benefit. o The criterion used in the model stopping rule was improvement in WOMAC total score. While this may not be commonly used in

		clinical practice to evaluate whether a patient should have access to treatment, clinicians consulted (CS Appendices P and Q) agreed that WOMAC total score is a good proxy for reflecting the criteria for continuation of treatment that might be used as it captures improvement in pain, stiffness and fatigue and that it could be implemented in a clinical setting. • The mechanism by which serum phosphate levels affect bone composition supports a clinical assessment at 1 year. When serum phosphate levels normalise, bone remodelling should take place over time due to the dynamic nature of bone tissues. Improvements in pain, stiffness and physical function are expected to result from this and should be assessed over a longer time horizon than 24 weeks. The clinical trials showed continued improvements in bone markers over time with continued treatment. Most of the improvement in patient-reported outcomes had occurred by one year.
Issue 14: Disutility for incident fractures	No	The EAG states that: "There is uncertainty about the magnitude and duration of the disutility associated with incident fractures and the assumption of independent effects when multiple events may occur over a lifetime horizon. EAG Scenario 19 considers the impact on cost-effectiveness when the disutility for incident fractures is applied in the first year of the event only". **Response** The Company agrees that there is uncertainty over the duration of disutility associated with incident fractures in patients with XLH, given that such data has not been collected. Evidence in osteoporosis shows that fractures can have a long-term impact on HRQoL. Data from osteoporotic fractures are not fully generalisable to XLH, because the bone structure and bone mineralisation in the two patient groups are different. Impaired bone mineralisation in XLH is likely to mean that fractures have a long-term on HRQoL, particularly in untreated patients. Fractures in XLH patients with uncorrected serum phosphate are slow to heal, and some untreated patients

		experience non-healing fractures.[11] Skrinar 2019 also reports that pain scores are higher in XLH patients with a history of fracture at any time in the past, which also indicates a long-term impact of fractures on HRQoL.[12] Thus it is plausible – indeed likely – that disutility from a fracture in XLH will continue for more than 1 year.
Issue 15: Utility benefit on caregivers and family members	No	The EAG states: "The EAG has a concern that the spillover effect may be overestimated by including an effect on two caregivers/family members, where two may be reasonable for a child but less so for an adult, particularly noting that burosumab is administered in a way that supports patients to be independent and less likely to impose additional burden on family members." "In the company's research study that was used to compare EQ-5D utility values of informal carers or family members of adults with XLH with age-matched general population utility values, only a small loss in utility was identified (0.081), when carers with XLH themselves were excluded from the analysis." **Response** Adult XLH patients do not require support with treatment administration (whether conventional treatment or burosumab). Rather, caregivers and family members can be affected in multiple ways: • Supporting the person with XLH with daily activities (e.g. getting in and out of the bath, transport) • Having to take on a larger share of day-to-day household and economic responsibilities due to the restricted abilities (mobility problems, pain, stiffness, fatigue) of the person with XLH • Being restricted in the activities the family can undertake (e.g. children may not be able to attend activities because a parent cannot take them there; outings may be difficult; social participation for the family may be restricted)

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Effects from the mental health effects suffered by the person with XLH.

As XLH is genetic, many families will have multiple affected members. Nonetheless, the utility benefit applied in the model remains well below the identified loss due to XLH (0.081) for even non-XLH carers (see table).
<table>
<tr><th>Year</th><th>Mean per family member</th><th>Mean in model (2 family members)</th></tr>
<tr><td>Year 1 on treatment</td><td>0.029</td><td>0.059</td></tr>
<tr><td>Year 2 on treatment</td><td>0.042</td><td>0.084</td></tr>
<tr><td>Year ≥3 on treatment</td><td>0.043</td><td>0.086</td></tr>
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Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Section 5.3.1 Model validation and face validity check: The EAG identified three errors in the programming of the model	Incremental QALYs: [redacted] Incremental costs: [redacted] ICER: [redacted]	The company accepts and has corrected the three programming errors identified by the EAG. The corrected incremental costs are: [redacted] No change to incremental QALYs	The changes resulted in an ICER of [redacted], a reduction of [redacted] from the company's original base-case ICER of [redacted].

Table 5 and Table 6 provide the disaggregated costs and QALYs in the company's corrected base case.

Table 1 Summary of the disaggregated costs in the company's deterministic base case results

Item	Cost of Burosumab (£)	Cost of SoC (£)	Incremental costs (£)	% of total incremental costs
Burosumab acquisition cost	[redacted]		[redacted]	[redacted]
Drug administration cost	£5,719	£5,413	£306	[redacted]
Morbidity cost (fracture)	£2,136	£4,080	-£1,944	[redacted]
Total	[redacted]	£9,493	[redacted]	100.0%

Table 2 Summary of the disaggregated QALYs in the company's deterministic base case results

Item	QALYs of Burosumab	QALYs of SoC	Incremental QALYs	% of total incremental QALYs
Burosumab treatment	[redacted]	0.00	[redacted]	[redacted]
Spill over to family members	[redacted]	0.00	[redacted]	[redacted]
Morbidities and baseline XLH impact	[redacted]	7.83	[redacted]	[redacted]
Total	[redacted]	7.83	[redacted]	100.0%

Sensitivity analyses around revised base case

Table 7 below provides the company's probabilistic sensitivity analysis results for 2,500 iterations with the model corrections as per the EAG report.

Table 3: Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Probabilistic							
SoC	£9,525	18.94	7.84				
Burosumab	[redacted]	19.42	[redacted]	[redacted]	0.48	[redacted]	[redacted]
Deterministic							
SoC	£9,493	18.90	7.83				
Burosumab	[redacted]	19.42	[redacted]	[redacted]	0.52	[redacted]	[redacted]

Table 8 presents the results of scenario analysis. The ICER is most affected when the utility impact on caregivers and family members is excluded analysis, which increases the ICER to [redacted] Varying the degree of reduction in morbidities also affected the ICER, leading to an increase in value of [redacted]

Table 4: Results of scenario analysis

Parameter	Base case	Scenario	Incremental Cost (£)	Incremental QALY	ICER (£/QALY)
Base Case			[redacted]	[redacted]	[redacted]
Time horizon	Lifetime	20 years	[redacted]	[redacted]	[redacted]
Annual discount rate (costs and health outputs)	3.50%	6.0%	[redacted]	[redacted]	[redacted]
		5.0%	[redacted]	[redacted]	[redacted]
		1.50%	[redacted]	[redacted]	[redacted]
		0.0%	[redacted]	[redacted]	[redacted]
Age distribution	CL303	CL001	[redacted]	[redacted]	[redacted]

Weight distribution	CL303 EU	CL303 All patients	[redacted]	[redacted]	[redacted]
Mortality	Use Hawley at least likely, 50% reduction in mortality for patients treated with burosumab	Use Hawley at least possibly, 50% reduction in mortality for patients treated with burosumab	[redacted]	[redacted]	[redacted]
		Use Hawley at least likely, 0% reduction in mortality for patients treated with burosumab	[redacted]	[redacted]	[redacted]
Spill-over burden	On	Off	[redacted]	[redacted]	[redacted]
Morbidities included in model		Include spinal stenosis, spinal surgery, dental abscess,	[redacted]	[redacted]	[redacted]
Mortality taper	On	Off	[redacted]	[redacted]	[redacted]
Morbidity taper	On	Off	[redacted]	[redacted]	[redacted]
Utility taper	On	Off	[redacted]	[redacted]	[redacted]
Treatment continuation rules	Stopping rule applied	No stopping rule	[redacted]	[redacted]	[redacted]
Degree of reduction in morbidities due to serum phosphate normalisation	100%	0%	[redacted]	[redacted]	[redacted]

[redacted]

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12. Skrinar, A. *et al.* The Lifelong Impact of X-Linked Hypophosphatemia: Results From a Burden of Disease Survey. *J Endocr Soc* **3**, 1321–1334 (2019).

Appendix A

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
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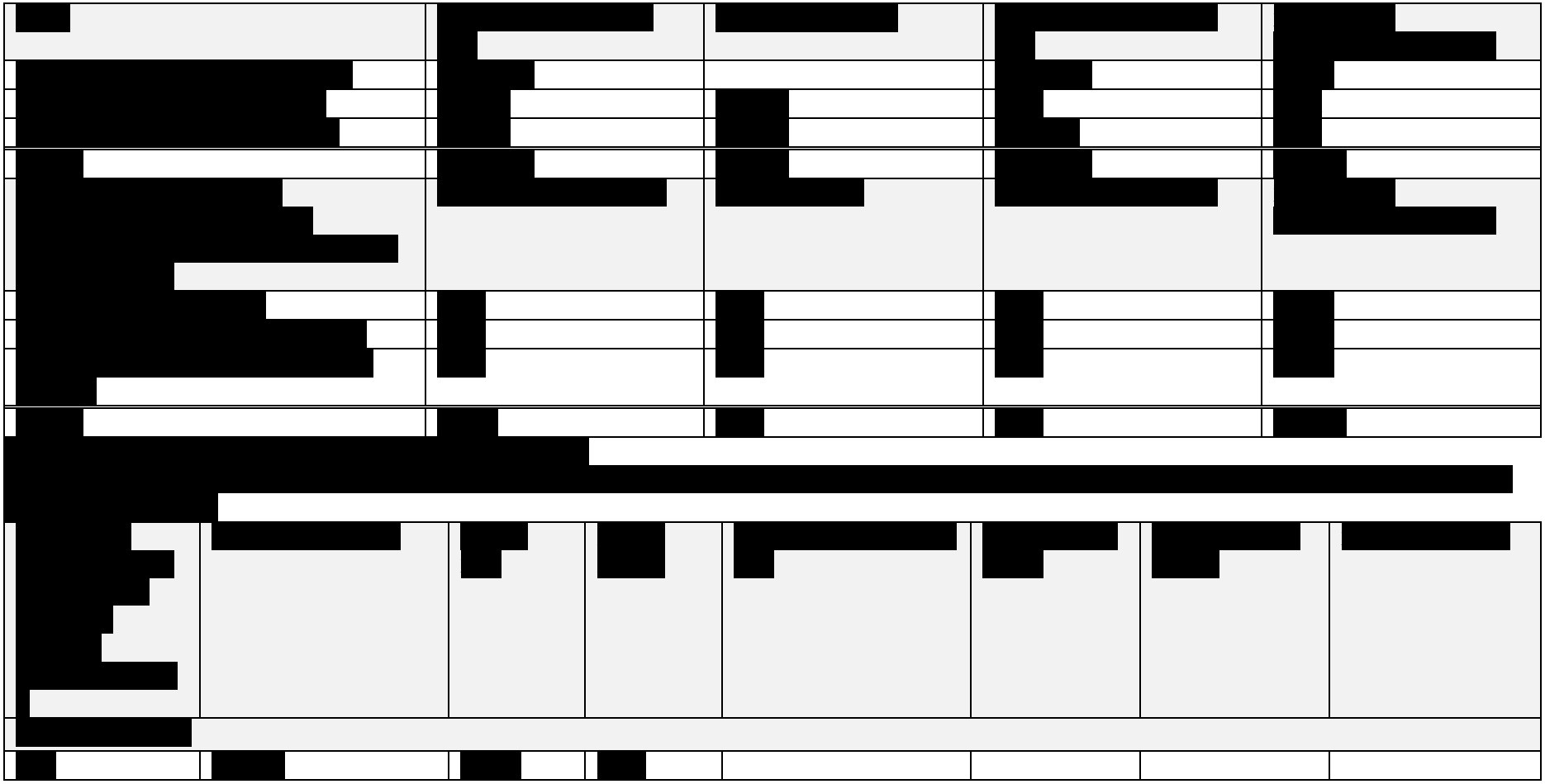
[redacted]



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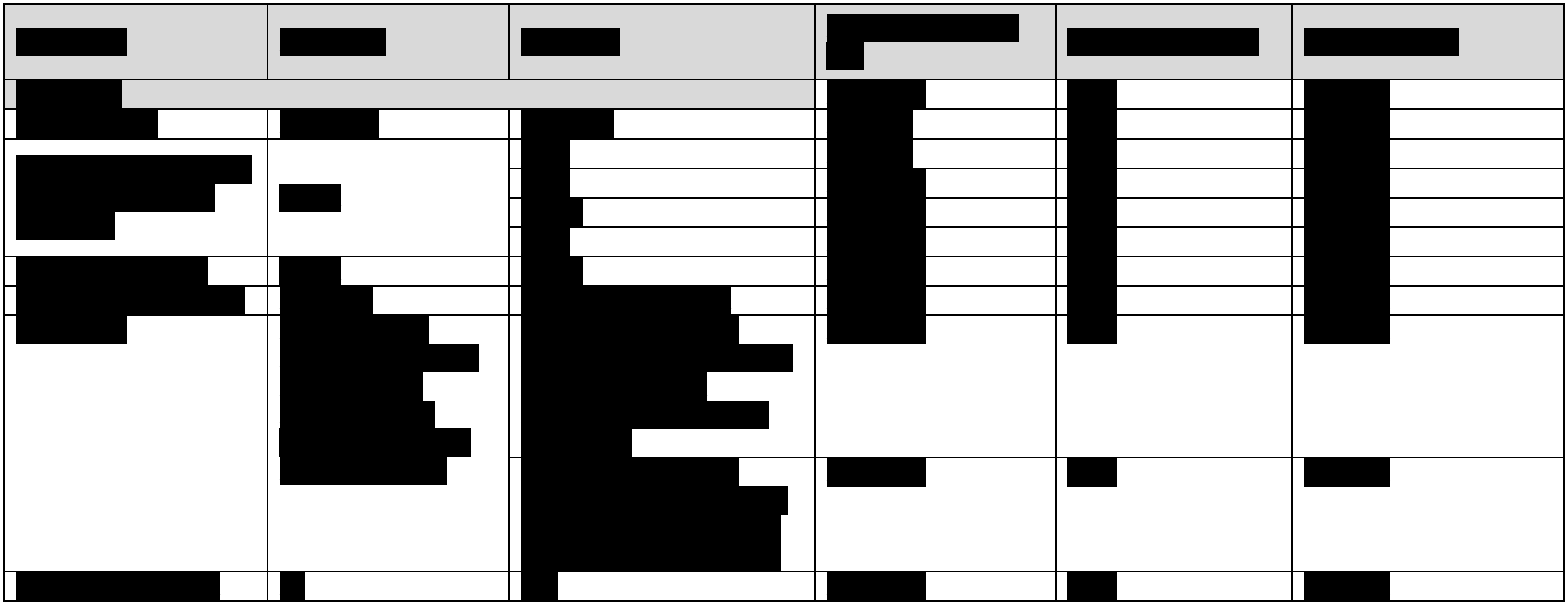

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **06 October 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Medical Expert for XLH UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Kywo Kiirin–** (£124,928.83, **Investigator initiated research grant to University of Oxford to describe the prevalence and natural history of XLH. Ceased** **Kywo Kiirin – < £ 10k, consultancy, speaker fees, advisory board <£10K . Ongoing.**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Nil**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Difference between NICE scope and company decision problem in terms of who is eligible for burosumab	Yes/No	The company decision problem is adults with a BPI ≥4 for whom conventional therapy is unsuitable. It is not clear if this is a BPI vs2 score of worst or average pain in the last 7 days and how this should be attributable to XLH and not osteo-arthritis of large joints and degeneration of spine. It would be preferable to broaden the scope to include pseudofractures as these are not invariably painful ≥4 as some adults limit their activities to reduce their pain to be manageable.
Key issue 2: Definition of treatment failure with conventional therapy and size of eligible adult population to receive burosumab in the NHS	Yes/No	The definition of treatment failure due to ineligibility or intolerance is reasonable. The definition of insufficient efficacy requires both a reasonable time interval (e.g. 12 weeks of therapy) and reasonable threshold for ineffectiveness based on pain reduction (< 30%) or fracture healing (no radiological evidence of healing). While there is uncertainty regarding the number of patients affected by debilitating symptoms and clinical complications, this is matched by uncertainty regarding the number of patients who would exit burosumab due to lack of sufficient clinical response or intolerability.
Key issue 3: Generalisability of the cost-effectiveness data and trial	Yes/No	There is a lack of specific trial data for the transition population from paediatric to adults with burosumab. Burosumab is generally well tolerated in childhood resulting in minimal symptoms. It is reasonable to expect the cessation of

evidence to a burosumab-experienced population		burosumab in the young adult setting would lead to a sudden and persistent lowering of serum phosphate. It is reasonable to assume this ongoing hypophosphataemia would have a progressive negative effect on the young adult's musculoskeletal status resulting in worsening bone fragility, increasing muscle stiffness and weakness, and joint disease including at the spine. It is reasonable to assume that once initiated, joint and spinal disease is irreversible and progressive. It is therefore plausible that the continued use of burosumab at a 4 not 2 weekly titrated dose would maintain serum phosphate levels and avoid these adverse clinical sequalae.
Key issue 4: Baseline imbalances in the CL303 trial	Yes/No	The CL303 was a randomised double blinded for the first 24 weeks. XLH in adults leads to a premature age-related onset of a wide range of progressive skeletal fragility and joint disease. While it is reasonable to expect regression to the mean for patients with higher pain score at the same age, it is unreasonable to assume the older adults with more pain, stiffness and worse function would undergo similar regression to the mean as age is a stronger predictor of complications in XLH. The placebo response to pain is noted but there was no placebo response to physical function (which worsened by 24 weeks) or stiffness (that remained unchanged).
Key issue 5: Lack of efficacy of burosumab on patient-reported outcomes	Yes/No	The trial patients with burosumab had been accruing musculoskeletal damage for approximately 40 years. It is reasonable to expect the benefits rom burosumab to accumulate over time. It is reasonable to interpret the benefits form the longer-term follow-up data as burosumab mediated as it is clearly shown that adults who stop burosumab lose benefits on pain, stiffness, reported function, observed function and fatigue (Karmenicky RMD Open 2023 PMID 36854566 figure 4).
Key issue 6: Age and weight distribution of CL303 population	Yes/No	I agree the age and weight of the EAP population is higher that CL303 population. However the EAP population over time will become less representative of the adult population as more adults continue burosumab following transition, which will reduce the age and potentially the weight.
Key issue 7: Modelling the incidence of morbidities and mortality as independent events	Yes/No	The precise mechanisms for the increased in mortality from XLH are unclear. From the natural history studies, it appears a diagnosis of XLH is associated with greater deprivation (Hawley Rheumatology 2021, PMID 33331900). Greater deprivation could be due to increased childhood morbidity negatively impacting on educational

		attainment and poorer adult health negatively impacting on employment opportunities as well as increased mortality through long-term analgesic use., poorer mental health and physical inactivity. These mechanisms represent a fracture-independent mechanism for burosumab reducing mortality. Further, while osteoporotic hip fractures are associated with significant mortality, the XLH associated hip fractures result from a different mechanism (pseuofractures) and I am not aware of the evidence for an increased mortality after hip fractures in XLH.
Key issue 8: Excess mortality for individuals with XLH		There may be methodological difference between the Hawley analyses and the CPRD Gold and Aurum analyses. In Hawley et al, the controls were matched by age, sex and GP practice. It would be critical to understand the control selection for the GOLD/ AURUM analysis and how they were matched as this could influence the HR.
Key issue 9: Treatment stopping criteria and long-term discontinuation rates		The indication for initiating burosumab in older adults is to improve symptoms and function. There is a burden of blood testing and injections with burosumab use. It is reasonable to assume a subset of adults will have experience a small benefit on their symptoms from burosumab that they feel does not justify the ongoing modest burden of continuing burosumab.
Key issue 10: Burosumab reduction in fracture incidence rates		At present, no adult has experienced an incident major pseudofracture on burosumab (Weber JCEM 2023, PMID 36072994). Further, the bones of adults with burosumab are wider with often higher bone density that adults without XLH and it is reasonable to expect in those initiate burosumab in adulthood will experience a very high reduction in fracture risk.
Key issue 11: Burosumab effect on mortality		I agree that there is no trial data supporting the reduction in mortality. Further, there are significant methodologic challenges in comparing mortality rates in those on long-term burosumab with those not on burosumab (and probably milder disease) and historical controls (given life-expectancy is not constant). It would be reasonable to include a mortality benefit and use a range of values from 20, 40 and 60%.
Key issue 12: The effect of burosumab treatment on utility		It would be unreasonable to exclude the 96 week data for assessing the benefit from burosumab. The adults in the trial had lived with XLH for over 40 years and it is clear that across mainly musculoskeletal disorders, there is a cumulative benefit

change from baseline and extrapolation of effect over time		from burosumab over time, most clearly demonstrated by the progressive healing of pseudofractures which is counter intuitive given the expected worsening of PROMS with aging, especially in XLH.
Key issue 13: Placebo-adjusted utility values. Uncertainty about whether the utility gain for burosumab compared to the baseline utility should be adjusted for the placebo effect observed		As already stated, the placebo effect was only seen for one of the patient reported outcomes (BPI pain) and not for stiffness, reported physical function or observed walkng distance in 6 minutes. It would reasonable to adjust the pain endpoints for a placebo effect but not the other patient reported outcomes.
Key issue 14: Disutility for incident fractures. Uncertainty about the magnitude and duration of the disutility associated with incident fractures and the assumption of independent effects when multiple events may occur over a lifetime horizon.		From the CL303, many patients entered the study with pseudofractures despite years of phosphate and activated vitamin D therapy. Only 7.7% of pseudofractures healed at 12 and 24 weeks in the placebo arm compared with 20% at 12 weeks, 43.1% at 24 weeks and 63.1% at 48 weeks. This suggests that XLH related pseudofractures are usually longstanding and it is unreasonable to expect the majority of these fractures to heal. Again, the fracture-specific mortality in the XLH setting is unlikely to be similar to that seen in osteoporotic fractures.
Key issue 15: Utility benefit on caregivers and family members. Uncertainty about the magnitude of treatment benefit on caregivers and family members who support adults		The increasing impact of XLH on adults results in a dynamic but progressive carer burden over time. In early adulthood, when impact is low, there maybe no carer burden. However, in later life, often the younger family members are giving significant informal care. I would need access to Appendix S to add further detail.

with XLH and the number of caregivers		

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Single Technology Appraisal (STA)

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

EAG addendum: review of company's response to technical engagement

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The authors have no competing interests to declare.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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Overview of the company response to the issues raised at technical engagement

The External Assessment Report (EAR) covered 15 key issues for consideration at technical engagement (Table 1). The company's response to technical engagement (TE) includes a response to six of these key issues: Issue 5, 8, 12, 13, 14 and 15. At the TE meeting with the company to discuss the EAR, the company confirmed that they had no new evidence or commentary to supply for issues 1 to 4, 6, 7, 9 (partial response included with issue 13), 10 and 11. Therefore, the EAG considers these issues to remain unresolved.
In response to TE, the company provides additional evidence to support one of the six issues considered: a recently published study on mortality in XLH to support issue 8. The company does not accept any of the External Assessment Group's (EAG) preferred assumptions and resulting incremental cost-effectiveness ratios (ICERs). However, the company does accept the modelling errors identified and corrected by the EAG. The company presents summary results of an updated base case analysis and scenario analyses incorporating the corrections identified by the EAG. The company's updated base case results match those reported by the EAG in Section 5.3 of the EAR. The additional analyses undertaken by the EAG and presented in Section 6 of the EAR already incorporate these corrections. Therefore, the results of the EAG base case and scenario analyses remain unchanged.
In this addendum, the EAG provides a response to the six issues addressed by the company at TE. The EAG's position remains unchanged from that expressed in the updated EAR of 26th September 2023. None of the issues raised at TE are resolved (see Table 1).

Table 1: Summary of the key issues

Issue		Resolved?
1	Difference between NICE scope and company decision problem in terms of who is eligible for burosumab	No (no company response)
2	Definition of treatment failure with conventional therapy and size of eligible adult population to receive burosumab in the NHS	No (no company response)
3	Generalisability of the cost-effectiveness data and trial evidence to a burosumab-experienced population	No (no company response)
4	Baseline imbalances in the CL303 trial	No (no company response)
5	Lack of efficacy of burosumab on patient-reported outcomes.	No
6	Age and weight distribution of CL303 population	No (no company response)
7	Modelling the incidence of morbidities and mortality as independent events	No (no company response)
8	Excess mortality for individuals with XLH	No
9	Treatment stopping criteria and long-term discontinuation rates	No (partial company response included with issue 13)
10	Burosumab reduction in fracture incidence rates	No (no company response)
11	Burosumab effect on mortality	No (no company response)

12	The effect of burosumab treatment on utility change from baseline and extrapolation of effect over time	No
13	Placebo-adjusted utility values	No
14	Disutility for incident fractures	No
15	Utility benefit on caregivers and family members	No

Critique of the company's response to the issues raised at technical engagement

Issue 5: Lack of efficacy of burosumab on patient-reported outcomes.

The EAG's original engagement point states:

> After accounting for possible regression to the mean (see Issue 4) and placebo effects, the EAG found no clear evidence of a difference between burosumab and placebo for most patient-reported outcomes (pain, physical functioning and fatigue); most differences between burosumab and placebo appeared not to be clinically meaningful, and were generally not statistically significant. This raises concerns as to how to interpret results in the non-randomised, open-label, longer-term follow-up data.

The company response covered 4 points:

1. Statistically significant improvements were seen in the CL303 trial.
2. The company's change from baseline analysis did account for regression to the mean and placebo effects.
3. Minimal Clinically Important Differences (MCID) do not represent meaningful benefits to patients.
4. EMA acceptance of meaningful HRQoL benefits with burosumab.

We respond to these points below.

The EAG's response

Point 1

The company claimed that: "At Week 24, participants had statistically significant improvements from baseline in WOMAC stiffness, BPI worst pain (average and greatest), BPI pain interference, and BFI worst fatigue (average and greatest), compared with placebo" The company cite the analysis of the trial by Isogna et al (2018)[1] to justify this claim. The EAG note that the paper actually reports the following:

> Burosumab significantly reduced the WOMAC stiffness subscale score at week 24 relative to placebo (–8.1±3.24; p=0.012); differences favoring burosumab over placebo for WOMAC physical function subscale score (–4.9±2.48; p-0.048) and reduction in BPI worst pain score (–0.5±0.28; p=0.092) at week 24 did not achieve the significance levels of 0.025 and 0.05, respectively, required with Hochberg adjustment.

The EAG therefore notes that only for WOMAC stiffness was burosumab had a conclusively statistically significant different from placebo at 24 weeks, based on the Isogna et al analysis[1]. This concurs with the EAG's own analysis (EAG report figure 10). We also note

that these are change-from-baseline analyses, which we consider may overestimate the effect of burosumab (see below).
The company also claimed: "At Week 48, statistically significant improvements from baseline were maintained for all WOMAC and BPI-SF scores", and similarly for Week 96. The EAG notes that these are **absolute** changes in scores from baseline, and not the **comparisons** with placebo that are required. The trial was not placebo controlled beyond 24 weeks, and there was evidence of a placebo effect for many outcomes (see EAG report Figure 9). Responder analyses for patient reported outcomes presented by the company also showed evidence of a placebo effect and no statistically significant difference between burosumab and placebo (see EAG report section 3.2.4). Therefore, it is not possible to assess whether burosumab is superior to placebo beyond 24 weeks. In addition, the lack of blinding of participants after 24 weeks follow-up means that results for patient-reported outcomes are at high risk of bias.

Point 2

The company claims that "The pre-specified 24 week trial analyses … compared change from baseline between burosumab and placebo. This adjusts for baseline imbalance." And "… analyses account for any placebo responses or regression to the mean effects…"
The EAG disagrees with these claims. We note that a change-from-baseline analysis only corrects for baseline imbalance **when there is no association between baseline values and effect of the intervention.** If an intervention is more effective in people with worse baseline values, then a change from baseline analysis may give a biased result.
The EAG considers that an association between baseline value and outcomes is certainly possible in XLH treatment due to regression to the mean: people with unusually high pain, for example, might see pain reducing to more typical levels over time regardless of treatment received. Pain and function outcomes were consistently worse at baseline in the burosumab arm of CL303. Therefore, the EAG is concerned that the effect of burosumab may be overestimated because at least some of the estimated benefit may be due to regression to the mean, or other impacts of baseline value on effect.
The EAG acknowledges that its *ad hoc* analysis of just the data at 24 weeks (EAG report Figure 11) may underestimate the effect of burosumab. However, the purpose of this analysis was to remove any impact of regression to the mean by asking the simple question "Do patients on burosumab have better pain/function than patients on placebo after 24 weeks?" We think that the small size of the effect estimates, and lack of statistical significance in these analyses, show that there is no substantive evidence that burosumab is superior to placebo in absolute terms. We think this is of concern and worthy of committee discussion.
The EAG further notes that analyses to correct for possible regression to the mean are feasible with the full data. For example, models could include an interaction with baseline values, or analyses matching placebo and burosumab patients by baseline values could have been performed and presented by the company to address this issue.
A post-hoc analysis of the trial by Brandi et al (2022)[2] highlights some of our concerns with possible regression to the mean. Figure 3 in that paper found that for WOMAC physical function there was no difference between burosumab and placebo in patients whose baseline function score was below 47.8. Burosumab was also less effective at reducing BFI worst pain in patients with less severe baseline pain (Figure 4).

Point 3

The company stated that MCID thresholds, which were derived from CL303, were based on "distribution and anchor" population-based approaches, using differences of 0.5 SDs in the outcomes and response.

The EAG thinks that achieving a 0.5 SD improvement represents an appropriate minimally important benefit for the purposes of trial analysis. We therefore think it is important to highlight that burosumab did not meet this threshold for any pain or function outcome in 24 weeks. We note that the EMA report considered the same MCID thresholds and stated:

> For WOMAC Stiffness, mean improvement corresponding to MCID was reached by approximately Week 36 and for WOMAC Physical function beyond Week 96, whereas the mean improvements did not reach MCID for BPI Worst pain during the course of the study.

The EAG notes that these are absolute changes in outcomes, and not comparisons with placebo as is really required.

The company claimed that "they [MCIDs] do not represent a threshold at which changes become meaningful for individual patients".

The EAG notes that no evidence was provided as to what would represent a meaningful threshold for patients, nor that the patient threshold would be lower than the MCIDs.

Point 4

The company quote the EMA report:

> The totality of these data and the consistency of effect among the assessments demonstrate that, despite the long-term complications and symptoms experienced by adults with XLH, burosumab improves symptoms and function that are clinically meaningful to patients.

However, the EAG notes that the same section of the EMA report (page 96) also states:

> …the results from the PRO endpoints are not fully concordant… the quantitative effect of burosumab on PROs is considered modest…

The EAG consider that the EMA opinion is more nuanced than the company suggest. We note also that the EMA report may be referring to absolute effects of burosumab, rather than comparisons with placebo, and that these conclusions are based on the change-from-baseline analyses, with which the

EAG has significant concerns (see above).

Given the substantial disagreement between the company and the EAG, and the lack of any new analysis which could clarify the issue, the EAG do not consider this issue to be resolved.

Issue 8: Excess mortality for individuals with XLH

The EAG raised the issue that the excess mortality risk for individuals with XLH compared to the general population hazard of death (hazard ratio of 2.88 [95% CI, 1.18 to 7.00]) was based on Hawley et al. (2020)[3] that used the UK Clinical Practice Research Datalink (CPRD) database from 1995 to 2016, whereas the company had provided a confirmatory study (Appendix R of CS) based on extending Hawley et al. on a larger sample of data from the UK CPRD GOLD and AURUM databases and with more recent data (data from CPRD GOLD available from 1995 to June 2022 and CPRD AURUM from 1995 to January 2022) using the same XLH grading algorithm. The EAG considers it more appropriate to use the observed excess mortality risk from the company's study (hazard ratio of 2.33 [95% CI, 1.16 to 4.67]), which was conducted using the same methods and subject to the same limitations as Hawley et al.

In response to TE, the company provides additional evidence in the form of a recently published study showing increased mortality and morbidity in patients with chronic idiopathic hypophosphatemia, induced by X-linked hypophosphatemic rickets or tumour-induced osteomalacia, for a Korean population (Kim et al. 2023)[4]. Using the Korean Health Insurance Review and Assessment claims database from 2003 to 2018, the study identified 154 patients with non-secondary and non-renal hypophosphatemia and compared outcomes

with ten matched controls of the same age, gender and index year. A higher risk of mortality for hypophosphatemic patients compared to controls (hazard ratio of 3.26 [95% CI, 1.83–5.81]) was shown [4].

The EAG's response

The EAG does not consider the additional evidence presented by the company sufficient to address issue 8 and resolve the discrepancy between the EAG and company's preferred source of evidence for the excess mortality risk for individuals with XLH. The study by Kim et al. (2023)[4] provides additional supportive evidence of a higher risk of mortality for individuals with XLH compared to the general population hazard of death. However, the EAG considers the UK CPRD GOLD and AURUM databases for the identification of XLH cases in the UK to be most relevant to inform the decision problem rather than data from a Korean population. In addition, the evidence from the larger sample of UK data that includes more recent data from 2016 to 2022 is the EAG's preferred source of evidence.
Therefore, the EAG's position on issue 8 remains unchanged, and we do not consider the issue to be resolved.

Issue 12: The effect of burosumab treatment on utility change from baseline and extrapolation of effect over time

The EAG noted that after 24 weeks, only open label and single arm data for less than 3 years of treatment are available to support burosumab benefits in relation to symptoms in the long-term with continuous treatment. The EAG raised the issue that the data informing the change from baseline in WOMAC scores for burosumab after week 96, which marks the end of the treatment continuation period of CL303, is based on different participant populations from CL303 (week 120 data was informed by US participants from CL303 only, week 132 data from BUR02, week 144 data from BUR02 and US participants from CL303, week 156 and 168 from BUR02). The EAG noted that the company's asymptotic model fit that is used to extrapolate the utility benefit of burosumab beyond the observed periods is heavily influenced by the post-week 96 data because there is a noticeable spike in the change from baseline mapped utility values from week 96 to week 120 (see Figure 1 below, reproduced from Figure 39 of CS), while after week 120, the data is increasingly uncertain due to low numbers of observations providing data in subsequent periods (only a total of 10 participants provide data in weeks 156 and 168). Therefore, the EAG considers the WOMAC data up to week 96 from the treatment continuation period of CL303 to be the only reliable source to inform the asymptotic model fit that is used to extrapolate the data over the long-term, in the absence of data from the burosumab Early Access Programme (EAP) in England.
In response to TE, the company argues that it is appropriate and valuable to make use of all the long-term data post 96 weeks and that the BUR02 long-term follow-up data should be included in the analysis. The company also clarified that the trial duration differed between European and US participants of CL303, where US participants were eligible to continue beyond 96 weeks under the CL303 protocol while European participants from CL303 were eligible for enrolment in the BUR02 study after week 96.

The EAG's response

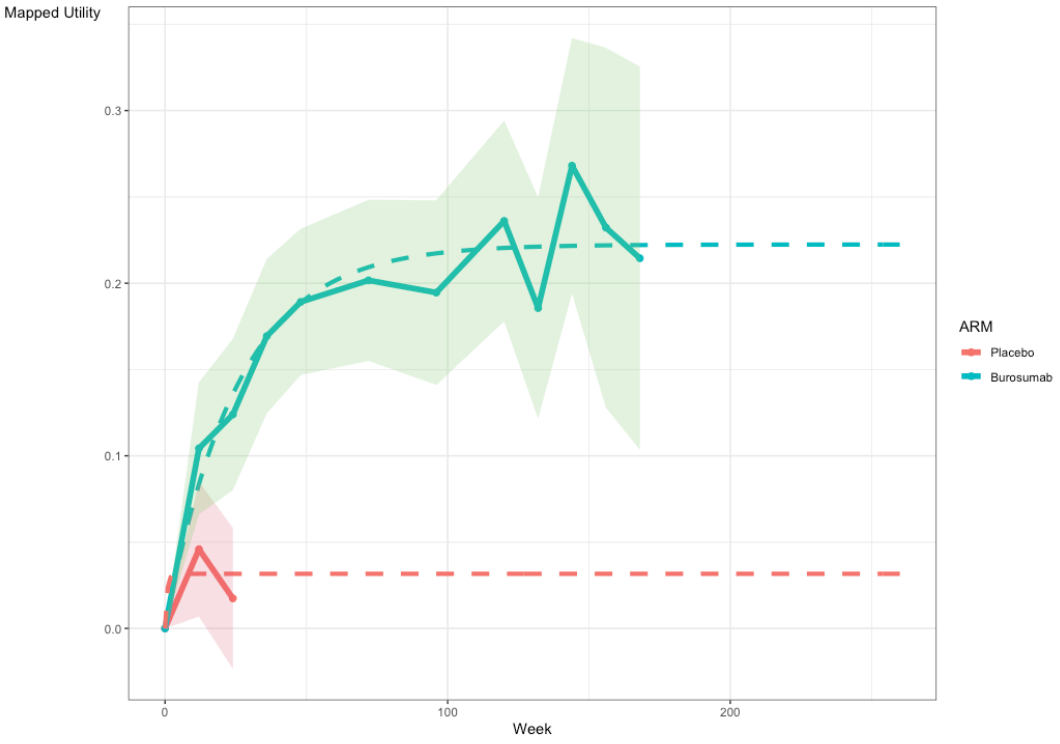
The EAG agrees, in principle, that it is appropriate to make use of all available long-term data. However, the EAG's key concern is that there are noticeable spikes in the change from baseline mapped utility values based on the post-week 96 data (see Figure 1 below) that give rise to an increase in the long-term mean change in utility while receiving burosumab, which

have not been explained in the company's response to TE. For example, the mean change in utility from baseline for year 3 and beyond is 0.215 based on using all available long-term data, while the corresponding mean change is 0.191 based on using data up to week 96 only; this difference of 0.024 extrapolated over a lifetime horizon is an important driver of the cost-effectiveness results. The difference pre- and post- 96 weeks also suggests that the asymptotic model is heavily influenced by the post-week 96 data, which is much more uncertain than the pre-week 96 data. By incorporating post-week 96 data from different participant populations of CL303 and very small samples of data, more variability is introduced in the asymptotic model, with the predicted utility change from baseline producing a much larger estimate than the observed utility change between weeks 72 and 96 (see Figure 1 below for comparison of the asymptotic model predictions [green dashed line] with observed utility change [green solid line]).

The EAG have not been presented with a comparison of the baseline characteristics for each of the participant populations used to provide data at each follow-up time point (clarification question B19c) in order to explore any potential differences between participants that might explain the increase in utility at weeks 120 and 144.

Therefore, the EAG's position on issue 12 remains unchanged, and we do not consider the issue to be resolved.

Figure 1 Asymptotic model fit for change from baseline in mapped utility values for burosumab and placebo (reproduced from Figure 39, p142 of CS)



Weeks	0	12	24	36	48	72	96	120	132	144	156	168
Tx Obs	55	55	55	54	55	50	49	42	11	23	10	10
Placebo Obs	65	65	65	0	0	0	0	0	0	0	0	0

Issue 13: Placebo-adjusted utility values

The EAG raised an issue regarding whether the change from baseline in mapped utility values for burosumab (green dashed line in Figure 1 above) should be adjusted for the placebo effect observed in the 24-week period of CL303 (red dashed line in Figure 1). The company uses the non-placebo-adjusted utility values in the model, which means that the placebo effect observed in the controlled period of the CL303 trial is not deducted from the mean change from baseline utility for burosumab. The EAG considers there to be uncertainty about whether to use the placebo-adjusted or non-placebo adjusted utility values in the model. In response to TE, the company justifies the choice of non-placebo adjustment for the following reasons:

- Placebo arm utilities showed an initial improvement at 12 weeks, followed by a return to near baseline levels at 24 weeks, suggesting that any placebo effect on utility is short-lived.
- WOMAC outcomes following burosumab interruption between finishing study CL303 and starting study BUR02 (reported in Kamenicky [2023][5]) show that patients returned to baseline WOMAC scores following withdrawal of treatment. This suggests that there is minimal regression to the mean. If there were significant regression to the mean, there would be a residual treatment effect following treatment interruption.

The EAG's response

The EAG considers the exploratory findings from Kamenicky et al. (2023)[5] to provide only limited evidence to support the argument for the use of non-placebo adjusted utility values in the model. More specifically, the findings from Kamenicky et al. are based on 7 participants only. The study indicates a return to 'similar' levels of baseline scores, but how similar the WOMAC scores in the interim period translate to the small placebo effect of 0.03 is unknown. Also, it is worth noting that the mean difference in WOMAC total and subscale scores between those who received compassionate burosumab treatment (23 participants) and those without burosumab (7 participants) during the interim period was statistically non-significant in the WOMAC total score and subscale scores (except for stiffness)[5]. Therefore, the EAG considers this study to provide limited evidence to support this issue which remains uncertain. Note that the EAG's preferred base case assumption is the same as the company's assumption (use of non-placebo adjusted utility values) but the EAG considers this a remaining important uncertainty, with a scenario presented using placebo-adjusted utility values.

Application of stopping criteria

In response to issue 13, the company also provides justification for the use of a stopping rule for burosumab treatment. The justification is based on clinical advice that it would be unreasonable to continue therapy in patients who do not experience some perceived clinical benefit of treatment, over and above normalisation of serum phosphate, and that the draft document on recommended management of XLH in adults in the NHS (Mohsin et al[6]; see p. 41-42 of CS) recommends that burosumab therapy should be reviewed annually. Furthermore, the mechanism by which serum phosphate levels affect bone composition supports a clinical assessment at 1 year.

The EAG's response

The continuation of treatment in the model is based on a requirement of reaching serum phosphate levels above the lower limit of normal range at 24 weeks and an improvement in WOMAC total score at 12 months after starting treatment. The EAG raised the issue (issue 9

in the EAR) about whether this second hurdle of requiring improvements in WOMAC is necessary given: (i) the absence of alternative treatments for this patient population; (ii) the fact that WOMAC is not commonly used in UK clinical practice; (iii) the patient has reached the target of serum phosphate normalisation after week 24 and has the potential to experience a reduction in morbidities and mortality with phosphate levels maintained; and (iv) there may be other benefits to treatment with burosumab such as a reduction in opioid use for pain management, even if the required improvement in WOMAC total score is not observed. The EAG also notes that no stopping criteria were applied in either the CL303 trial or in the EAP in England.
Therefore, the EAG considers this issue to remain uncertain and unresolved.

Issue 14: Disutility for incident fractures

The EAG raised an issue that there is uncertainty about the magnitude and duration of the disutility associated with incident fractures and the assumption of independent effects when multiple events may occur over a lifetime horizon.
In response to TE, the company agrees that there is uncertainty over the duration of disutility associated with incident fractures in patients with XLH, given that such data has not been collected. Moreover, the company states that impaired bone mineralisation in XLH is likely to mean that fractures have a long-term impact on health-related quality of life (HRQoL), particularly in untreated patients. Fractures in XLH patients with uncorrected serum phosphate are slow to heal, and some untreated patients experience non-healing fractures. The company also states that Skrinar 2019[7] reports that pain scores are higher in XLH patients with a history of fracture at any time in the past, which indicates a long-term impact of fractures on HRQoL.

The EAG's response

The EAG considers this issue to remain uncertain. In the company's model some of the fractures (tibia/fibula, femur/pelvis, foot, and vertebrae/spinal fractures) accrue a lifetime utility decrement. The EAG has a concern that this may overestimate the disutility associated with fractures. First, it does not reflect the likelihood of fracture healing over time, which could lead to improvements in HRQoL rather than assuming a constant lifetime disutility after the event (post-year 1). Second, because mortality and morbidities are modelled independently, the duration of lifetime disutility associated with fracture events is not adjusting for fracture-specific mortality. Third, the disutilities associated with fractures in addition to the treatment-specific utilities may represent some double counting of morbidity effects because the treatment-specific utility values are extrapolated over a lifetime. Note that the EAG's preferred base case assumption is the same as the company's assumption in the absence of alternative estimates (i.e., lifetime utility decrement associated with incident fractures), but the EAG considers this a remaining important uncertainty, with a scenario presented that assumes the disutility for incident fractures applies in the first year of the event only.
Therefore, the EAG considers this issue to remain uncertain and unresolved.

Issue 15: Utility benefit on caregivers and family members

The EAG raised an issue that there is uncertainty about the magnitude of treatment benefit on caregivers and family members who support adults with XLH and the number of caregivers. The company's base case assumes a spillover benefit on family members and caregivers equal to 20% of the patient utility benefit of burosumab and applied to two caregivers/family

members, which results in a utility improvement associated with burosumab of 0.086 from year 3 and beyond. The EAG has a concern that the spillover effect may be overestimated by including an effect on two caregivers/family members, where two may be reasonable for a child but less so for an adult, particularly noting that burosumab is administered in a way that supports patients to be independent and less likely to impose additional burden on family members. The EAG also notes that there is no evidence to support a 20% patient utility benefit on caregivers and family members.
In response to TE, the company agrees that adult XLH patients do not require support with treatment administration but caregivers and family members can be affected in multiple ways:

- Supporting the person with XLH with daily activities (e.g. getting in and out of the bath, transport);
- Having to take on a larger share of day-to-day household and economic responsibilities due to the restricted abilities (mobility problems, pain, stiffness, fatigue) of the person with XLH;
- Being restricted in the activities the family can undertake (e.g. children may not be able to attend activities because a parent cannot take them there; outings may be difficult; social participation for the family may be restricted)

The company also states that the utility improvement for family members and caregivers in the model is less than the loss of utility identified (0.081) for the impact of caring for an adult with XLH based on the company's research study.

The EAG's response

The EAG considers this issue to remain uncertain. In the company's research study (see Appendix S of CS) using the EQ-5D-5L with informal carers or family members of adults diagnosed with XLH in the UK (a total of 16 participants without XLH providing informal care), the mean difference in observed (for carers without XLH) versus expected EQ-5D utilities, when compared with age-linked UK general population utility data, was -0.081 (95% CI: -0.190 to 0.029), which is not statistically significant. The company also undertook a targeted literature review exploring the burden and spillover effects on carers and family members of adults with musculoskeletal conditions and found conflicting results, with quantitative research studies indicating minimal spillover effects while qualitative studies reveal significant impacts.
Therefore, the EAG considers this issue to remain uncertain and unresolved. The EAG's preferred base case assumption includes a utility benefit for caregivers and family members but for one caregiver/family member only.

Modelling assumptions and results

In response to the issues noted in the EAR, the company have not updated their base case modelling assumptions. The EAG preferred base case assumptions and alternative scenarios also remain unchanged. However, the company does accept the modelling errors identified and corrected by the EAG in Section 5.3 of the EAR. In response to TE, the company presents summary results of an updated base case analysis and scenario analyses incorporating the corrections identified by the EAG. The company's updated base case results match those reported by the EAG in Section 5.3 of the EAR. The additional analyses undertaken by the EAG and presented in Section 6 of the EAR already incorporate these

corrections. Therefore, the results of the EAG base case and scenario analyses remain unchanged.

[redacted]

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