NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

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   - **Clinical expert**, nominated by British Paediatric & Adolescent Bone Group (BPABG) and Birmingham Women's & Children's NHS Foundation Trust
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Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Burosumab for treating X-linked hypophosphataemia [ID1151]

This slide set is the pre-meeting briefing for this evaluation. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

Key issues for consideration

Clinical effectiveness

- How is burosumab expected to be used in practice?
  - Marketing authorisation: for children and adolescents with growing skeletons; expected up to age 16 in girls and 17 in boys
- Does the clinical evidence provide a suitable basis to establish the effectiveness of burosumab, compared with conventional therapy?
  - Children aged 1–4: CL205 single-arm study
  - Children aged 5–12: CL201 vs CL002 – naïve and adjusted comparisons
  - Children aged 13+: no evidence presented
- Is burosumab clinically effective?
  - Do RSS and RGI-C capture important aspects of XLH?
  - Significance of the findings from CL205 and CL201?

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Key issues for consideration

Cost-effectiveness

- Is the economic model suitable for decision-making?
  - Do the model health states (based on RSS) appropriately map the course of XLH and capture the key elements of the disease?
  - Is it appropriate to assume lifetime disease stabilisation at the end of treatment?
- What are the most appropriate assumptions?
  - Transition probabilities: ERG amendments?
  - Utility values: company vs ERG values? Decline in utility after 20 years?
  - Discount rate: 1.5% or 3.5%?
- What is the committee's view on the probabilistic analyses?
- What is the committee's view on additional uncertainties in the model?
  - Difference in effect between age groups
  - Baseline weight, age and disease severity
  - Adverse events
- What factors affecting the guidance need to be taken into account?
  - Population contains children: any additional considerations required?
- What are the most plausible ICERs?
- Application of QALY weighting?

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Disease background

- X-linked hypophosphataemia (XLH) is a rare, chronically debilitating and deforming disease
- It is a genetic, X-linked dominant disorder caused by mutations in the PHEX gene
  - Inactivates PHEX enzyme, leading to an erroneous signal in phosphate sensing, which leads to increased levels of fibroblast growth factor 23 (FGF23)
- Excess FGF23 drives pathophysiology, leading to impaired phosphate conservation and excessive phosphate excretion. It also supresses vitamin-D production, decreasing calcium and phosphate absorption
- Clinical expression of XLH is widely variable, partly due to genetic differences. Males are more severely affected than females
- Estimated population size in England aged 1 – 17 years: [redacted] and [redacted]

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Patient organisation and clinical expert estimate around 1:20,000 to 1:60,000 new births with XLH in the UK

Course of the disease

- Symptoms of XLH usually begin in early childhood
  - Heterogeneity in the occurrence and severity of symptoms in children and adults
- Early signs include skeletal abnormalities such as noticeably bowed or bent legs, short stature, and irregular growth of the skull
- Children may present with delayed walking or a waddling gait
- Over time, symptoms may progress to include further skeletal and non-skeletal manifestations (next slide)
- Bone deformities become irreversible when growth stops
- If undiagnosed in childhood, adults present with bone/joint pain, fractures, mineralisation defects, dental anomalies and fatigue
- Patients often need orthopaedic surgery to correct bone deformities

Children		Adults
Progressive damage to growing skeleton	→	Impact of established skeletal damage
	→	Further progression of skeletal damage?
Other physiological effects of low phosphate (e.g. fatigue, muscle function)	→	Ongoing non-skeletal physiological effects

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Symptoms and complications

- Rickets is associated with substantial skeletal deformities which limit physical function and lead to life long disability and pain – lower HRQoL
  - Bowing of the femur, tibia and/or fibula can be substantial and severe
  - Further deformities – e.g. hip deformity (coxa vara), tibia rotation, craniosynostosis, spinal deformities
  - Children often have difficulties with motor activities – e.g. walking, running
  - Impairment of growth and short stature – can have psychosocial consequences
- Further skeletal effects: bone pain, joint pain caused by hardening (calcification) of tendons and ligaments, and dental abscesses
- Some patients experience hearing loss (predominately sensorineural)
- Low serum phosphorous may also cause further physiological effects: muscle dysfunction, reduced physical functioning, and fatigue

XLH Symptoms	
Rickets related	**Other bone defects**
• Leg bowing • Delayed walking • Enlarged cartilages • Waddling gait • Short stature • Bone and/or joint pain • Fractures • Dental problems	• Craniosynostosis • Calcification • Osteoarthritis
	Other symptoms
	• Hearing loss and vertigo • Fatigue • Muscle dysfunction

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Patient perspectives: *XLH*

Impact of XLH	
Children	**Adults**
• Physical pain • Missing schooling, and being unable to participate in sporting activities • Teasing and bullying due to appearance • Significant emotional and social impact in children	• Adverse outcomes continue in to adulthood, impacting working choices and subsequently finances • Appearance can affect relationships • Family planning has an impact on mental wellbeing and relationships • Amplified burden when XLH is passed to children – physical and emotional

- *"My daughter is regularly upset at not being able to take part in sports for example and comments from other children about her height and her knock knees."*
- *" … missed a lot of school due to pain meaning he's unable to attend, also long periods of time off school due to operations"*

- *"I have been emotionally and physically impacted by this condition."*

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Patient perspectives: *Living with XLH*

- XLH causes physical pain:
  - When doing exercise or walking too long
  - Can result in an inability to attend work or school
  - Reliant on care and assistance from others – loss of independence
- The condition causes emotional suffering:
  - Having a noticeable physical difference means people stare. Children with XLH are bullied, which has an impact on both parents and children.
  - Parents can feel responsible for suffering in children
- In older age XLH can cause spinal stenosis and severe leg bowing
  - Leaving people unable to walk and potentially bedbound
- As XLH can be passed on to children, multiple individuals in one family are often diagnosed with XLH:
  - Reproductive decisions are complicated and emotionally challenging
  - You can't rely on family members who are also suffering

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Patient perspectives: *Diagnosis*

Diagnosis

- Testing of children of parents with XLH reduces diagnosis time
- Adults with XLH report diagnosis delays due to lack of knowledge
- Earlier treatment improves outcomes
- Misdiagnosis of rickets in children can delay XLH diagnosis until 3 years +
- Delayed diagnosis can lead to a need for corrective surgery

- *"I was misdiagnosed at 18 months of age as having Rickets so given Alphacalcidol drops only."*
- *"At around 10 years of age, I was diagnosed with XLH. I already had severe bowing by this age…"*
- *"Diagnosis is particularly a challenge in those where there is no family history of XLH…"*
- *"It's also challenging to learn that delays in obtaining the diagnosis means a delay in treatment at a critical time for bone growth."*

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Current treatment options

- There are no therapies that treat the underlying cause of XLH
- Conventional therapy focuses on renal phosphate wasting, and vitamin D deficiency
  - Oral administration of phosphate and active vitamin D analogues (alfacalcidol, once daily) is commonly used
- Conventional therapy has poor adherence because:
  - It requires complex dosing (4 to 6 doses a day) regimens, and
  - Phosphate has an unpleasant taste and causes side effects
- Early treatment can result in improved outcomes
- In children, treatment aim at alleviating bone or joint pain, preventing skeletal deformities caused by rickets and improving growth
- The goals of treatment in adults are to reduce pain symptoms, the extent of osteomalacia, and/or to improve fracture healing or surgical recovery
- Corrective surgery of skeletal deformities is often required
- Root canals and tooth extractions are often performed due to dental disease caused by XLH

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Patient perspectives: *current treatment options*

- Current treatment options are flawed:
  - Children starting current treatment at birth still have significant leg bowing – does not stop symptoms
  - Phosphate solution is unpleasant to take and has unpleasant side effects - can cause diarrhoea and stomach pain
  - Administering 6 times a day and keeping phosphate cold is not practical
  - Many children will avoid taking treatment when inconvenient – they don't think about the long term impact
- There is an unmet need for an effective and practical treatment
  - An injection every 2 weeks is easier to manage – far preferable to phosphate
  - Side effects are less common and more manageable than current treatment
- Children stand to benefit most from an effective treatment as they are still growing and can avoid deformities – improved long term physical and emotional wellbeing
  - Treatment will also benefit adults as deformities can still occur later in life and the management of phosphate levels remains a challenge

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Clinical experts: *Current treatment experience*

Treatment aims to:	
• Promote healing of rickets • Improve growth rate • Prevent limb deformities • Improve dental health	• Improve myopathy • Reduce bone pain • Avoid or reduce complications • Avoid cranio-facial abnormalities
Current treatments for XLH	
• Phosphate and vitamin D – 4–6 times a day	• Surgery for lower limb deformity
Side effects of conventional therapy	
• Nausea • Calcification in the kidneys • Hyperparathyroidism	• Diarrhoea • Abdominal pain
Without treatment	
• Normal height not achieved	• Deformity is likely

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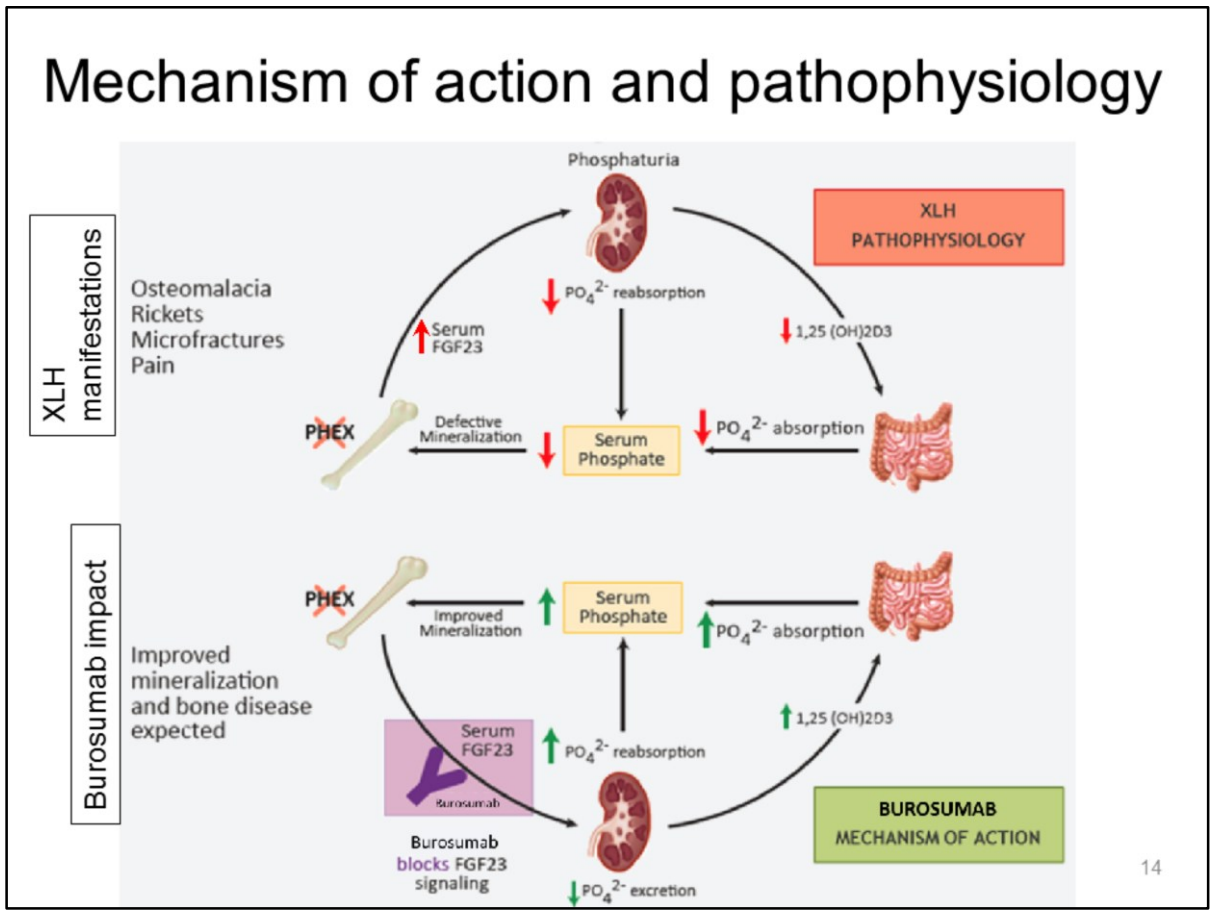
Burosumab (Crysvita, Kyowa Kirin)

Marketing authorisation	"for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons"
Mechanism of action	Monoclonal antibody that binds to and inhibits the activity of FGF23
Administration & dose	Subcutaneous injection, once every 2 weeks. Starting dose is 0.4 mg/kg, maintenance dose is 0.8 mg/kg. Dose can be escalated up to 2mg/kg, up to a maximum of 90mg. 16 week titration period in the burosumab studies.
List price	10 mg, 20 mg and 30 mg vials: £2,992, £5,984 and £8,976 per vial
Treatment course length	Treatment may begin from one year of age, and will continue until the skeleton ceases to grow (16 in girls and 17 in boys)

Source: Company submission



Source: Figure 1 company submission

PO4,2, phosphate
1,25(OH)2D3, vitamin D

Clinical experts: *Burosumab*

Innovation	
• Targets pathophysiology of XLH • No advances in 35 years	• Innovative administration compared to complex dosing of current treatments
Benefits of burosumab	
• Improved adherence • Improvements in growth rate • Reduced need for orthopaedic surgery • Improved quality of life	• Improved healing of rickets • Improved muscle function • No impact on length of life • Fewer side effects
Subgroups	
• Growing children with XLH rickets aged 6 months to 16 years are expected to benefit most	
Stopping treatment	
• Treatment expected to stop around age 13 to 16 years when growing halts	

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Patient perspective: *Burosumab*

Innovation of burosumab

"[burosumab] treats the underlying cause so would prevent many of the symptoms [...] this will mean less pain […] and also improve patients' mental state…"

Benefits of burosumab

- Improvement in pain, fatigue and physical function/mobility
- Improvements in growth and walking ability
- Fewer unpleasant side effects
- Potential reduction in surgery
- Improvement in rickets
- Reduced stiffness
- Treatment in early life would mean improvements in quality of life
- Less frequent dose is more practical
- Less monitoring / fewer doctors' visits

Limitations of burosumab

- Cannot reverse bone defects
- Administration could be challenging in children with a phobia of needles
- Trips to metabolic bone units for treatment could be costly

Subgroups

- Children treated before onset of symptoms could avoid bone defects
- Lesser benefit in adults (outside the MA), but can still improve pain

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Decision problem

	Final Scope	
Population	Children and young people with X-linked hypophosphataemia	
Intervention	Burosumab	
Comparator	Established clinical management without burosumab	
Outcomes	• fractures • severity of rickets • pain (including bone pain, joint pain and joint stiffness) • motor skills • growth (including height) • tooth loss and pain • skull and spinal deformities • health-related quality of life (for patients and carers). • adverse effects of treatment	• neurological complications (increased intracranial pressure, craniosynostosis, problems with hearing and balance, and spinal cord compression) • radiographic response • renal function • parathyroid hormone levels • alkaline phosphatase levels • mortality
Outcomes not captured in the studies	• fractures • tooth loss and pain • skull and spinal deformities	• neurological complications (as above) • mortality

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Source: Final scope and company submission

Clinical effectiveness evidence

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Clinical evidence summary

- Study CL205 (1-4 years)
  - Multicentre, open-label, single-arm, Phase 2 study
- Study CL201 (5-12 years)
  - Randomised, multicentre, open-label, dose-finding Phase 2 study
- Study CL002 (5-12 years)*:
  - Reference group for comparative analysis of outcomes in study CL201
  - Evaluates long-term safety and efficacy of conventional therapy

Additional studies:

- UK chart review:
  - Longitudinal review of patient records (n=43) from 3 expert centres
  - Informs economic model only
- Study CL301 – in progress, no data available yet
  - Phase III study evaluating safety and efficacy of burosumab compared to conventional therapy
  - Paediatric patients aged 1 to ≤12 years with XLH who have confirmed evidence of rickets (n=60)

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Clinical evidence summary (1)

Burosumab studies

Study	Study type	Location, duration and patient numbers	Primary outcome(s)
CL205	multicentre, open-label, single-arm, Phase 2 study	• 3 US centres • 40 week primary analysis of data • N=13, aged 1-4 years	Change from baseline in serum phosphorus
CL201	randomised, multicentre, open-label, dose-finding Phase 2 study	• US* • 40 week primary efficacy analysis, 64 week extended • N=52, aged 5 -12 years	Change from baseline rickets severity score (RSS)

Dosage

- CL205: **Q2W**; starting dose **0.8 mg/kg**, could increase up to 1.2 mg/kg
- CL201: **randomised to Q2W or Q4W**; starting dose **0.1, 0.2 or 0.3 mg/kg** Q2W (or equivalent Q4W), 16-week titration period
- *Licensed dose: **Q2W**; starting dose **0.4 mg/kg**, maintenance 0.8 mg/kg, maximum 2 mg/kg*

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Source: row 2 adapted from table 10 CS, row 3 adapted from table 11
*See company response to clarification question A12 (AIC)

Baseline characteristics (1)

	CL205	CL201	Study CL002
	(n=13)	Q2W (n=26)	Radiographic analysis set (n=[redacted])
Age (years), mean (SD)	2.9 (1.15)	8.7 (1.72)	[redacted]
Sex, male n (%)	9 (69.2%)	12 (46.2%)	[redacted]
Race White Black/ African-American Other	 12 (92.3%) 1 (7.7%) 0	 23 (88.5%) 2 (7.7%) 1 (3.8%)	[redacted]
Weight (kg), mean (SD)	12.92 (1.81)	31.87 (7.92)	[redacted]
Height (percentile for age and gender), mean (SD)	[redacted]	[redacted]	[redacted]
Standing Height (z-score), mean (SD)	-1.38 (1.19)	-1.72, 1.03	[redacted]
Renal ultrasound score, (0 – 5 scale) – n (%) 0 1 2	NR	[redacted]	[redacted]

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Source: table 13 CS

Baseline characteristics (2)

	CL205	CL201	Study CL002
	(n=13)	Q2W (n=26)	Radiographic analysis set (n=[redacted])
Number (%) of patients who received prior conventional therapy	13 (100%)	24 (92.3%)	[redacted]
Duration of prior conventional therapy, mean (SD)	16.7 (14.39) months	7.02 (2.14) years	[redacted]
Age when conventional therapy was initiated (years), mean (SD)	[redacted]	[redacted]	[redacted]
Pharmacodynamic parameters, mean (SD) Serum Phosphorus, mg/dL TmP/GFR (mg/dL) Serum 1,25(OH)2 D (pg/mL) ALP (U/L)	[redacted]	[redacted]	[redacted]
Rickets severity RSS Total score, mean (SD)	2.92 (1.37)	1.92 (1.17)	[redacted]

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Source: table 13 CS

Clinical evidence

ERG comments

- The main limitation of the clinical evidence is the design of the studies
  - Most of the presented evidence comes from single-arm studies*
  - The results from the phase III study CL301 (see slide 19) will reduce the uncertainty in the effectiveness of burosumab compared to conventional therapy
- CL201 has more restrictive inclusion criteria than CL002, only including people with more severe XLH (see previous slide)
- The historical control study CL002 does not include patients under 5 years old, therefore only provides comparison with CL201, not CL205
  - Therefore no comparison with conventional therapy can be made for children aged 1 to 4 years**
- Only 13 children are enrolled in CL205, therefore results in this age group (1 to 4 years) are very uncertain

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*CL201 was a randomised controlled dosing study. However, only the Q2W arm was used for comparison with conventional therapy.
**The proposed MA includes people aged 1 and over

Bone outcomes: RSS and RGI-C

Rickets Severity Score (RSS): radiographic measure of rickets severity

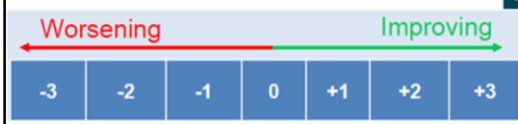
- Scores abnormalities in the wrists and knees
- 10-point score: 0 no rickets, 10 most severe

In XLH, RSS scores usually 0–6.5

Radiographic global impression of change (RGI-C)

- 7-point scale describing change in abnormalities over time*

Wrist	
1	Widened growth plate, irregularity of metaphyseal margin, but without cupping
2	Metaphyseal concavity with fraying of margins
Knee	
1	Partial lucency, smooth margin of metaphysis visible
2	Partial lucency, smooth margin not visible
3	Complete lucency, epiphysis widely separated from distal metaphysis
Multiplier	
0.5	*≤ 1 condyle or plateau*
1	*2 condyles or plateaus*
Total: Wrist (radius+ulna) + knee (tibia*multiplier + femur*multiplier), /10	



*Improvement in rickets = **decrease** in RSS, **positive** RGI-C*

ERG comment, RGI-C: The company states RGI-C ≥+2.0 implies 'substantial healing'. Scores indicates an improvement in radiographic abnormalities and does not mean healing has been observed

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Source: table 6 CS

RSS is a measure of rickets, therefore it does not capture all manifestations of XLH. Other aspects of XLH not captured by RSS are as follows: fatigue, muscle weakness, hearing loss, coxa vara (leg length disrepency and gait abnormalities), tibial torsion (a twisting of the shins that causes the feet to turn inward), and genu varum (bowing) or genu valgum (knock knees). Therefore, the wider physiological impacts of hypophosphataemia, which may be independent of rickets, will not be captured by RSS.

*Radiographs assessed using RSS are scored independent of any other radiographs

Summary of clinical efficacy analyses (1)

Studies

- Burosumab CL205 (children aged 1-4 years) no comparison available
- Burosumab CL201 (children aged 5-12 years)
- Conventional therapy CL002 (children age 5-12 years) comparison to CL201

Outcomes

- Rickets was evaluated using the following measures (naïve and matched comparisons):
  - Rickets severity score (RSS) (see slide 24)
  - Radiographic Global Impression of Change (RGI-C)
- Growth
- Walking ability by 6MWT* distance
- Functional disability and pain measured using the POSNA-PODCI^
  - a score below 40 is considered under the normal range
  - Sport/physical function and pain/comfort scales are most appropriate
- Phosphate homeostasis and bone metabolism

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*6 minute walk test
^Pediatric Orthopedic Society of North America - Pediatric Outcomes Data Collection Instrument

Summary of clinical efficacy analyses (2)

Comparison methods

Baseline vs post-baseline assessments

- Company notes that baseline assessments indicate effectiveness of conventional management prior to study entry
- Comparison of baseline vs post-baseline shows effect of burosumab

Naïve comparison:

- Comparison of observed RSS and RGI-C scores

Matched comparison:

- Matched to account for imbalances in baseline characteristics
- Company presented analysis based on inverse probability of treatment weighting (IPTW), propensity score matching with and without replacement
- For brevity only IPTW is presented, other methods provided consistent findings**

ERG comment:

- Due to differences in inclusion criteria (CL201 includes more severe patients*) a naïve comparison is unreliable - people included in CL201 have a [redacted] RSS compared to the CL002 cohort
- Matched comparison is unreliable due to limitations with this method of matching
  - Subjects can only be matched on measured variables
  - Selection of matching variable not fully explained (age, gender, and RSS)
  - Possibly insufficient number of variable to create a propensity score

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Baseline characteristics and demographics can be seen in table 20 CS

*Additional inclusion criteria in CL201:

- biochemical findings associated with XLH,
- standing height < 50th percentile for age and gender, and
- radiographic evidence of active bone disease including rickets in the wrists and/or knees, and/or femoral/tibial bowing, or, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read

**see figures 19-22 in the CS

Clinical effectiveness – results

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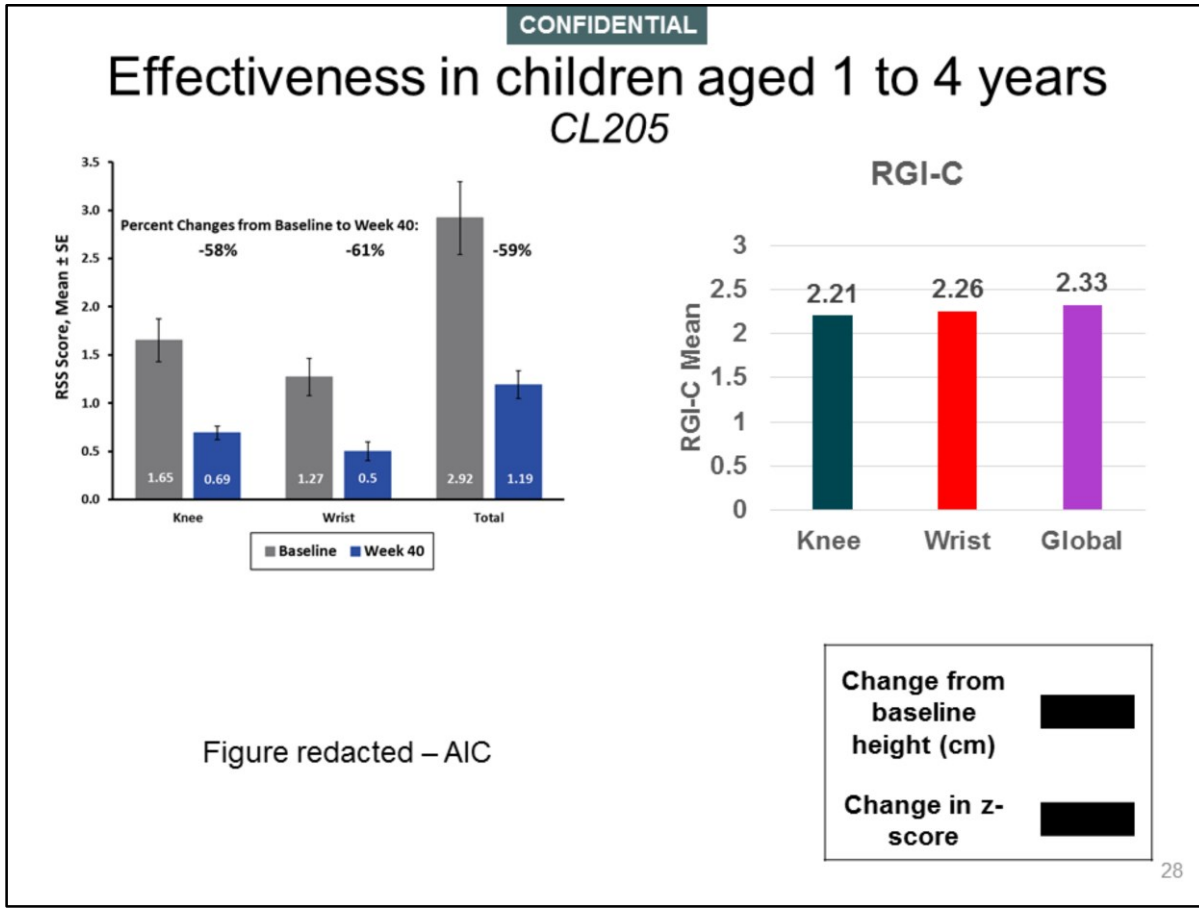

Source: figure 15 CS, table 25 CS, P114 CS

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Effectiveness in children aged 1 to 4 years

CL205: Burosumab pharmacodynamics

- All patients achieved clinically meaningful increases in serum phosphorus, 77% achieved levels in a normal range at week 40
- Vitamin-D: $1,25(OH)_2D$ levels increased from Baseline to Week 40 in the Q2W dose group by [redacted]
  - The increase in vitamin D was not associated with significant changes in serum or urinary calcium
  - Phosphate homeostasis was restored with burosumab after a peak in vitamin D 1 week after the first dose
- ALP % mean change from baseline -36.3%, $p < 0.0001$

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Effectiveness in children 5–12: rickets healing

CL201 and CL002, naïve comparison

- 58% reduction in RSS on burosumab, compared to [redacted] with long-term conventional therapy
- [redacted] on burosumab after 64 weeks than conventional therapy after 102 weeks

Figure redacted - AIC

Figure redacted - AIC

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Source: figure 17 and 18 CS

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Effectiveness in children 5–12: rickets healing

Matched comparison

Figure redacted - AIC

Figure redacted - AIC

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Source: figure 20 CS
a N=52 burosumab, 30 conventional therapy
b N=52 burosumab, 30 conventional therapy
c N=29.7 burosumab, 29.7 conventional therapy (mean sample sizes based on 1000 iterations of PS matching without replacement)
d N=52 burosumab, 29 conventional therapy

All methods show broadly similar results

Effectiveness in children 5–12: Other outcomes

CL201 v CL002

	Week 40 (n=26)		Week 64 (n=26)		Conventional Therapy
	Effect Size	p-value	Effect Size	p-value	Effect Size
Growth velocity Mean change, comparing pre- and post-treatment* (cm/year)	-	-	[redacted]	[redacted]	[redacted]
Standing Height Z-score LS mean change from Baseline**	-	-	[redacted]	[redacted]	[redacted]
6MWT Distance LS mean change from Baseline** (m)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sports/Physical Functioning Scale (POSNA-PODCI) [10 = 1 SD] LS mean change from Baseline**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain/Comfort Scale (POSNA-PODCI) [10 = 1 SD] LS mean change from Baseline**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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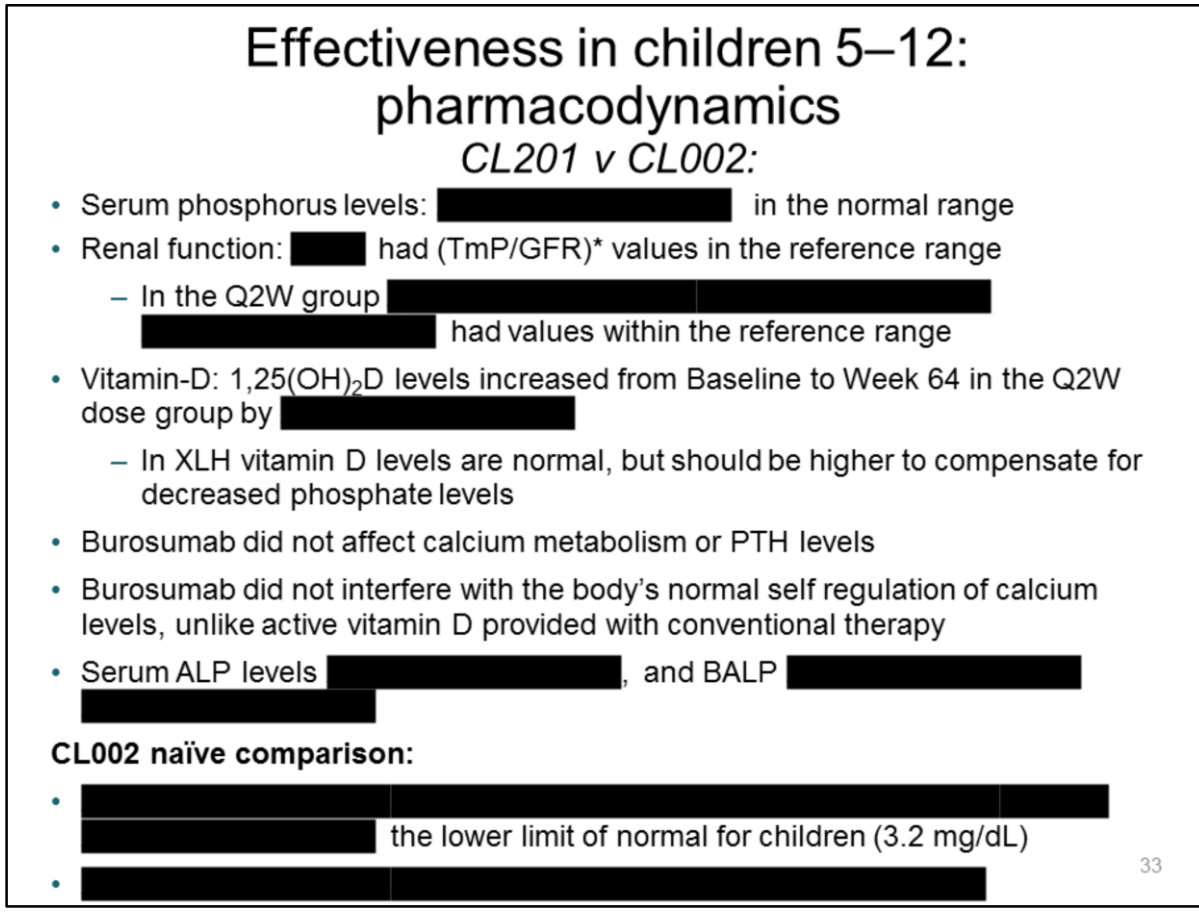
*pre-treatment (2 years before study entry)
**LS mean and p-value based on GEE model. Scores scaled to 50 (SD=10) for a normal population, a score under 40 represents a score below the normal range.



*Ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR)

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Subgroups: low vs high RSS

CL201 v CL002: RSS total score

Figure redacted - AIC

Figure redacted - AIC

Subgroup analysis on Q2W:

- Higher RSS subgroup (RSS total score ≥ 1.5; N=17 (CL201))
- Lower RSS subgroup (RSS total score <1.5; N= 9 (CL201))

Consistent with the reduction in RSS total score at week 40 (-59%) observed in the younger cohort (CL205)

- Larger improvements in patients with more severe rickets at baseline (higher RSS group)

Subgroups: low vs high RSS

CL201 v CL002: Mean RGI-C global scores

Figure redacted - AIC

Figure redacted - AIC

Subgroup analysis on Q2W:

- Higher RSS subgroup (RSS total score ≥ 1.5; N=17 (CL201))
- Lower RSS subgroup (RSS total score <1.5; N= 9 (CL201))

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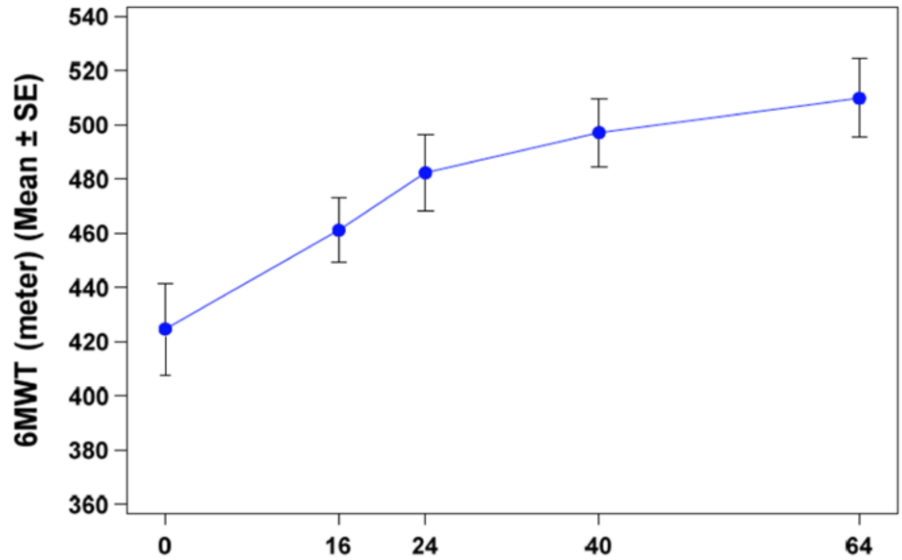
- Scores > 0 indicate healing of rickets, with higher scores implying greater healing

Subgroups: low baseline mobility

CL201: Patients with <80% predicted 6MWT



The graph shows an improvement in the burosumab patients who were <80% of predicted 6MWT (based on age, gender, and height) at baseline

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- Source: figure 11 CS

<80% predicted 6MWT implies worse outcomes.

Adverse events (AEs)

CL201 **N=52***** **Age 5 to 12 years**	• Company noted that the TEAEs* indicated no significant safety concerns (no subject discontinued or died) • 1 serious TEAE, [redacted] • The most frequent TEAEs were [redacted] • 1 SAE** [redacted] • [redacted]
CL205 **N=13** **Age 1 to 4 years**	• No significant safety concerns (no subject discontinued or died) • 1 SEA [redacted], concerned unlikely related to burosumab • 100% experienced at least 1 TEAE • Frequent TEAEs were [redacted] • 5 treatment-related TEAEs, most frequently related to administration

ERG comment: Relative safety and toxicity cannot be assessed as AEs with conventional therapy were not reported

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*TEAE= treatment emergent adverse event
**SEA = serious adverse event
***N=26 in each dose cohort (Q2W and Q4W)

No TEAEs of hypophosphataemia or increased or decrease iPTH were reported during CL201

Results indicate no serious safety concerns with burosumab, with SC administration AEs all mild in severity, not resulting in discontinuation

Cost-effectiveness evidence

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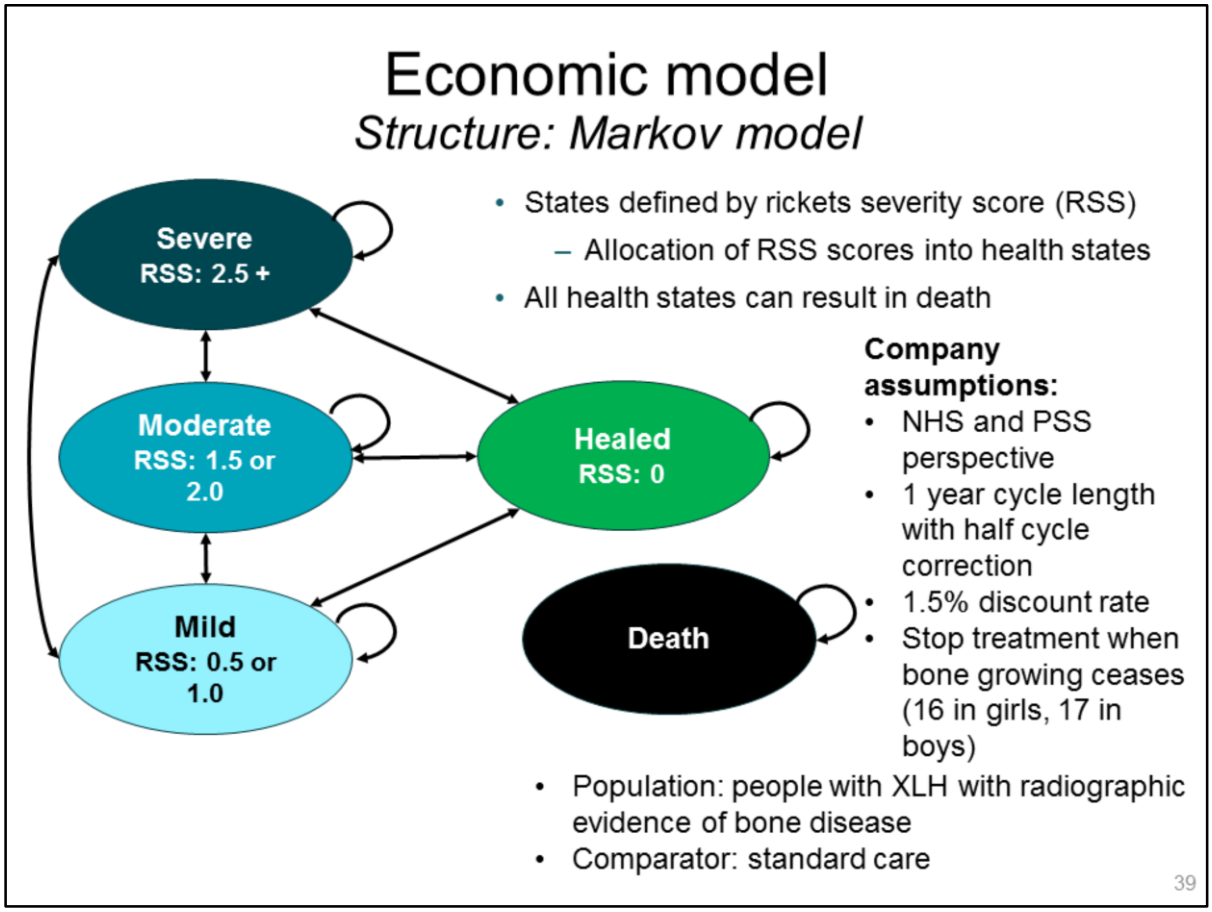

Source: model diagram adapted from CS figure 24. Adapted to include RSS scores

Source: allocation of RSS to health states, provided in company response to clarification (figure 6)

Rickets and the RSS do not necessarily capture all aspects of XLH symptoms and progression, but the RSS measure provides a reasonable indication of patients' health status which is why rickets severity was also the primary endpoint of the CL201 study

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Cost effectiveness analysis

Clinical evidence applied in the model

CL205 and CL201:

- Data used for transition probabilities
- Used to define the baseline distribution of age and disease severity (starting health state distribution) in the model

UK Chart review:

- The company commissioned a review of patient records from 3 expert UK centres to provide an alternative to CL002 (a US study). The review provided data for 38 people with 2 radiographic scores. The UK study has a wider age range (up to age 18). However, it is not as well matched to CL201
- These data were used to estimate the transition probabilities for standard care

Lloyd et al:

- Vignette utility study used to inform health state utilities

ONS life tables:

- Used to apply background mortality in the model

UK growth charts:

- Used to define distribution of baseline weights in the model

Using rickets severity score to define modelled health states

- In the model RSS is used as a proxy for XLH health status
- RSS does not capture all aspects of XLH symptoms and progression
  - E.g. some people with mild rickets could have other XLH manifestations which are more severe
  - This is acknowledged as a limitation of the model structure
  - However, RSS measure provides a reasonable indication of patients' status
- RSS is scored independently (without reference to previous measures) which may result in inconsistent scores between time points → this could impact on the calculation of transition probabilities
- RGI-C does capture changes over time, but it does not provide an indication of health status so it cannot be considered as an alternative measure to define modelled health states

ERG comment:

- RSS may improve but there can be residual deformity and increased fracture risk. These factors are likely to be negatively associated with utility, therefore defining health states by RSS may overestimate burosumab benefits

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Baseline age, disease severity and weight

Age and disease severity	This distribution of the patients age and by health states (disease severity) at the start of the model was matched to the baseline distribution of patients in studies CL205 and CL201
Weight	The weight by age and gender for ages 1 to 17 years was taken from UK growth chart. In the base case the median (50th percentile) weight is used. Due to the short stature of people with XLH, the 25th percentile is explored in the sensitivity analysis.

→

	Age		Total
	1–4	5–12	
Severe	12%	32%	43%
Moderate	7%	23%	28%
Mild	2%	26%	25%
Healed	0%	5%	5%

ERG comment:

- The rationale for the choice of data source for age, disease severity and weight is unclear. Data were available from the UK chart review dataset (representative cohort of UK XLH patients) but the company opted not to use this

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Transition probabilities (1)

Based on RSS data

- For burosumab:
  - Ages 1-4 years old are based on data up to week 40 in CL205
  - Ages 5 + are based on data from week 0 to week 64 in CL201 (Q2W only)
    - Transitions for 13-17 year olds extrapolated from data for 5-12 year olds
- For standard care:
  - Based on data from a UK patient chart review
  - Observations more than 3 years apart are excluded
    - Missed data is accounted for by assuming last observation carried forwards (LOCF) for missing years
- It is assumed there is no mortality risk with XLH - risk is based on general population figures (ONS life tables)
- Transitions between states stop after treatment stops

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Transition probabilities (2)

Transition matrices

Burosumab ages 1-4 years (CL205)

From \ To	Healed	Mild	Mod	Severe
Healed	100%	0%	0%	0%
Mild	0%	100%	0%	0%
Moderate	0%	59%	41%	0%
Severe	0%	50%	50%	0%

Burosumab ages 5 years + (CL201)

From \ To	Healed	Mild	Mod	Severe
Healed	100%	0%	0%	0%
Mild	43%	57%	0%	0%
Moderate	12%	37%	52%	0%
Severe	8%	53%	25%	14%

Rickets improves ← → *Rickets declines*

SoC: UK chart review (assuming LOCF for missing data)

From \ To	Healed	Mild	Mod	Severe
Healed	71%	7%	7%	14%
Mild	9%	70%	11%	9%
Moderate	4%	18%	69%	10%
Severe	4%	5%	12%	79%

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Source (burosumab transition matrices): tables 5.7 and 5.8 ERG report (transitions corrected in company post-clarification model).

Source (Soc matrices): table 5.4

Alternative transition probabilities for SoC using CL002 can be seen in table 5.6 of the ERG report (sourced from the company's post-clarification model).

Transition probabilities

ERG comments

- Due to the evidence sources used to generate the transition probabilities having different observed time periods, the company had to create annualised risk from the probabilities and then convert them back to transition probabilities, adjusting each row so it sums to 1 (100%)
  - The company's method is flawed and can introduce bias because – in models with > 2 health states – it ignores competing risks between model health states
  - ERG alternative method used to generate transition probabilities for burosumab
  - Unclear if the distinction between age groups (1-4 years, 5 +) was due to different XLH manifestation or different burosumab treatment effect. If the former a different SoC transition matrix should be used for patients aged 1 to 4.

Burosumab ages 1-4 years (CL205)

From \ To	Healed	Mild	Mod	Severe
Healed	100%	0%	0%	0%
Mild	0%	100%	0%	0%
Moderate	0%	59%	41%	0%
Severe	0%	**59%**	**41%**	0%

Burosumab ages 5 years + (CL201)

From \ To	Healed	Mild	Mod	Severe
Healed	100%	0%	0%	0%
Mild	43%	57%	0%	0%
Moderate	**10%**	**40%**	**50%**	0%
Severe	**3%**	**62%**	**35%**	**0%**

*Colours show **increased** and **decreased** probabilities vs company matrix*

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Source: adapted from tables 6.1, 6.2, ERG report

Health-related Quality of Life (HRQoL)

Health state vignettes

- To generate utilities 6 physicians experienced in treating XLH acted as a proxy to estimate HRQoL using the EQ-5D-5L
- Case study descriptions were developed for:
  - 4 severities of rickets (healed, mild, moderate, severe defined by RSS), in
  - 3 age groups (1-4 years, 5-12 years, and 13 years +*)
- Steps taken to avoid the limitations of vignettes
  - Clinical experts encourages to incorporate their clinical experience to interpret the burden in the health states
  - Standard EQ-5D preference weights were used to align with NICE reference case
- A small sample of clinical experts means significant variation around the mean – this affects probabilistic analysis
  - To account for variability and ensure values were plausible, the moderate health state was used as an anchor
- The reported utility values in Lloyd et al did not account for some respondents not providing estimates for the healed or severe health states – the company adjusted the utilities to account for missing values

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Full details of the utility study can be seen in Lloyd et al 2018
Vignettes found in 17.10 of the appendices.

*13 years + utility values are assumed to be applicable to adults

XLH does not have a mortality risk, therefore utilities are applied for the full life time horizon

Health-related Quality of Life (HRQoL)

Health state vignettes

	Age 1–4	Age 5–12	Age 13+
Healed (RSS=0)			
Mild (RSS=0.5–1)			
Moderate (RSS=1.5–2)			
Severe (RSS=2.5+)			

For each state/age group:

- Diagnosis
- Walking/gait
- Usual activities and school/work
- Stature
- Strength/mobility
- Pain
- Sleep and fatigue
- Mood/psychological state
- Relationships
- Respiratory function
- Dental problems
- History of fractures

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Utility values

Company

Health state	Utility value
Age 1-4	
Healed rickets	0.872
Mild rickets	0.774
Moderate rickets	0.685
Severe rickets	0.545
Age 5-12	
Healed rickets	0.969
Mild rickets	0.757
Moderate rickets	0.613
Severe rickets	0.521
Age 13 and over	
Healed rickets	0.862
Mild rickets	0.671
Moderate rickets	0.575
Severe rickets	0.462

Utility multipliers	
Age 18-24	1.000
Age 25-34	0.992
Age 35-44	0.966
Age 45-54	0.930
Age 55-64	0.888
Age 65-74	0.851
Age 75+	0.781
Adverse events	None

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Source: table 31 CS

Utility values
ERG comment (1)

- Obtaining utilities from experts not XLH patients or parents is a limitation
- Vignettes imply a perfect association between rickets severity and other outcomes (such as pain) – not always true in XLH
- Utility values in the company submission do not match those reported in the published report of the vignette study (Lloyd et al)
  - ERG use utilities from Lloyd et al report
- Mild and moderate values consistent with the company values

Company response:

- Adjusted Lloyd et al utilities to account for missing estimates for some of the healed and severe healed states
- Adjustments were anchored around the moderate health state

Health state	Utility value
Age (1-4)	
Healed rickets	**0.800**
Mild rickets	0.774
Moderate rickets	0.685
Severe rickets	**0.610**
Age 5-12	
Healed rickets	**0.890**
Mild rickets	0.757
Moderate rickets	0.613
Severe rickets	**0.602**
Age 13 and over	
Healed rickets	**0.811**
Mild rickets	0.671
Moderate rickets	0.575
Severe rickets	**0.479**

*Colours show **increased** and **decreased** values vs company base case* 49

Source: table 6.3 ERG report

Utility values

Continued treatment benefit

- The company assume that after age 17 (the closure of the growth plate) patients remain in the same health state

ERG comment:

- The model assumes a life time treatment effect of rickets healing – this is overly optimistic
- The ERG assume 20 years after the end of treatment patients would experience a decline in quality of life
  - After 20 years people are moved to the next (more severe) utility value (the next state down in the table)

Health state	Utility value (13 to 37 years)	Utility value (38 years and older)
Healed rickets	0.811	0.671
Mild rickets	0.671	0.575
Moderate rickets	0.575	0.479
Severe rickets	0.479	0.479

Source: table 6.4 ERG report

Treatment cost

Cost element			Value
Treatment costs			
Burosumab cost per 10mg vial			£2,992
Burosumab acquisition cost: based on 0.8 mg/kg			
Age (years)	**Weight (kg)**	**Rounded dose (mg)***	**Annual cost**
1 to 5	Up to 18.5	10	£ 77,792.00
6 to 9	Up to 28.7	20	£ 155,584.00
10 to 12	Up to 39.1	30	£ 233,376.00
13 to 15	Up to 54.2	40	£ 311,168.00
16 and 17***	Up to 60.7	50	£ 388,960.00
Burosumab monitoring costs			
Costs associated with burosumab dose adjustments			£126.35****
Conventional therapy acquisition cost			
Annual cost of alfacalcidol and oral phosphate			£492.57

Source: adapted from table 48, 49, 50, 51 CS

*SPC indicates that all doses should be rounded to the nearest 10mg (up or down). A scenario analysis explored rounding dose up to the next 10mg
**Treatment stops after age 17 in boys
***For the first year after burosumab treatment initiation

Health state costs

	Total health state costs (per year)			
	Severe	Moderate	Mild	Healed
Children	£1,266.23	£1,266.23	£1,142.93	£1,142.93
Adults	£1,128.68	£1,128.68	£939.86	£235.90

1	Orthopaedic intervention costs			
2		Pain & mobility costs		
3		Drug costs*		
4		Surveillance costs		

1. Hip arthroplasty, osteotomy and dental abnormalities
2. Physiotherapy costs (5% of children and 57.4% of adults). No pain management costs are applied
3. 9.68grams of phosphate** and 1.125micrograms of alfacalidol per day
4. Current cost of UK clinical management. Equal for all health states
   - Such as: specialist consultation, lab monitoring, radiography, renal ultrasonography, and dental check up

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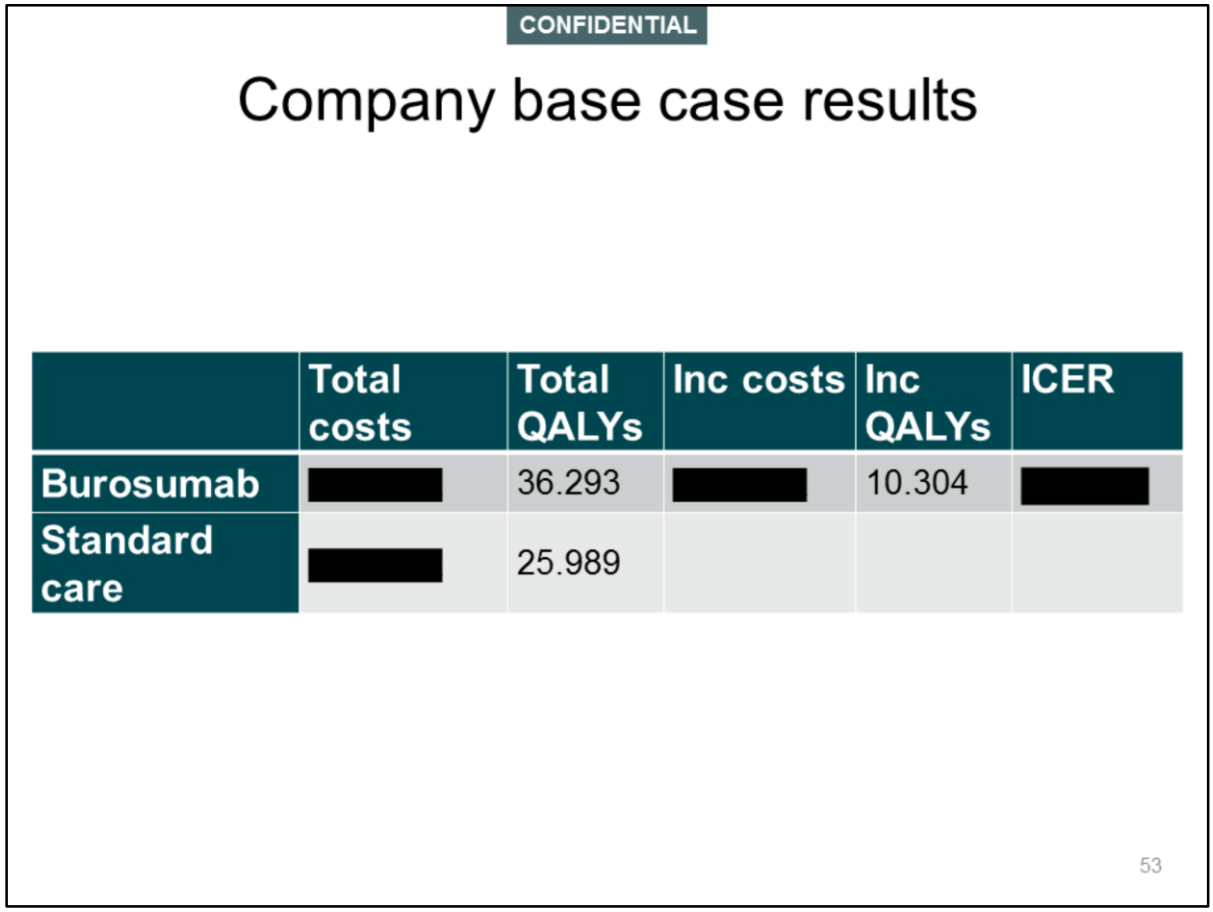
Source: figure 26 CS

See table 52 of the CS for a detailed breakdown of unit costs and resource use for health states

*Costs for phosphate and vitamin D only (not for burosumab)
**5 x oral phosphate tablets

Modelled health states generally correlate with costs, with higher costs in more severe health states.
No adverse event costs or pock of pocket costs have been included in the analysis.



	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
Burosumab	[redacted]	36.293	[redacted]	10.304	[redacted]
Standard care	[redacted]	25.989			

Source: economic model post clarification

A break down of QALYs and costs by health state can be seen in tables 5.15 and 5.16 of the ERG report.

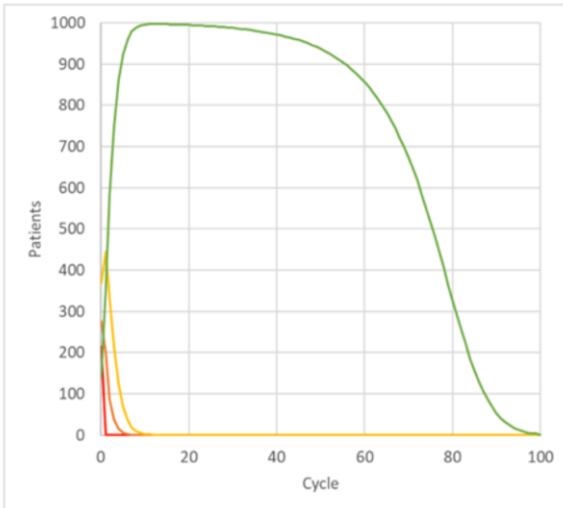
The markov traces show that after 3 years 92% of burosumab treated patients were in the healed rickets health state. The traces for SoC show that the distribution of patients across health states remains fairly consistent across the modelled time horizon.

Markov traces

Proportion of patients in each health state over time (based on each 1-year cycle)

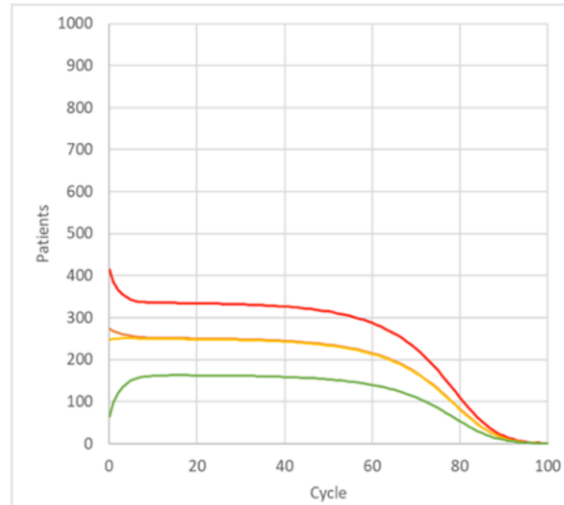
Severe Moderate Mild Healed

Burosumab



- Most patients in 'healed' state by yr 10
- Very few patients in 'severe' state after yr 3

Standard care



- Small decline in 'severe' and increase in 'healed' over yrs 1–10
- Stable from this point on

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Source: figure 27 and 28 CS

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Company scenario analysis (1)

Scenario	Scenario info	ICER (£)
	Company base case	[redacted]
	Discount rate	
1	Discount rate (3.5%)	[redacted]
	Starting distribution	
2	Even age distribution of cohort aged 1-12 years	[redacted]
3	Age and severity distribution: only use Q2W group	[redacted]
4	25th percentile children weight distribution	[redacted]
	Treatment discontinuation	
5	Treatment stops at 15 years, both genders	[redacted]
6	Treatment stops at 16 years, both genders	[redacted]
7	Treatment stops at 17 years, both genders	[redacted]
8	Continuing SoC drug treatment in adults with healed rickets	[redacted]
	Burosumab dose	
9	Mean burosumab dose 1.05 mg/kg	[redacted]
10	Rounding up the dosage of burosumab (closest 10mg)	[redacted]
11	Patients receive exact dose	[redacted]

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Company scenario analysis (2)

Scenario	Scenario info	ICER (£)
	Company base case	[redacted]
	Transition probabilities	
12	Transition probabilities (ages 1-4 years) 40-week observations	[redacted]
13	Transition probabilities (ages 5 years +) 64-week observations	[redacted]
14	SoC transition probabilities imputing missing data (not LOCF)	[redacted]
15	Study CL002 data for SoC transition probabilities	[redacted]
16	Combining CL205 and CL201 transition probabilities	[redacted]
	Surveillance costs	
17	No surveillance in adulthood for children with healed rickets	[redacted]
	Mortality	
18	Double mortality risk in severe health state after 50 years	[redacted]

Source: model (after clarification)

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Company sensitivity analysis

Deterministic

Figure redacted - AIC

- The ICER is sensitive to the utility values in the ***healed, mild and severe*** health states for people 13 years +. This is because patients remain in the same health state when treatment is discontinued
- The ICER is also sensitive to burosumab transition probabilities in people aged 5 years +

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Source: figure 31

1-way DSA in parameter value ranges can be seen in table 54

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ERG preferred analysis

- The ERG made the following changes to the company base-case:
  1. Included costs for adverse events
     - £5 applied for injection site reactions (£0 in company base case)
  2. Corrected burosumab transition probabilities to account for completing risks between modelled health states (see slide 49)
  3. Applied utilities from Lloyd et al 2018 (see slide 53)
  4. Decline in QoL 20 years after the end of treatment (see slide 66)
  5. Discounting at 3.5%
     - The application of a 1.5% discount rate is only appropriate if the achievement of long-term benefit is highly likely

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ERG-preferred base-case analysis					
Burosumab	[redacted]	20.122	[redacted]	3.947	[redacted]
Standard care	32,626	16.175			

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Source: Table 6.5 ERG report

The ERG base their modelling on company's model received after clarification which includes the following changes to their original model:

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ERG preferred analysis

Impact of ERG changes on company base-case

- Analyses added 1 by 1
- Scenario 5 shows the cumulative impact of all ERG changes

Scenario	Scenario info	ICER (£)	Δ
	Company base-case	[redacted]	
1	Including AE cost	[redacted]	[redacted]
2	Transition matrices burosumab: alternative methodology to calculate transitions	[redacted]	[redacted]
3	Utilities from Lloyd et al	[redacted]	[redacted]
4	Utilities decline 20 years after end of treatment	[redacted]	[redacted]
5	Discount rate 3.5% (costs and benefits)	[redacted]	[redacted]

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Source: Table 6.5 ERG report

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ERG scenario analysis (1)

Scenario	Scenario info	ICER (£)
	ERG base case	[redacted]
1	Using utilities from the company submission (Lloyd et al adjusted for missing estimates)	[redacted]
2	Rounding up burosumab treatment dose (to the next 10mg)	[redacted]

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Source: p121 ERG report

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ERG scenario analysis (2)

- The ERG queried the assumption that burosumab would have a lifetime treatment effect
  - To account for this they incorporated applying a decline in utility after 20 years in the preferred analysis
  - Scenario analysis explored the impact of changing the time at which the disutility is applied

Figure redacted - AIC

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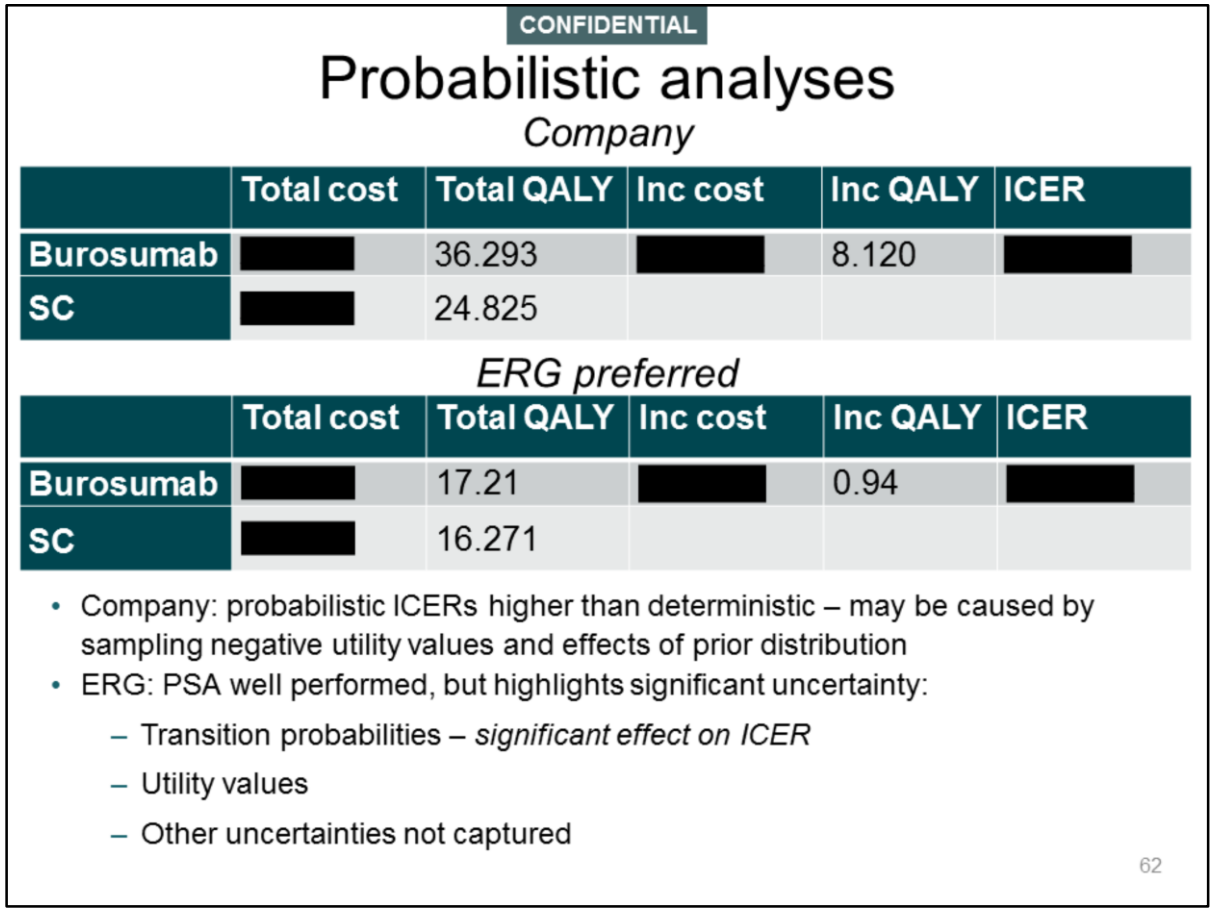
Source: Table 6.7 ERG report



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Probabilistic analyses

Company

	Total cost	Total QALY	Inc cost	Inc QALY	ICER
Burosumab	[redacted]	36.293	[redacted]	8.120	[redacted]
SC	[redacted]	24.825			

ERG preferred

	Total cost	Total QALY	Inc cost	Inc QALY	ICER
Burosumab	[redacted]	17.21	[redacted]	0.94	[redacted]
SC	[redacted]	16.271			

- Company: probabilistic ICERs higher than deterministic – may be caused by sampling negative utility values and effects of prior distribution
- ERG: PSA well performed, but highlights significant uncertainty:
  - Transition probabilities – *significant effect on ICER*
  - Utility values
  - Other uncertainties not captured

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Source: Figure 10 and 11 clarification letter

Company comment: the probabilistic ICERs are high due to a reduction in QALYs gained. This could be caused by the simulation sampling negative utility values.

Probabilistic analyses
ERG comments

Transition probabilities

- Uncertainty in transitions captured using 'prior' distribution of probabilities – reasonable in principle, but choice of factor (0.05) was arbitrary
- Because the amount of trial data was very low (very few observations), results are very sensitive to the choice of prior distribution
- ERG prefers a uniform prior distribution that applies greater weigh to the prior distribution (factor of 1)

Utilities

- Company used SD not SE when sampling random values for utilities
- Sample utilities 'bounded' so that utility values in less severe states are higher (i.e. healed ≥ mild ≥ moderate ≥ severe)
  - Given that RSS does not capture all aspects of XLH, bounding utilities in this way is not necessary

Other uncertainties not captured

- Uncertainty likely to be underestimated, because some factors were not included:
  - Initial distribution of patients per health state
  - Gender and weight distribution

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Probabilistic analyses
ERG scenario analysis

	ICER (£)
ERG preferred: deterministic	[redacted]
ERG preferred: probabilistic	[redacted]

Transition probabilities: Effect of choice of prior distribution

	ICER (£)
ERG preferred: probabilistic	[redacted]
Assuming prior distribution (dirichlet (0.05,0.05,0.05,0.05))	[redacted]
Assuming prior distribution (dirichlet (0.1,0.1,0.1,0.1))	[redacted]
Assuming prior distribution (dirichlet (0.5,0.5,0.5,0.5))	[redacted]
Assuming prior distribution (dirichlet (1, 1, 1, 1))	[redacted]

Utilities: Effect of 'bounded' utilities

	ICER (£)
ERG preferred: probabilistic	[redacted]
Running PSA with bounded utilities	[redacted]

Source: p121 ERG report

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime inc QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal inc)
Greater than or equal to 30	3

Scenario	QALY gain	
	Undiscounted	Discounted (***discount rate***)
Company base case	17.01	10.30 (***1.5%***)
ERG preferred analysis	8.29	3.95 (***3.5%***)
ERG's scenario analysis with the highest QALY gains (burosumab life time treatment effect)	13.56	4.91 (***3.5%***)

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Budget Impact

- Estimated UK prevalence of XLH is [redacted]
- Number of eligible patients [redacted] (per year)

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected uptake of burosumab	40%	65%	90%	90%	90%
Burosumab treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of continuing patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of burosumab (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offsets in drug costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG comment: Real-world data suggests there could be [redacted] patients, with this number of patients the year 5 costs would be [redacted]

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Impact of the technology beyond direct health benefits

- Through a reduction or elimination of XLH symptoms, people treated with burosumab may be able to gain further education and work more
- In the short term fewer work hours may be lost to carer or patient burdens
- The impact on other government bodies has not been quantified, but it is expected to be reduced as treatment increases independence

ERG comment:

- ERG highlights that the company was unable to quantify costs and benefits incurred outside NHS
  - Interruptions to schooling to attend hospital appointments
  - Limited specialist centres means considerable travel
- [redacted]
- [redacted]

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Service design and delivery

- NHSE does not have a specified service for XLH or rare bone disease
  - Pathway depends on the referring clinician
- NHSE states that the pathway of care would be made clearer if burosumab were to be restricted to expert centres
  - Treatment should be initiated and monitored at expert centres
  - Company reports discussions with NHS England have suggested that burosumab would only be prescribed by specialist centres that are members of ERN-BOND: European Reference Network on Rare Bone Disorders.
- It is planned that burosumab will be supplied via a homecare provider once patients have been established on a maintenance dose.*
  - Investment in training for parents and older children could allow home delivery
- During the initial dose titration period burosumab will be supplied directly to designated hospitals where this option is required.

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*Company response to clarification question A22 “Once titration is completed, patients will receive burosumab via a homecare service”

Innovation

- Burosumab is a first in-class disease-modifying drug that inhibits the action of excess FGF23
- Awarded Promising Innovative Medicine (PIM) designation by the MHRA
- Burosumab is a recombinant human IgG monoclonal antibody that binds to the FGF23 protein, neutralising its activity and allowing the kidneys to reabsorb phosphate and restore normal levels of phosphate in the blood
- By restoring a more physiological level of phosphate homeostasis it is expected to improve the symptoms of the disease and physical function in patients of all ages
- Administration is less burdensome that conventional therapy, meaning the child and their family can have a more normal daily life while improving long-term outcomes
- Burosumab is well tolerated and avoids complications that are associated with conventional therapies

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Equality

- No potential equality issues were identified during the scoping process
- Burosumab is indicated for the treatment of children and adolescents
- Company states that a refusal to recommend a treatment that principally affects children is discriminatory based on age

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Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

CONFIDENTIAL

Managed access agreement

[redacted]

- [redacted]
- [redacted]

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Key issues for consideration

Clinical effectiveness

- How is burosumab expected to be used in practice?
  - Marketing authorisation: for children and adolescents with growing skeletons; expected up to age 16 in girls and 17 in boys
- Does the clinical evidence provide a suitable basis to establish the effectiveness of burosumab, compared with conventional therapy?
  - Children aged 1–4: CL205 single-arm study
  - Children aged 5–12: CL201 vs CL002 – naïve and adjusted comparisons
  - Children aged 13+: no evidence presented
- Is burosumab clinically effective?
  - Do RSS and RGI-C capture important aspects of XLH?
  - Significance of the findings from CL205 and CL201?

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Key issues for consideration

Cost-effectiveness

- Is the economic model suitable for decision-making?
  - Do the model health states (based on RSS) appropriately map the course of XLH and capture the key elements of the disease?
  - Is it appropriate to assume lifetime disease stabilisation at the end of treatment?
- What are the most appropriate assumptions?
  - Transition probabilities: ERG amendments?
  - Utility values: company vs ERG values? Decline in utility after 20 years?
  - Discount rate: 1.5% or 3.5%?
- What is the committee's view on the probabilistic analyses?
- What is the committee's view on additional uncertainties in the model?
  - Difference in effect between age groups
  - Baseline weight, age and disease severity
  - Adverse events
- What factors affecting the guidance need to be taken into account?
  - Population contains children: any additional considerations required?
- What are the most plausible ICERs?
- Application of QALY weighting?

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Authors

- **Thomas Paling**
  Technical Lead
- **Ian Watson**
  Technical Adviser
- with input from the Lead Team
  - Stuart Davies (Cost)
  - Glenda Sobey (Clinical)
  - Jeremy Manuel (Lay)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Burosumab for treating X-linked hypophosphataemia

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of burosumab within its licensed indication for treating X-linked hypophosphataemia for national commissioning by NHS England.

Background

X-linked hypophosphataemia (XLH) is a genetic disorder characterised by low levels of phosphate in the blood. Excess activity of a type of hormone FGF23 results in phosphate being abnormally processed in the kidneys, which causes a loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones.

It is the most common form of hereditary hypophosphatemia and is equally common in both sexes. Clinical manifestations of XLH vary in severity, but patients most commonly present in childhood with bowed or bent legs, disproportionate short stature, bone pain, delayed walking, and dental anomalies[1]. Symptoms generally present at 12–15 months of age, and diagnosis can be sooner if there is a family history of XLH[2]. In adults, the main manifestations of XLH include bone pain and fractures, joint stiffness and restricted movement (as a result of enthesopathy), neurological complications and, in severe cases, spinal cord compression. Many adults will eventually develop hyperparathyroidism.

It is estimated that there are approximately 250 children and young people with XLH in England, and up to 2,500 adults with the condition.

There are currently no treatments that target the underlying cause of XLH and medical management is aimed at improving growth, decreasing morbidity, and preventing skeletal deformities. XLH does not respond to vitamin D supplementation alone. The current standard of care for children is multiple daily doses of phosphate, in combination with active vitamin D analogues (alfacalcidol or calcitriol) to prevent secondary hyperparathyroidism that can be induced by phosphate administration. The effectiveness of this treatment is limited because phosphate levels cannot be maintained at appropriate levels to allow mineralisation of bone and improve skeletal outcomes, and high-dose oral phosphates have potential safety and tolerability issues. Frequent monitoring and dose adjustment is required. The management of XLH in adults is less consistent; phosphate is not always offered to adults because of the risks of treatment-related complications. Corrective surgery of skeletal deformities and joint replacements may be required.

The technology

Burosumab (brand name unknown, Kyowa Kirin) is an anti-FGF23 human monoclonal antibody which improves phosphate homeostasis by targeting excess FGF23. Burosumab binds to FGF23 rendering it inactive, and thereby restores renal tubular reabsorption of phosphate and increases the production of 1,25-dihydroxyvitamin D which enhances intestinal absorption of calcium and phosphate. Burosumab is administered by subcutaneous injection.

Burosumab does not currently have a marketing authorisation in the UK. It is being studied in clinical trials in children and adults with XLH. The phase III trial in children compares burosumab with phosphate and vitamin D treatment. The phase III trials in adults are either single arm (no comparator) or placebo-controlled.

Intervention(s)	Burosumab
Population(s)	Children and young people with X-linked hypophosphataemia
Comparators	Established clinical management without burosumab
Outcomes	The outcome measures to be considered include: • fractures • severity of rickets • pain (including bone pain, joint pain and joint stiffness) • motor skills • growth (including height) • tooth loss and pain • skull and spinal deformities • neurological complications (including increased intracranial pressure, craniosynostosis, problems with hearing and balance, and spinal cord compression) • radiographic response • renal function • parathyroid hormone levels • alkaline phosphatase levels • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).

Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation • Guidance will take into account any Managed Access Arrangements
Related NICE recommendations and NICE Pathways	None
Related National	Department of Health (2016) NHS Outcomes

Policy	Framework 2015-2016. Domains 1, 2, 4 and 5. Department of Health (2013) The UK strategy for rare diseases Nottingham University hospitals NHS trust (2016), Guideline for the Treatment of Hypophosphataemia in Adults NHS England, NHS standard contract 2013/2014: Paediatric medicine: endocrinology and diabetes NHS England, NHS standard contract 2013/2014: Specialised Endocrinology Services (Adult) NHS England, NHS standard contract 2013/2014: Metabolic Disorders (Adult)

References

1. Cochrane Database of Systematic Reviews (2005): Recombinant growth hormone therapy for X-linked hypophosphatemia in children
2. XLH Network. Familial hypophosphatemia. Accessed November 2017 http://xlhnetwork.org/xlh.pl?f=larry/website/VitaminD/Famhypo.html

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Kyowa Kirin (burosumab) Patient/carer groups • Action for Sick Children • Brittle Bone Society • Children Living with Inherited Metabolic Diseases (CLIMB) • Contact a Family • Findacure • Genetic Alliance UK • Muslim Council of Britain • National Children's Bureau • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Genetic Nurses and Counsellors • British Paediatric and Adolescent Bone Group • British Society for Genetic Medicine • British Society for Paediatric Endocrinology and Diabetes • Royal College of General Practitioners • Royal College of Nursing • Royal College of Paediatrics and Child Health • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • RUDY • Society for Endocrinology • UK Clinical Pharmacy Association • UK Genetic Testing Network Others • Birmingham Children's Hospital NHS Foundation Trust • Department of Health	General • All Wales Therapeutics and Toxicology Centre • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • NHS National Services Scotland • Scottish Medicines Consortium • Welsh Government • Welsh Health Specialised Services Committee Comparator companies • None Relevant research groups • Cochrane Cystic Fibrosis and Genetic Disorders Group • MRC Clinical Trials Unit • National Institute for Health Research • NIHR Musculoskeletal Biomedical Research Unit, University of Oxford (Nuffield Orthopaedic Centre) • NIHR BioResource for Translational Research in Common and Rare Diseases Associated Public Health Groups • Public Health England • Public Health Wales

Consultees	Commentators (no right to submit or appeal)
• Evelina London Children's Hospital • Great Ormond Street Hospital • Guy's and St Thomas' NHS Foundation Trust • NHS England • Oxford University Hospitals Foundation Trust • Royal Manchester Children's Hospital • Royal Orthopaedic Hospital NHS Trust • University Dental Hospital of Manchester	

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the evaluation; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the recommendations.

All non-company/sponsor consultees are invited to make an evidence submission or submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the recommendations.

Commentators

Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the final evaluation documentation for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary*)*.

All non-company/sponsor commentators are invited to nominate clinical specialists or patient experts.

[1] Non-companyconsultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

INTERIM

Specification for company submission of evidence

Burosumab for treating X-linked hypophosphataemia [ID1151]

February 2018

Contents

List of tables and figures

Glossary of terms

Term	Definition
Craniosynostosis (craniostenosis)	One or more of the fibrous sutures in an infant skull prematurely fuses by turning into bone (ossification).
Enthesitis	Inflammation at tendon, ligament or joint capsule insertions.
Enthesopathy	Abnormality of tendon or ligament attachment to the bone.
Epiphysiodesis	The epiphyseal (growth) plate of a bone is fused either temporarily or permanently to delay growth of a long bone.
Genu varum	Bow legs
Hypercalcaemia	Calcium level in blood is above normal.
Hypercalciuria	Calcium level in urine is above normal.
Hypophosphataemia	Phosphate level in blood is below normal.
Nephrocalcinosis	Deposition of calcium phosphate in the renal parenchyma due to hyperparathyroidism.
Rickets/Osteomalacia	Softening of the bones caused by impaired bone metabolism primarily due to inadequate levels of available phosphate, calcium, and vitamin D.
Osteotomy	A surgical operation whereby a bone is cut to shorten or lengthen it or to change its alignment.
Secondary/tertiary hyperparathyroidism	Excessive secretion of parathyroid hormone (PTH) resulting in high blood calcium levels.
Tibial torsion	Deformity of the tibia such that the toes point inwards – 'in-toeing'

List of Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
6MWT	six minute walk test
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
BALP	bone-specific alkaline phosphatase
BBS	Brittle Bone Society
BNF	British National Formulary
BPABG	British Paediatric and Adolescent Bone Group
BPI	Brief Pain Inventory
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRF	case report form
DSA	deterministic sensitivity analysis
ECG	electrocardiogram
ECHO	echocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D-5L	Euroqol 5-dimension 5-level questionnaire
ERN-BOND	European Reference Network on Rare Bone Disorders
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GEE	generalised estimating equations
HPO	Human Phenotype Ontology
HR	hypophosphataemic rickets
HRG	healthcare resource group
HRQL	health-related quality of life
HS	health state
ICER	incremental cost-effectiveness ratio
IgG1	human immunoglobulin G1
iPTH	intact parathyroid hormone
ITT	intent to-treat
IWRS	interactive web response system
LLN	lower limit of normal
LS	least squares

LVH	left ventricular hypertrophy
MHRA	Medicines and Healthcare Products Regulatory Agency
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
PAS	patient access scheme
PbR	payments by results
PCS	physical component summary
PD	pharmacodynamic(s)
PDMA	Pharmaceuticals and Medical Devices Agency
PHEX	phosphate-regulating endopeptidase homolog, X-linked (phosphate-regulating gene with homology to endopeptidases located on the X chromosome)
PIM	Promising Innovative Medicine
PK	pharmacokinetic(s)
PODCI	Pediatric Outcomes Data Collection Instrument
POSNA	Pediatric Orthopedic Society of North America
PRO	patient reported outcome
PSA	probabilistic sensitivity analysis
PSS	personal social services
PTH	parathyroid hormone
Q2W	biweekly, once every 2 weeks
Q4W	monthly, once every 4 weeks
QALY	quality-adjusted life year
RCPCH	Royal College of Paediatrics and Child Health
RCT	randomised control trials
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
RUDY	Rare and Undiagnosed Diseases Study
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDS	standard deviation scores
SE	standard error
SF-10	SF-10 Health Survey for Children
SF-36	36-Item Short Form Survey
SoC	standard of care

SOC	system organ class (for adverse events coding by MedDRA)
SPC	Summary of Product Characteristics
TEAE	treatment emergent adverse event
TmP/GFR	ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR)
ULN	upper limit of normal
VUS	variant of unknown significance
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphatemia

Executive Summary

Nature of the condition

X-linked hypophosphataemia (XLH) is a rare, genetic, chronically debilitating and deforming disease that profoundly impacts the affected individual's day to day functioning and health-related quality of life (HRQL). As a genetic disease it can affect whole families and consequently have a wide impact on the quality of life of generations of families.

In XLH, genetic mutations result in an inactive phosphate-regulating enzyme and lead to high levels of circulating fibroblast growth factor 23 (FGF23). Excess FGF23 leads to increased urinary phosphate excretion, reduced 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) synthesis, and hypophosphataemia.

XLH is characterised by dysfunction of mineral metabolism (serum phosphate, serum calcium), endocrine function and renal function. The corresponding clinical manifestations of XLH include delayed walking, waddling gait, leg bowing, enlarged cartilages, bone and/or joint pain, craniosynostosis, spontaneous dental abscesses, growth failure, fractures, mineralisation defects (rickets and osteomalacia), severe dental anomalies, hearing loss and fatigue. Rickets, the hallmark of XLH in children, is associated with substantial skeletal deformities that cause daily pain and impair physical functioning. Children may be severely limited in their daily activities, such as walking, due to deformity and antalgic gait. When these deformities become permanent, people with XLH suffer lifelong disability and pain.

Children with XLH often have trouble performing age-appropriate gross motor activities, such as walking, running, and jumping, due to bowing of the femur, tibia, and/or fibula and the rotation of the tibia that causes the feet to turn in toward each other. This impaired functionality from an early age can inhibit a child's participation in physical, educational and social activities. It may also result in them being teased, bullied and stigmatised by their peers, particularly once they start going to school. In adults, osteomalacia and skeletal deformities lead to development of early osteoarthritis and enthesopathy that cause pain and continue to limit physical function. A UK case note review illustrates the impact of XLH in affected adults, with symptomatic or progressive deformity being the most common lower limb manifestation of the disease and nearly half of the adults having had some form of corrective surgery (Chesher et al., 2018).

The long-term goal of therapy in children with XLH is to:

- Improve or heal rickets and prevent or correct the skeletal abnormalities associated with it.
- Prevent the ongoing mechanical dysfunction associated with chronic weight bearing on poorly aligned bones and joints (Linglart et al., 2014).
- Reduce the child's pain and disability.

Current management

There is no approved or available therapy that specifically treats the underlying pathophysiology. Most children with XLH receive conventional therapy, consisting of: unpalatable oral phosphorus supplementation with multiple daily doses to compensate for renal phosphate wasting; and active vitamin D analogues (alfacalcidol or calcitriol) to counter the $1,25(OH)_2D$ deficiency (Linglart et al., 2014). Conventional therapy does not address the underlying mechanism of the disease and oral phosphate produces only a transient increase in phosphate levels.

Furthermore, administering conventional therapy is complicated, requiring dosing multiple times per day and individualised dosing adjustment based on tolerability or evidence of secondary complications (Carpenter et al., 2011). Regular laboratory, clinical and radiological monitoring is required because of the frequent occurrence of hypercalcaemia, hypercalciuria, hyperphosphataemia, nephrocalcinosis and hyperthyroidism. The complexity of the dosing regimen creates challenges with patient adherence to therapy and therefore may compromise treatment benefit. To administer divided doses at strict regular intervals, parents or caregivers are often required to disturb their child's sleep. Furthermore, the challenge of unpalatable preparations leads to poor compliance and additional stress for parents and caregivers.

Earlier initiation of conventional therapy in XLH children results in improved outcomes, but does not completely normalise skeletal development (Mäkitie et al., 2003).

In the UK, despite optimised treatment in expert centres, many children continue to have severe rickets. The lack of an effective treatment in childhood that targets the underlying cause of XLH results in progressive disease and multiple lifelong complications, such as unresolved skeletal abnormalities, bone and joint pain, dental abscesses, early onset osteoarthritis and persistent osteomalacia. Early arthritic complications are common, resulting in the need for early knee and hip replacements in some patients. There is a significant unmet medical need in the treatment of XLH.

The technology

Burosumab (Crysvita™) is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the activity of FGF23. By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney and through the production of $1,25(OH)_2D$ enhances intestinal absorption of calcium and phosphate (Carpenter et al., 2014). Burosumab improves phosphate homeostasis and its major pathologic consequences (rickets and osteomalacia), and consequently resolves the skeletal and non-skeletal manifestations of XLH. In doing so, burosumab can significantly alter the natural history of the disease.

Burosumab received orphan drug designation in October 2014 and is being reviewed under a centralised procedure by the European Medicines Agency. The proposed indication is for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. Burosumab received a positive CHMP opinion on the 15th December 2017. The European Commission is expected to grant conditional marketing authorisation in February 2018, reflecting the significant unmet need in XLH.

Furthermore, the MHRA recognised XLH as a seriously debilitating condition with high unmet need, and that burosumab offers major advantage over current UK practice, and therefore granted burosumab a 'Promising Innovative Medicine' (PIM) designation on the 31st January 2017 [reference EAMS 16508/0001]. On the 23rd January 2018, burosumab was also recognised by the European Medicines Agency as representing a significant improvement in the therapy area and an outstanding contribution to public health.

Burosumab is administered by subcutaneous injection every two weeks. It is presented as a preservative-free solution in single-use 5 mL vials containing 1 mL of burosumab at a concentration of 10 mg/mL, 20 mg/mL or 30 mg/mL for subcutaneous injection, which have a list price of £2,992, £5,984 and £8,976 per vial. The recommended starting dose is 0.4 mg/kg of body weight and the normal maintenance dose is 0.8 mg/kg. Oral phosphate and vitamin D analogues should be discontinued one week prior to initiation of treatment with burosumab (Summary of Product Characteristics (Crysvita), 2017).

Burosumab may be initiated from one year of age. To prevent skeletal deformities, as well as disproportional growth and stunting, treatment should be initiated early in life. Treatment is expected to be continued until skeletal growth has ceased i.e. closure of growth plates, which is expected to be at age 16 years in girls and age 17 years in boys (Royal College of Paediatrics and Child Health, 2013b, 2013a).

Impact of the new technology

The CHMP gave a positive opinion on the conditional marketing authorisation application for burosumab in children and adolescents with XLH, based on a review of evidence that included data from Phase 2 clinical trials of burosumab in children aged 5-12 years (Study CL201) and in children aged 1-4 years (Study CL205). Study CL201, which included children from three clinical trial sites in the UK, included 52 children with XLH aged 5-12 years and compared two dosing frequencies of burosumab: once every two weeks (n=26) or once every four weeks (n=26). Based on the findings from Study CL201, the bi-weekly dosing is considered the optimal dosing regimen and is the expected licensed dose frequency. Therefore, the evidence presented focuses on the biweekly dose. Children had received conventional therapy for a mean duration of 6.9 years before entering the study.

Comparisons of post-baseline to baseline assessments of rickets therefore serve as comparisons of burosumab treatment to conventional therapy.

A historical control study, Study CL002, provides reference group data in a similar paediatric XLH population to those enrolled in Study CL201. The children in CL002 had received long-term (approximately eight years) conventional therapy with oral phosphate and active vitamin D ([redacted] in the Radiographic Analysis Set). Although not a matched control cohort, Study CL002 provides an indication of the degree of change in rickets severity, growth and lower extremity deformity that may occur with prolonged phosphate/active vitamin D treatment and allows the outcomes achieved after 64 weeks of burosumab treatment to be further put into context. Since CL002 was a US study, Kyowa Kirin also commissioned a longitudinal review of patient records from three expert UK centres to provide additional data (n=43).

An additional open-label paediatric study in 13 infants and children with XLH aged 1 to 4 years (Study CL205) is ongoing to provide pharmacokinetic, pharmacodynamics, efficacy, and safety information in a younger population. A Phase 3 randomised controlled trial (targeted to enrol 60 patients) will provide direct comparative evidence for burosumab versus current conventional therapy; data are expected [redacted].

Burosumab is the only treatment for children with XLH that addresses the underlying pathophysiology and as a result can substantially improve children's long term, physical and mental wellbeing, reducing the overall burden on the NHS.

Two radiographic scoring methods, the Thacher Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C), were used in CL201, CL205 and CL002. These instruments provide complementary analyses of the severity of rickets. The RSS provides the absolute score of epiphyseal/distal metaphyseal abnormalities, whilst the RGI-C indicates the change in abnormalities and deformities between time points. The RSS was developed to assess the severity of nutritional rickets based on a 10-point scoring method, where 10 indicates the highest severity of rickets (Thacher et al., 2000), however the usual range of RSS total scores in XLH is between 0 and 6.5. This may limit the sensitivity of the RSS, hence the reason for including the RGI-C is that provides a complementary method that allows for comparison with previous radiographs. Together, these measures provide a broader insight into bone disease that any one score alone.

Results from CL201 show that burosumab significantly improves rickets at Week 40 and Week 64, compared to baseline. The primary endpoint, the rickets severity score (RSS) was reduced from Baseline by 61% at Week 40 ($p<0.0001$) and maintained at Week 64 (58% reduction from Baseline ($p < 0.0001$) with biweekly burosumab. This improvement was more than [redacted] that seen with long-term conventional therapy in CL002 ([redacted] over a median of 102 weeks). Similarly, burosumab treatment resulted in healing of rickets as assessed by RGI-C scores. The RGI-C score at Week 64 was +1.62 compared to [redacted] with conventional therapy in Study CL002 (median 102 weeks). At Week 64, [redacted]% of children treated with biweekly burosumab had healing of rickets (RGI-C global scores ≥ 1.0). Furthermore, 57.7% of children

treated with burosumab had substantial healing of rickets (RGI-C global scores ≥ 2.0), compared to [redacted] treated with conventional therapy in Study CL002 ([redacted]).

After long-term treatment with conventional therapy in Study CL002, [redacted]. In comparison, growth velocity increased by [redacted]) in children treated with burosumab every two weeks, with a corresponding least-squared (LS) mean change in standing height z-score of +[redacted]. The results correlate with improvements in rickets. Burosumab is not a growth hormone, and its effects on phosphate metabolism are expected to affect the growth plate but are not expected to stimulate growth directly. Burosumab may allow children with XLH to achieve a normal pace of growth, but they would not be expected to achieve recovery of the growth they have lost. This highlights the need to treat children early before loss of growth in line with the licensed indication from one year of age.

Consistent with these clinical outcomes, biweekly burosumab also resulted in improved functional assessments and patient-reported outcomes in CL201. Walking ability, as assessed by LS mean distance walked in the six-minute walk test (6MWT), increased from baseline by [redacted] at Week 64 (p [redacted]). In a subgroup with impaired walking ability (<80% of predicted normal; N = 14), there was a functionally meaningful increase in 6MWT distance of [redacted]at week 64 [redacted] to achieve normal mean values (≥ 80% of predicted normal). Functional disability was assessed using the Pediatric Orthopedic Society of North America - Pediatric Outcomes Data Collection Instrument (POSNA-PODCI). Biweekly burosumab treatment increased scores for Sports/Physical Functioning and Pain/Comfort into the normal range seen in healthy children; LS mean scores showed improvements of +[redacted] at Week 64, respectively.

Results were consistent in CL205 (13 children with XLH aged 1-4 years), where burosumab treatment for 40 weeks significantly reduced RSS total score at Week 40 by 59% (LS mean change of -1.73, $p < 0.0001$, ANCOVA model).

Burosumab has a safety profile appropriate for the treatment of children with XLH:

- Treatment in children showed no adverse impacts on phosphate-calcium metabolism; no adverse events of hyperphosphataemia or clinically meaningful changes in serum or urinary calcium, serum iPTH, or renal ultrasounds (including nephrocalcinosis) were observed.
- No subject died or discontinued from CL201 or CL205 for any reason; all subjects continued treatment on study as of the data cut-off dates.
- Injection site reactions, while frequently reported, [redacted] and did not result in discontinuation.
- Other commonly reported TEAEs were [redacted].

- [redacted].

Improvements in bone disease as evidenced by assessments of rickets, lower extremity deformity, and increased growth after burosumab treatment in XLH children were accompanied by improvements in the ability to walk and play sports and a reduction in pain. By improving the skeletal and non-skeletal manifestations of XLH in childhood, burosumab will alter the natural progression of the disease and provide benefit from lifelong improvements in functional outcomes and quality of life.

Early treatment with burosumab is expected to prevent lower extremity deformity, improve mobility and overall physical functioning and optimise growth potential in younger children, with the benefits continuing into adolescence and adulthood. It is expected that, four to five years after the introduction of burosumab, very few children would start treatment after the age of 12 years, as early treatment would be expected to have the greatest benefit in terms of impacting long-term sequelae and minimising the chronic impact of the disease in adulthood. [redacted]

Clinical heterogeneity has been reported among children and adults with XLH (Linglart et al., 2014; Carpenter et al., 2011). This clinical heterogeneity can be explained by differences in underlying severity of the disease or by the inability of current treatment to address the underlying disease. Burosumab showed consistent benefits across the treated population irrespective of initial disease severity at initiation. Due to these observed consistent beneficial treatment effects, treatment continuation should be maintained whilst children's skeletons are continuing to grow.

Value for money

A cost-effectiveness model has been constructed to attempt to quantify the value for money offered with burosumab. Limitations in the published evidence outlining the current disease progression in XLH have presented challenges in demonstrating the value of burosumab; long-term impacts of healing rickets and normalising children's function is likely to result in a transformative impact on the patient's whole life but the extent to which this can be modelled is limited. To address the limitations in the published evidence and better model the pathway of a child and adult with XLH, Kyowa Kirin have collected the following data to support the evidence package for burosumab, alongside the clinical trial data:

- Utility elicitation study to estimate the utility of children with XLH, stratified by age and severity, to populate the economic model
- Caregiver survey to understand the burden that XLH places on children (e.g. lost days of schooling) and their parents / caregivers
- A case record survey to collect the age, height, weight and longitudinal RSS scores of children with XLH from specialist centres in the UK
    - This provided transition probabilities for the cost-effectiveness model
- A prevalence study based on primary care data to estimate the number of eligible patients for burosumab in the UK

The cost-effectiveness model has been constructed on the basis of the primary endpoint of the CL201 clinical trial – rickets severity, which is the hallmark clinical manifestation of XLH. The rickets severity scores at Weeks 0 and 64 from CL201 and Weeks 0 and 40 from CL205 have been annualised to generate probabilities of moving between health states: healed rickets (RSS 0), mild rickets (RSS 0.5 and 1.0), moderate rickets (RSS 1.5 and 2.0) and severe rickets (RSS 2.5 or greater). Probabilities of moving between these health states with standard of care (SoC) were derived from the UK chart review providing 34 patient transitions over a median follow-up of approximately 5 years. A scenario was explored in which data from Study CL002 was used for the SoC transition probabilities, which included RSS scores for 34 children two-years apart. In the absence of data from the clinical trials or published literature that could be used to generate utilities, a vignette approach was used to estimate EQ-5D utilities for children with XLH through clinician and specialist nurse UK interviews. Cost categories include drug costs, surveillance costs, pain/mobility costs and orthopaedic intervention costs.

Using weight data for the average child in the UK, at the maintenance dose of 0.8 mg/kg, children aged between 1 and 5 years require one 10mg vial, children aged between 6 and 9 years require one 20mg vial, children aged between 10 and 12 years require one 30 mg vial. Children aged over 13 require 40mg or 50mg of burosumab. At the list price of £2,992, £5,984 and £8,976 for 10 mg, 20 mg and 30 mg vials, respectively, this equates to annual treatment costs of £77,792 in children aged between 1 and 5 years, £155,584 in children aged between 6 and 9 years, £233,376 in children aged between 10 and 12 years, £311,168 in children aged between 13 and 15 and £388,960 in children aged over 16.

The results indicate that patients treated with burosumab are likely to spend most of their lives with healed rickets, whereas with conventional UK treatment, patients have mild, moderate or severe XLH over their lifetime. The base case ICER is [redacted] with incremental undiscounted QALYs of 17.01. The results are most sensitive to utilities for the model health states and parameters relating to treatment costs such as weight and dosage. [redacted]

[redacted] Given that XLH is associated with skeletal deformations, pain and functional impairment, it is unlikely that there are undiagnosed children that would benefit from treatment with burosumab.

Using the prevalence estimate of [redacted] children and assuming a 40% uptake of burosumab in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children being treated with burosumab in Year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every two weeks for the first three months of treatment, so up to five additional nurse visits and blood tests per patient are expected in the first year of treatment only, equating to a cost of £127 per child treated with burosumab. Following this, burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by Kyowa Kirin and will therefore not have any additional financial or resource impact on the NHS.

The cost of offset drugs (phosphate and alfacalcidol [a vitamin D analogue]) in children are approximately £492.57 per year. [redacted].

Impact of the technology beyond direct health benefits

The substantial skeletal deformities caused by XLH cause daily pain and impair physical functioning, such that a young child may be severely limited in his/her daily activities and will suffer lifelong disability and pain as these deformities become permanent. This impaired functionality from an early age can inhibit a child's participation in physical, educational and social activities. By healing rickets and preventing the fixed skeletal deformities that typify this disease in adulthood, burosumab can enable children with XLH to lead normal, healthy lives with the associated benefits on their education and social activities. This benefit is expected to continue through to adulthood such that they could lead normal working lives, with the associated economic and social benefits. Furthermore, decisions around having children might be easier for XLH families if they know there is an effective treatment available.

Therefore, although it is not possible to quantify at this stage in development, it is highly likely that there will be significant savings to patients through healing of rickets

and overall reduction or elimination of symptoms with burosumab, since patients may lead normal lives and be less impacted by their symptoms, thus markedly improving their quality of life. For example, patients may be able to work more, or obtain further career progression through improved education not inhibited by XLH. In the short term, parents might not have to take time off from work to care for their child suffering with XLH.

The overall pathway of care is not expected to change following the introduction of burosumab. Given the challenges in managing XLH, burosumab treatment should be initiated at a specialist centre by an expert physician experienced in the management of children with metabolic or bone disorders. This is consistent with current clinical management of children with XLH. Titration of burosumab will be carried out by the initiating physician. Once initial titration is complete and children are receiving their maintenance dose, burosumab will be provided via homecare.

Burosumab offers the ability transform the lives of people with XLH, not only individually but for whole families, enabling them to experience a better quality of life.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Children and young people with X-linked hypophosphataemia	The anticipated indication is: for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons	As per draft summary of product characteristics
Intervention	Burosumab		
Comparator(s)	Established clinical management without burosumab		
Outcomes	The outcome measures to be considered include: • fractures • severity of rickets • pain (including bone pain, joint pain and joint stiffness) • motor skills • growth (including height) • tooth loss and pain • skull and spinal deformities • neurological complications (including increased intracranial pressure, craniosynostosis, problems with hearing and balance, and spinal cord compression) • radiographic response • 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 could not be accounted for: • fractures • tooth loss and pain • skull and spinal deformities • neurological complications (including increased intracranial pressure, craniosynostosis, problems with hearing and balance, and spinal cord compression) • mortality	These outcomes were not captured in clinical studies. Quality of life data collected in the studies (POSNA-PODCI and SF-10) could not be used to derive utility data for the health economic modelling because there is no valuation set. Therefore utility values have been derived from a UK study.
Subgroups to be considered	N/A		
Nature of the	• disease morbidity and patient clinical disability		

condition	with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options		
Cost to the NHS and PSS, and Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used		
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise		
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation • Guidance will take into account any Managed Access Arrangements		

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Crysvita™

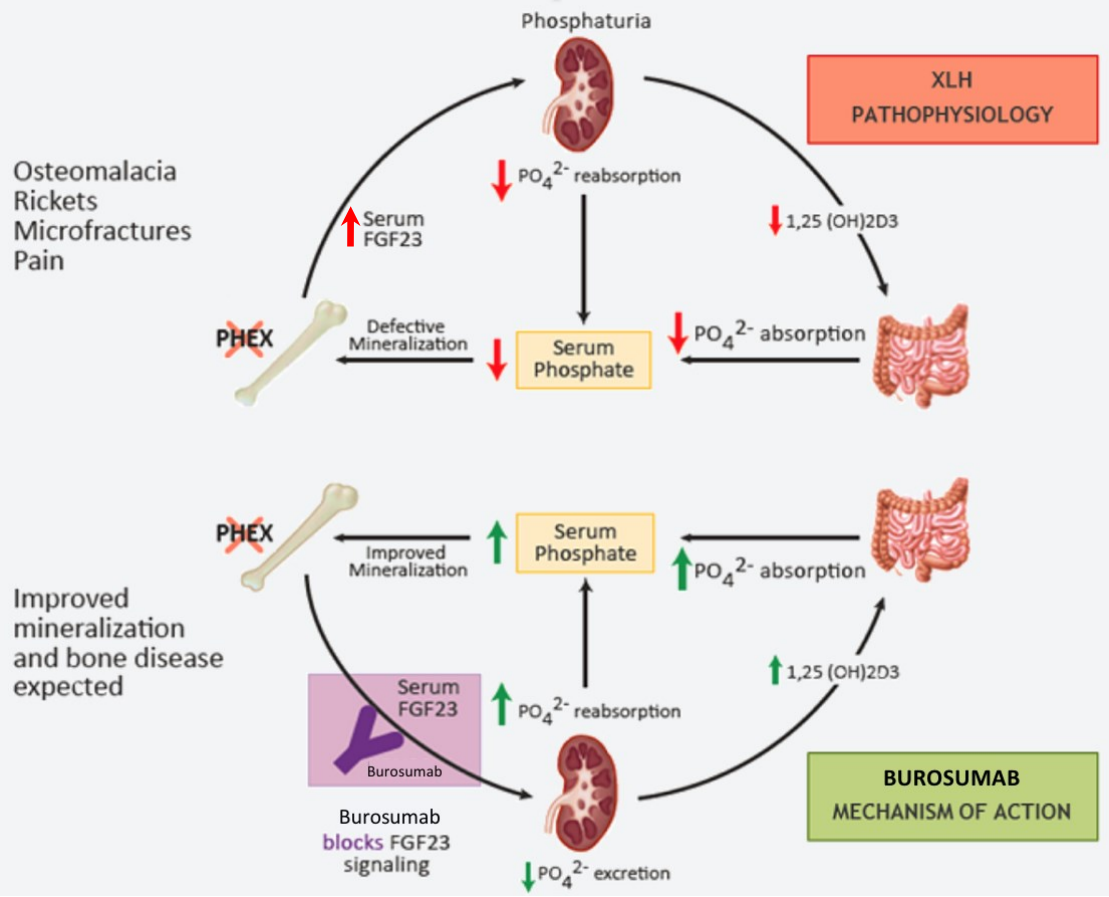
Approved name: Burosumab

Therapeutic class: Drugs for treatment of bone diseases (M05)

2.2 What is the principal mechanism of action of the technology?

Burosumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23) (Figure 1). By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney and increases the production of serum concentration of 1, 25 dihydroxy-Vitamin D [1,25$(OH)_2$D] that enhances intestinal absorption of calcium and phosphate (Carpenter et al., 2014; Summary of Product Characteristics (Crysvita), 2017). By directly inhibiting excess FGF23, improving phosphate homeostasis, and healing rickets, burosumab has the potential to significantly alter the natural history of the disease.

Figure 1. XLH Pathophysiology and Mechanism of Action for burosumab



2.3 Please complete the table below.

Table 2. Dosing Information of technology being evaluated

Pharmaceutical formulation	Burosumab is a sterile, clear to slightly opalescent, colourless to pale brownish yellow, and preservative-free solution in single-use 5 mL vials containing 1 mL of burosumab at a concentration of 10 mg/mL, 20 mg/mL or 30 mg/mL. Burosumab is formulated in 10 mmol/L L-histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80 and 10 mmol/L L-methionine, pH 6.25.
Method of administration	Burosumab is administered by subcutaneous (SC) injection.
Doses	The recommended starting dose is 0.4 mg/kg of body weight and the normal maintenance dose is 0.8 mg/kg, given every two weeks. The maximum dose is 90 mg. All doses should be rounded to the nearest 10 mg.
Dosing frequency	Every two weeks (Q2W)
Average length of a course of treatment	Current clinical guidelines advise that active treatment of XLH continues during the whole of the paediatric growth period, with earlier initiation favoured. Burosumab may be initiated from one year old until end of skeletal growth – see section 10.1.16.

Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	*Dose increase* If fasting serum phosphate is below the reference range for age, the dose may be increased stepwise by 0.4 mg/kg up to a maximum dose of 2.0 mg/kg (maximum dose of 90 mg). Fasting serum phosphate should be measured 4 weeks after dose adjustment. Burosumab dose should not be adjusted more frequently than every 4 weeks. *Dose decrease* If fasting serum phosphate is above the reference range for age, the next dose should be withheld and the fasting serum phosphate reassessed within 4 weeks. The patient must have fasting serum phosphate below the reference range for age to restart burosumab at approximately half of the previous dose.

Source: (Summary of Product Characteristics (Crysvita), 2017)

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Burosumab received orphan drug designation (EU/3/14/1351) by the European Commission for the treatment of XLH on 15th October 2014.

Burosumab is being reviewed under a centralised procedure by the European Medicines Agency (EMA). Burosumab received a positive CHMP opinion on the 15th of December 2017. The European Commission is expected to grant conditional marketing authorisation in February 2018.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that burosumab will be commercially available in the EU upon regulatory approval.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Burosumab has not received regulatory approval in any European countries. As stated above, burosumab received a positive CHMP opinion on the 15th of December 2017. The European Commission is expected to grant marketing authorisation in February 2018.

Orphan designation (EU/3/14/1351) was granted by the European Commission for burosumab for the treatment of X-linked hypophosphataemia on 15th October 2014.

The United States Food and Drug Administration's (FDA) Office of Orphan Drug Development (OOPD) has designated burosumab for the treatment of XLH as a drug for a "rare paediatric disease". A regulatory application is under review by the FDA and has priority review status.

3.4 If the technology has been launched in the UK provide information on the use in England.

Not applicable.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Two paediatric Phase II studies, UX023-CL201 (CL201) and UX023-CL205 (CL205) are evaluating the safety and efficacy of burosumab dosed Q2W and Q4W in children aged 5-12 years of age and the safety, pharmacokinetics (PK) and pharmacodynamics (PD) effects of burosumab administered with Q2W dosing in children aged 1-4 years respectively (Table 3). Data from these studies are used to support this submission. Data from the 40-week analysis (primary endpoint) and the extended analysis up to 64 weeks, that were used to support the marketing application, are included. The database lock for data analysis at 64 weeks was the 1st of December 2016. A long-term extension study is expected to complete in [redacted]. Data from the 40-week interim analysis of Study 205 are also presented (database lock 20th April 2017). These data were also used to support the marketing authorisation application. The final 64-week analysis is expected in [redacted].

The historical control study UX023-CL002 (CL002) was a single centre, retrospective radiographic and medical chart review of children with XLH who had repeat historical radiographs taken when between 5 and 14 years of age. The study was conducted to provide reference group data to use for comparative analyses of rickets, growth, and lower extremity deformity in Study CL201 in a similar paediatric XLH population who had received long-term conventional therapy with oral phosphate and active vitamin D.

UX023-CL301 is a Phase III study evaluating the safety and efficacy of burosumab compared to conventional therapy in 60 paediatric patients aged 1 to ≤12 years with XLH who have confirmed evidence of rickets. In addition, this study will evaluate whether every two-week dosing of burosumab improves mobility and health-related quality of life in children with XLH. The primary efficacy and safety analysis from study UX023-CL301 is expected to be available [redacted].

Two additional studies are planned:

- UX023-CL207, open-Label, Phase 3 study, assessing safety, pharmacodynamics and efficacy of burosumab in paediatric patients under one year with XLH.

- UX023-CL401, XLH Disease Monitoring Program, observing disease progression and associated side effects for up to 250 children and adults with XLH.

Finally, an XLH burden of illness study (UX203-CL001) collected data on the prevalence and burden of XLH-specific morbidities with respect to health care resource utilisation and quality-of-life impairment as characterised by a range of patient reported outcome (PRO) measures (Table 4).

Table 3: Completed/ ongoing/ planned clinical studies in paediatric patients with XLH

Study Number (Status)	Study Title	Patient Population (Type/ Number of Subjects)	Duration of Treatment	Treatment and Controls	Objectives and Control	Planned analyses (data availability)
UX023-CL201 (ongoing)	Randomised, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 antibody, burosumab, in Paediatric Patients with XLH	Paediatric patients with XLH, 5 to 12 years old 52 initiated treatment	Repeat dose, up to 64 weeks	**Multi-dose burosumab** Biweekly or monthly administration of burosumab (doses 0.1 to 2.0 mg/kg)	**Primary/Secondary Objectives:** PD, Bone markers, Rickets, Growth, Lower Extremity Deformity, Physical Function, PRO, PK, Safety	Primary analysis: 52 pts 40 weeks (Available) Week 64 analysis: 52 pts 64 weeks (Available)
UX023-CL205 (ongoing)	An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics and Efficacy of Burosumab in Children from 1 to 4 Years old with XLH	Paediatric patients with XLH, 1 to 4 years old 13 patients enrolled	Repeat dose, Up to 64 weeks	**Multi-dose burosumab** Biweekly administration of burosumab at a target dose of 0.8 mg/kg.	**Primary Objectives:** Safety, PD **Additional Study Objectives:** Rickets, Growth, Lower Extremity Deformity, Physical function, PK	Interim analysis: 5 pts, 4 weeks (Available) Interim analysis: 13 pts, 24 weeks (Available) Primary analysis: 13 pts, 40 weeks (Available)
UX023-CL301 (ongoing)	Randomised, Open-Label, Phase 3 Study to Assess with the Efficacy and Safety of Burosumab versus Oral Phosphate and Active Vitamin D Treatment in Paediatric Patients with XLH	Paediatric patients with XLH, 1 to ≤ 12 years old with open growth plates. Targeted to enrol 60 patients	Repeat Dose, Open label up to 64 weeks	**Multi-dose burosumab** Biweekly administration of burosumab at a target dose of 0.8 mg/kg **Control:** Oral phosphate/active vitamin D	**Primary Objectives:** Change in rickets at week 40 **Secondary objectives**: Growth, Lower Extremity Deformity, PD, Bone markers, Physical function, PK, Safety	Primary analysis: 60 pts, 40 weeks ([redacted])

Table 4: Other studies to support burosumab in paediatric & adult patients with XLH

Study Number (Status)	Study Title	Patient Population (Type/ Number of Subjects)	Duration of Treatment	Treatment and Controls	Objectives and Control
UX023-CL001 (completed)	Natural History Survey via Online Questionnaire to Characterise the Burden of Illness in Adults and Children with XLH	Paediatric and Adult patients	N/A, no burosumab administered in this study	Survey only; no burosumab administered **Control:** None	**Evaluations:** Demographics, XLH-specific medical history, PRO (WOMAC, SF-36, BPI, POSNA-PODCI, SF-10)
UX023-CL002 (completed)	A retrospective longitudinal study of skeletal outcomes in children with XLH	Paediatric Patients with XLH, 5 – 14 years old.	N/A, no burosumab administered in this study	No burosumab administered **Control:** None	**Objectives:** Retrospective review of existing radiographs and medical record data from paediatric XLH patients who have at least two paired sets of wrist and knee x-rays (unilateral or bilateral) taken between 9 and 27 months apart. A set is defined as both wrist and knee x-rays (unilateral or bilateral) taken on the same date.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

The European Commission is expected to grant conditional marketing authorisation in February 2018. The proposed indication is for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. On the 31st January 2017, burosumab received a 'Promising Innovative Medicine' (PIM) designation from the MHRA, confirming its potential to address a high unmet need in children with a seriously debilitating condition [reference EAMS 16508/0001]. A submission to the Scottish Medicines Consortium is expected to be made later in 2018.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

This evaluation may have an impact on equality issues. Burosumab in this indication is for the treatment of children and adolescents. A refusal to recommend a treatment that principally affects children is discriminatory based on age, contrary to Article 14 of the European Convention on Human Rights.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

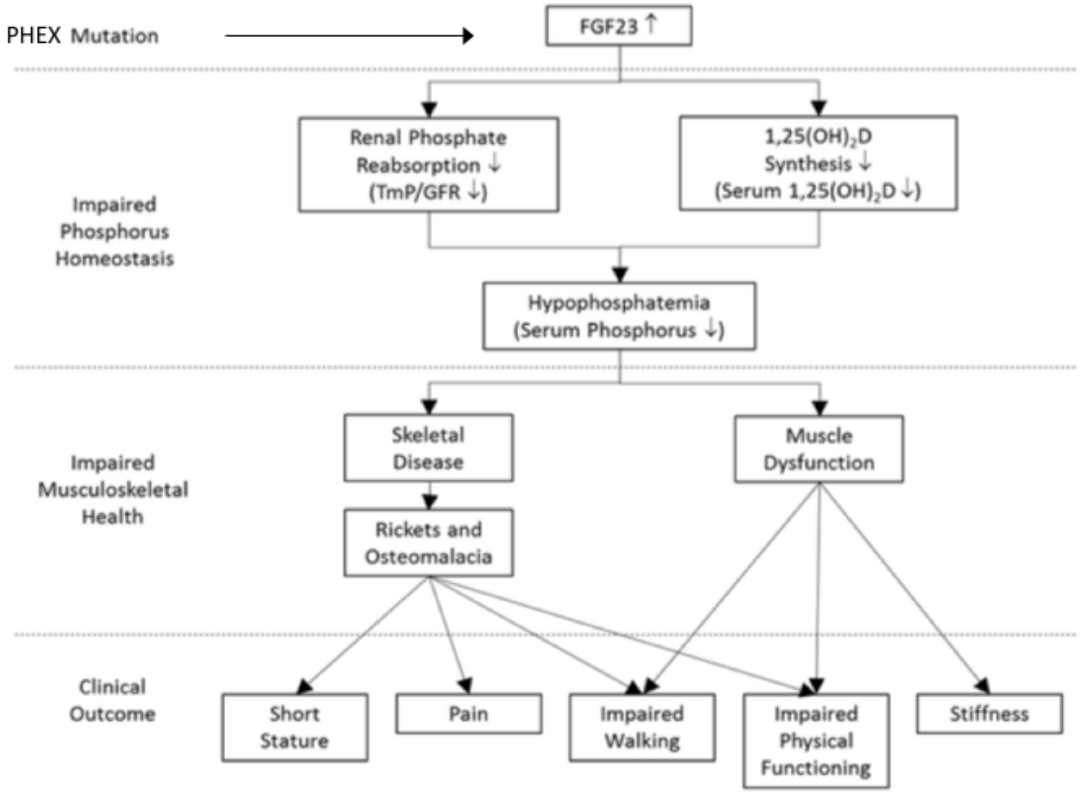
Overview of X-linked hypophosphataemia

X-linked hypophosphataemia (XLH) is a rare, genetic, chronically debilitating and deformative bone disease that profoundly impacts the affected individual's day-to-day functioning and quality of life, starting from an early age and throughout life.

In XLH high levels of circulating FGF23 lead to excess urinary phosphate excretion and subsequent hypophosphataemia, resulting in defective bone and tooth mineralisation.

The two major pathologic consequences in the bone are rickets and osteomalacia (Figure 2). Rickets, the hallmark of XLH in children, is associated with substantial skeletal deformities that cause daily pain and impair physical functioning, such that a young child may be limited in his/her daily activities and will suffer lifelong disability and pain as these deformities become irreversible when growth ceases. Children with XLH often experience difficulty performing age-appropriate gross motor activities, such as walking, running and jumping, due to bowing of the femur, tibia, and/or fibula and the tibia rotation that causes the feet to turn in toward each other. In addition, children experience muscle weakness, fatigue, and other physical functioning deficits that are likely caused by the diverse physiological impacts of hypophosphataemia, which may be independent of rickets. Bowing of the legs in children with XLH can be substantial and severe. Defects in the growth plate also lead to impairment in growth and growth potential. The combination of height loss caused by the bowing of the legs and the growth plate defects can lead to a permanent loss of growth potential and short stature which can have psychosocial consequences for the individual (Carpenter et al., 2011). Because XLH is a lifelong disease, bone and joint damage, osteomalacia and reduced mobility acquired during childhood, are continued into adulthood.

Figure 2. Schematic of XLH Pathophysiology



There is no approved therapy that specifically treats the underlying pathophysiology of elevated FGF23-induced hypophosphataemia. Most children with XLH receive conventional therapy, consisting of multiple daily doses of oral phosphate and active vitamin D analogues (Linglart et al., 2014). The goal of therapy with oral phosphate and active vitamin D analogues in children is to provide just sufficient phosphorous to allow partially improved mineralisation of bone and improve skeletal outcomes, without providing so much that there is ectopic calcification. However, conventional therapy is complicated, requiring regular dosing multiple times per day and individualised dosing adjustment based on tolerability or evidence of secondary complications (Linglart et al., 2014). Moreover, conventional therapy does not address the underlying mechanism of the disease and oral phosphate produces only a transient increase in phosphate levels. Frequent daily dosing and gastrointestinal distress and diarrhoea may compromise treatment persistence/compliance (Imel and Carpenter, 2015) and as a result the therapeutic benefit of conventional therapy. Suboptimal therapy in childhood can result in lifelong disability. In adults, the reduced bone quality from chronic osteomalacia increases the risk for non-traumatic pseudofractures, or Looser zones, and causes bone and joint pain (Shore and Chesney, 2013a), while ongoing skeletal deformities lead to the development of early osteoarthritis and stiffness that cause pain and continue to limit mobility and physical function. Patients with XLH have a clear unmet medical need.

Aetiology of XLH

XLH is an X-linked disorder caused by a defect in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) peptidase which is part of the phosphate sensing system in osteocytes. Only one mutated copy of the gene is enough to cause the condition in both males and females, therefore a female with XLH has a 50% chance of passing along a mutation to each of her children. Because males only have one X-chromosome, a male with XLH will pass along the condition to all of his daughters, but to none of his sons. PHEX mutations are usually inherited through families, but they can also occur in people with no family history of the disorder as a new (de novo) mutation.

Patients with XLH carry mutations in the PHEX gene, however the mechanism by which PHEX disruption results in elevated FGF23 is still unclear (Carpenter et al., 2011). More than 400 mutations in the PHEX gene have been found to cause XLH (*The Human Gene Mutation Database (at the Institute of Medical Genetics in Cardiff*). These mutations inactivate the PHEX enzyme, leaving it unable to cleave other proteins. Approximately 20% of PHEX mutations are de novo (i.e. not inherited from a parent) based on genetic testing and clinical observations in non-familial XLH patients (Dixon et al., 1998; Whyte et al., 1996).

The defect in PHEX leads to an erroneous signal in the phosphate sensing control system that leads to inappropriate excess levels of FGF23 (Jonsson et al., 2003; Yamazaki et al., 2002). Excess FGF23 drives the pathophysiology of XLH leading to impaired conservation of phosphate by the kidney and consequent hypophosphatemia (Jonsson et al., 2003; Yamazaki et al., 2002). FGF23 also suppresses $1,25(OH)_2D$ production (Perwad et al., 2005), resulting in decreased intestinal absorption of calcium and phosphate, further impairing the body's phosphorus supply (Sabbagh et al., 2008). As a consequence, patients with XLH have defective bone mineralisation (osteomalacia) resulting in low bone turnover and poor quality bone (Shore and Chesney, 2013a). In addition, many patients have muscle function deficits (Reid et al., 1989; Veilleux et al., 2013) that may be related to insufficient quantities of adenosine triphosphate (ATP) as a consequence of chronically low concentrations of extracellular phosphate (Andersen et al., 2012; Reid et al., 1989). The musculoskeletal effects of chronic hypophosphatemia further lead to the clinical manifestations and morbidities seen in both children and adults with XLH.

Biochemical imbalance

XLH is characterised by high levels of circulating FGF23 that lead to excessive urinary phosphate excretion, reduced $1,25(OH)_2D$ synthesis, and subsequent hypophosphatemia, resulting in defective bone and tooth mineralisation.

XLH is characterised by biochemical imbalance, in particular regarding:

- Measures of mineral metabolism (serum phosphate, serum calcium)

- Measures of endocrine function (serum values of FGF23, 1,25(OH)$_2$D, insulin-like growth factor I, alkaline phosphatase (ALP), osteocalcin, growth hormone)
- Measures of renal function (urinary calcium to creatinine ratio, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate (TmP/GFR)).

Levels of parathyroid hormone (PTH) are generally normal, although mildly elevated circulating levels of PTH may occur in patients naive to therapy.

Target ranges for these biochemical measures are established in the general population. Age-specific target ranges are reported:

- for children aged 4-11 years phosphate should be 1.20-1.80 mmol/l (Lockitch et al., 1988);
- for children aged 2-15 years TmP/GFR should be 1.15-2.60 mmol/l (Payne, 1998).

Phosphate homeostasis remains an important clinical objective to avoid morbidities associated with hypophosphataemia (Manghat et al., 2014), and as such is a useful endpoint in clinical trials and as a measure of treatment response.

Serum ALP activity is elevated in children with XLH, to two to three times the upper limit of normal (Carpenter et al., 2014). The magnitude of total and bone-specific ALP elevation correlates with the magnitude of rickets (Carpenter et al., 2011). These parameters are commonly used as indicators of the presence and severity of rickets and is one of the primary methods used by physicians managing conventional therapy of XLH as a tool to assess results, since repeated X-rays are not advisable for children. Healing rickets by normalising ALP is the primary objective in children (Linglart et al., 2014).

Studies have shown that treatment with conventional therapy (oral phosphorus and/or active vitamin D) does not normalise serum phosphate or TmP/GFR, as these supplements do not enhance proximal tubular phosphate reabsorption. Improvements in serum phosphorous following administration of oral phosphate are transient, with a peak in serum phosphorus after each administration and then a return to baseline levels. A Japanese national survey conducted in 2010 (Endo et al., 2015), obtained both before and after the treatment from 11 patients with XLH and also corrected serum phosphate data from 12 XLH patients who already had been treated with active vitamin D and/or phosphate. Both serum phosphate and TmP/GFR measures were below the lower limits of reference ranges for all XLH patients. Mean serum phosphate in the genetic hypophosphataemia group was 2.47 (± 0.58) mg/dL (0.79 ± 0.19 mmol/L), and mean TmP/GFR was 2.17 (± 0.71) mg/dL (0.7 ± 0.23 mmol/L). In the retrospective case review study CL002, in children who had received long-term therapy with conventional therapy, [redacted] (Ultragenyx, 2016).

Clinical Manifestations of XLH

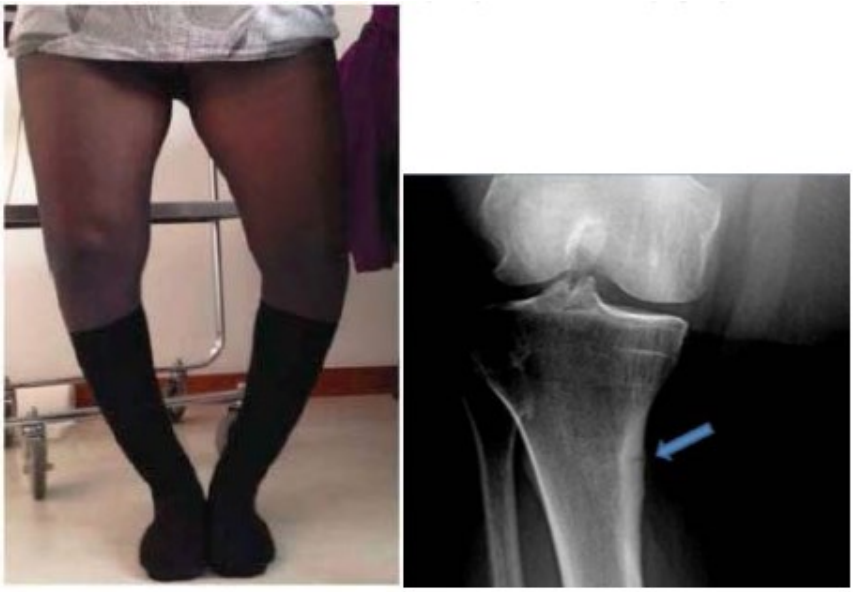
Overview

The most common clinically evident manifestations of XLH are short stature and limb deformities (Figure 3). Growth abnormalities and limb deformities are both more evident in the lower extremities, since they represent the fastest growing body segment before puberty and, being weight bearing, will manifest with deformities earlier than non-weight-bearing bones. Most affected children exhibit clinical evidence of rickets, varying from enlargement of the wrists and/or knees to severe malalignment defects such as bowing or knock-knee deformities. Such defects may result in waddling gait and leg length abnormalities (Williams and Winters, 1983; Carpenter et al., 2014). Children with rickets are also more likely to fracture their bones.

Symptoms of XLH usually begin in early childhood and can vary in severity. Early signs include skeletal abnormalities such as noticeably bowed or bent legs (Figure 3), short stature, and irregular growth of the skull. Children may present with delayed walking or a waddling gait. Over time, symptoms may progress to include bone pain, joint pain caused by hardening (calcification) of tendons and ligaments, and dental pain. Some people with XLH may also experience hearing loss (NIH, GARD, 2017)(Chesher et al., 2018). In addition to the substantial impacts on skeletal disease, low serum phosphorous in XLH patients may contribute to muscle dysfunction, reduced mobility and physical functioning, and fatigue.

If undiagnosed during childhood, patients with hypophosphataemia present with bone and/or joint pain, fractures, mineralisation defects such as osteomalacia, enthesopathy (abnormality of tendon or ligament attachment to the bone), severe dental anomalies, hearing loss, and fatigue.

Figure 3. Clinical Presentation of XLH Children (left) and Adults (right)



Left: 13-year-old girl with XLH who presented with persistent leg bowing despite being treated with current therapy since she was 3 years old (Linglart, et al., 2014). Right: a small fracture in an adult patient with XLH (Carpenter, et al., 2011)

Few studies exist to evaluate the burden of disease in XLH. To further characterise the burden of illness in a larger population of paediatric and adult patients with XLH, the online survey Study CL001 was conducted. This study was conducted online in the form of web-based questionnaires and an electronic consent form. Responders were recruited through the sponsor, XLH patient advocacy networks, and clinicians with a research interest in XLH or experience in the clinical management of patients with XLH. Interim survey results include responses from 71 children and 195 adults:

Children

- The 71 children were 1-18 years of age with a median age of nine years. The median age at diagnosis was two years of age and nearly all children were being treated with oral phosphate and active vitamin D (70/71 [99%]) reflecting current UK clinical practice. The children were from 16 countries (US, Australia, France, UK, India, Belgium, Ireland, Morocco, Canada, South Korea, Pakistan, Finland, Austria, Netherlands, Spain, and Russia).
- The majority of paediatric respondents experienced bowing of the legs. High levels of pain and limitations in mobility were reported (Table 5). Paediatric Orthopaedic Society of North America - Paediatric Outcomes Data Collection Instrument (POSNA-PODCI) scores for the Sports and Physical Function and Pain and Comfort domains were one standard deviation or more below the normative healthy population mean, further suggesting that children with XLH have issues with mobility, gross motor function, and pain relative to healthy children. Some of the complications known to be associated with conventional therapy were reported, including [redacted] with nephrocalcinosis and [redacted] with hyperparathyroidism.

Adults

- The 195 adults had a mean age of [redacted]. [redacted] of the adults were being treated with phosphate and active vitamin D therapy, and there is no evidence to suggest this is different to current practice in the UK. The adults were from 16 countries, including the USA, UK, France, Australia, Canada, Austria, Belgium, Bulgaria, China, India, Italy, Korea, Pakistan, Romania, Russia and Switzerland.
- Adult participants (n=195) experienced the long-term consequences of unresolved skeletal disease in childhood, including bowing deformities of the legs, short stature, and/or inward twisting of the tibiae (in-toeing), as well as early onset osteoarthritis and persistent osteomalacia. [redacted]

In addition, a recent UK case-note review documents the clinical features and the complications of treatment in 59 adults (19 male, 40 female) with XLH, attending a single inherited metabolic disease service from 1998 (Chesher et al., 2018). The results of this study (described further in the sections below) confirm the substantial impact that XLH has in adult life.

Clearly, the prevalence and severity of disease in adults and children in the burden of illness studies characterises a population with an inadequately treated disease despite best efforts with conventional therapy for the last 30 plus years.

Table 5: Reported signs and symptoms of XLH in children and adults

Assessment	Respondents
Paediatrics	N=71
Short stature	80%
Bowing of the tibia/fibula	73%
Bowing of the femur	63%
Tibial torsion (in-toeing)	52%
Genu valgum (knock-knees)	31%
Craniosynostosis	[redacted]%
Gait Disturbances	86%
Bone pain (in the previous year)	59%
Joint pain (in the previous year)	65%
Muscle pain	58%
Restricted range of motion	42%

Assessment	Respondents
Adults	N=195
Short stature	[redacted]%
Bowing of the tibia/fibula	[redacted]%
Bowing of the femur	[redacted]%
Tibial torsion (in-toeing)	[redacted]%
Genu valgum (knock-knees)	[redacted]%
Craniosynostosis	[redacted]%
Fractures	[redacted]%
Osteoarthritis	[redacted]%
Bone pain (in the previous year)	[redacted]%
Joint pain (in the previous year)	[redacted]%
Limited range of motion	[redacted]%
Gait Disturbances	[redacted]%

Source: online survey Study UX023-CL001 interim survey results.(Ultragenix, 2016; Linglart et al., 2015b, 2015a)

Skeletal deformities

In the burden of illness study (CL001), complications resulting from skeletal abnormalities included bowing of the femur, tibia/fibula, gait disturbance, joint pain, bone pain and restricted range of motion. Over 30% of responders had undergone at least one surgery to correct a skeletal defect (Linglart et al., 2015a). In the UK case note review that included adult patients, symptomatic or progressive deformity was the most common lower limb manifestation of the disease with 27 patients having undergone long bone osteotomies or guided growth surgery with physeal stapling. Overall, osteotomy ("cutting of the bone") was performed in 42% of patients. Three patients had undergone a total of five cemented total knee replacements (two bilateral) and two patients had undergone unilateral un-cemented total hip replacements with all arthroplasty operations having been undertaken at greater than 48 years of age. Seven patients developed symptomatic degenerative ankle or foot joint disease with three having undergone operative microfracture treatment for osteochondral defects or resection of symptomatic osteophytes for bony impingement (Chesher et al., 2018).

Many studies have also reported spinal involvement manifestations through increased osteophyte formation (Beck-Nielsen et al., 2010; Xie et al., 2014; Vera et al., 1997; Lee et al., 2012) and also cranial structure manifestations (significant cephalometric differences between HR patients and controls) (Gjørup et al., 2011). In the UK case note review seven adults were investigated, clinically and radiologically, for symptoms attributable to the spine. Four patients requiring spinal surgery (for cervical, thoracic or lumbar stenosis) were all older than 40 years (Chesher et al., 2018).

In addition, regarding related patients, a Chinese genetic study (Yue et al., 2014) that included 16 XLH patients showed that adults have more severe phenotypes with

similar or worsening symptoms than their children, including hip and knee joint pain, high bone mineral density and fewer teeth.

Skeletal abnormities, including bowing of the legs, and the associated misaligned joints, disproportionate growth and difficulty walking, persist despite treatment from an early age with conventional therapy (oral phosphate and active vitamin D) (Rafaelsen et al., 2016).

Growth

Linear growth failure appears frequently in children with XLH. The combination of height loss caused by the bowing of the legs and growth plate defects can lead to a permanent loss of growth potential despite the fact that children with XLH experience a normal pubertal growth spurt (Carpenter et al., 2011). In the burden of illness study, CL001, diminished height was reported for (57/71 [80%]) of children.

Children with XLH who are on conventional treatment with alfacalcidol or calcitriol and phosphate show progressive stunting and body disproportion during childhood that is mainly due to diminished growth capacity in legs (Živičnjak et al., 2011). 25–40% of patients with well-controlled XLH show linear growth failure despite optimal treatment and have a final height under -2 [Standard Deviation Scores (SDS)] (Glorieux et al., 1980; Verge et al., 1991; Berndt et al., 1996; Friedman et al., 1993; Haffner et al., 1999, 2004; Steendijk and Hauspie, 1992; Jehan et al., 2008; Ariceta and Langman, 2007). In a study of 28 XLH patients from 1971 to 2011, a significant difference was found between the initial stature and the final stature in only six patients who were treated with vitamin D and phosphate (Borghi et al., 2005).

Dental

Additional signs of the disease may include delayed dentition and dental abscesses, which are thought to arise from the limited mineralisation of the dentine compartment of the tooth. Oral findings in XLH have been enamel and dentine abnormalities, high pulp horns, large pulp chambers, and some cases of periapical abscesses related to teeth without caries or traumatic injuries (Cremonesi et al., 2014). In study CL001, [redacted]% of children and adolescents had had dental surgery (Ultragenix, 2016). In the UK case note review dental disease was very common with 37 (63%) of adult patients having at least one form of dental disease, with many having multiple problems with caries, periodontal disease and failing crowns and restorations and missing teeth being the most common. Twenty-four (41%) had a history of dental abscess *de novo* or associated with teeth that had been root filled and 29 (49%) required at least one dental extraction (Chesher et al., 2018). A further study (Andersen et al., 2012) of 53 patients with confirmed hypophosphataemic rickets (HR) found that endodontically affected teeth are common, and the number of affected teeth increased significantly with age. Hence, the need for endodontic treatment among HR patients is comprehensive.

Clinical and genetic heterogeneity

Clinical heterogeneity among XLH child and adult patients has been frequently reported (Linglart et al., 2014; Carpenter et al., 2011). The clinical expression of the disease is widely variable, ranging from a mild abnormality, the apparent isolated occurrence of hypophosphataemia, to severe bone disease (Carpenter et al., 2014). Varied clinical findings are reported even among siblings with the condition (Surender et al., 2014).

Differing levels of hypophosphataemia, rickets severity (in children), and other signs and symptoms may be partly due to genetic differences between subjects (Morey et al., 2011; Song et al., 2007), but is likely also affected by the timing of implementation of conventional therapy or secondary factors that might alter phosphate metabolism in general. Males are more severely affected than females due to random inactivation of the affected X chromosome (Lyonisation) (Pai and Shaw, 2015).

Radiographs are the gold standard for assessment of rickets. The Rickets Severity Score (RSS), is a radiographic scoring method developed to assess the severity of nutritional rickets. It scores abnormalities in the wrists and knees based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected (Thacher et al., 2000) (Table 6). The RSS is a 10-point scoring method, where a score of 0 indicates no rickets and a score of 10 indicates the highest severity of rickets.

The usual range of RSS total scores in XLH is between 0 and 6.5 but reflects only the epiphyseal/distal metaphyseal portion of the skeletal abnormalities that are common in affected children as there are other aspects of XLH not fully captured in the RSS. These other findings include coxa vara (a hip deformity that causes leg length discrepancies and gait abnormalities), tibial torsion (a twisting of the shins that causes the feet to turn inward), and genu varum (bowing) or genu valgum (knock knees).

Table 6. Rickets Severity Score (RSS): 10-point radiographic scoring methods for rickets

Wrist[a] – score both radius and ulna separately			
	Grade		
	1	Widened growth plate, irregularity of metaphyseal margin, but without cupping	2 bones x 2 points = 4 points possible
	2	Metaphyseal concavity with fraying of margins	
Knee[a] – score both femur and tibia separately Multiply the grade in A by the multiplier in B for each bone, then add femur and tibia scores together			
A	1	Partial lucency, smooth margin of metaphysis visible	2 bones x 1 points x 3 points = 6 points possible
	2	Partial lucency, smooth margin of metaphysis not visible	
	3	Complete lucency, epiphysis appears widely separated from distal metaphysis	
B	Multiplier	Point of growth plate affected	
	0.5	≤ 1 condyle or plateau	
	1	2 condyles or plateaus	
	Total		10 points possible

a Score the worst knee and the worst wrist
Source: Thacher et al 2000.(Thacher et al., 2000)

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

[redacted]

The incidence of XLH has been estimated to be 3.9 per 100,000 live births (Beck-Nielsen et al., 2009). Given there were 663,157 births in England in 2016, this equates to approximately 26 patients per year which is implausible given a prevalent pool of [redacted] patients and the fact that XLH is not associated with an increased risk of mortality. We therefore assume that the number of patients eligible for treatment will remain constant at [redacted] patients per year.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

No empirical evidence documenting the impact of XLH on mortality has been identified. XLH is not thought to have an impact on the life expectancy of patients.

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

From a young age, XLH has a detrimental impact on the quality of life of patients and families which continues throughout aging to adulthood. Familial cases are particularly burdensome since many members of the family may have the condition, such that a patient may also be a caregiver and vice versa.

As a rare, orphan disease area, XLH has not been the subject of extensive quality-of-life studies. Systematic reviews identified very few studies including empirical evidence documenting the impact of XLH on quality-of-life which are predominantly conducted in adult XLH patients. However, publications in the literature have attempted to describe the burden of XLH in terms of the manifestations and these are discussed below.

Quality of life in children with XLH

As children grow up, they may notice the ways in which they are different from their peers; this can become more apparent to them when they go to school and can result in teasing and bullying by their peers. These differences could be associated with physical appearance, as their legs may develop ‘bowing,’ or their ability to join in with sports or at playtime. It is also possible the child will need to wear leg braces for a time, which may cause them to feel self-conscious. Even if physical appearance is not an issue, the child may begin to question why they have to take regular medication when their peers do not (XLH Link, 2018a). Difficulties may also be experienced in gross motor skills such as walking, running and jumping, due to symptoms such as bowing of the femur/tibia and/or fibula and the rotation of the tibia which causes the feet to turn inwards. Surgery is often required to correct skeletal defects (Linglart et al., 2015a).

In the online survey to characterise the burden of illness people with XLH (CL001) high levels of pain and limitations in mobility were reported by paediatric respondents with POSNA-PODCI scores for the Sports and Physical Function and Pain and Comfort domains below the normative healthy population mean (Linglart et al., 2015b), suggesting that children with XLH have issues with mobility, gross motor function and pain relative to healthy children. Similarly, in the phase 2 burosumab study (CL201), in children five to 12 years of age that had received conventional therapy for on average seven years, 55% had substantial functional impairment at baseline, defined as the POSNA-PODCI Global Functioning score <40, with particular functional impairments in the Sports/Physical Functioning and Pain/Comfort domains (Imel et al., 2017b). In particular, children with more severe rickets at baseline [redacted].

In CL001, the mean SF-10 physical health score of 35.5 was 1.5 standard deviations below the general population norm of 50, also indicating substantially diminished physical health status in children with XLH (Linglart et al., 2015a). In Study CL201, the mean SF-10 physical health score at baseline was also below the population norm ([redacted]).

A further online survey, carried out in January 2018, collected background data from regarding the impact of XLH and treatments that the child had received to help manage their condition (Acaster Lloyd Consulting, 2018). [redacted]

Quality of life in adults with XLH

Adult patients with XLH have significant morbidity as a consequence of the long-term hypophosphataemia, and the continued weight bearing on lower extremities with mechanical axis defects cause long-term complications as patients age. The clinical presentation of XLH in adults is characterised by osteoarthritis, non-traumatic fractures, bone and joint pain, joint stiffness, mineralisation of tendons/ligaments (enthesopathy) and recurrent dental abscesses. Most adults have at some point had corrective surgery for lower-leg deformities, with [redacted]% of adults in CL001 having undergone corrective osteotomies on at least one occasion (Ultragenix, 2016). Adults

with XLH also have muscle dysfunction, likely due to the importance of phosphate in energy metabolism, which may contribute significantly to the feelings of fatigue and weakness expressed by these patients (Reid et al., 1989; Veilleux et al., 2013; Sabbagh et al., 2008).

A member of the Brittle Bone Society (BBS), in responding to the draft scope for this appraisal, described the complications related to the XLH disease:

"*Having inherited XLH from a family that currently has thirteen family members affected, through four generations, I have seen the significant impact that the condition can have in all areas of one's life. My personal experience includes requiring 18+ surgeries to correct bone abnormalities, as well as requiring multiple restorative dental treatments from having 15+ dental abscesses all over a period of 30 years. I'm now paying the price of having those surgeries as my bones do not heal well and as a result, are bolted together with rods, nails, plates, staples, fixators and ilizarovs. I'm now entering a time in my life where I have recurring pseudo fractures, from bone that won't respond to treatment, to other parts of my body where the bone deposits itself around the spine, hips, and knees. XLH is a debilitating chronic disorder, a treatment that offers the prospects of reducing the need for surgical intervention is incredibly important to reducing the impact of XLH on patients' lives and reducing the costs associated with these interventions*."

Most adults with XLH report suffering from joint or bone pain. The pain associated with XLH can also be overwhelming as described by an XLH patient (XLH Link, 2018b):

"*Your bones ache all the time. You can't sleep from pain. You can't concentrate at work from pain. You're going a week between showers...You don't want to hang out with your few friends because it's too hard to move and you're just too tired. You're showing signs of real depression…*"

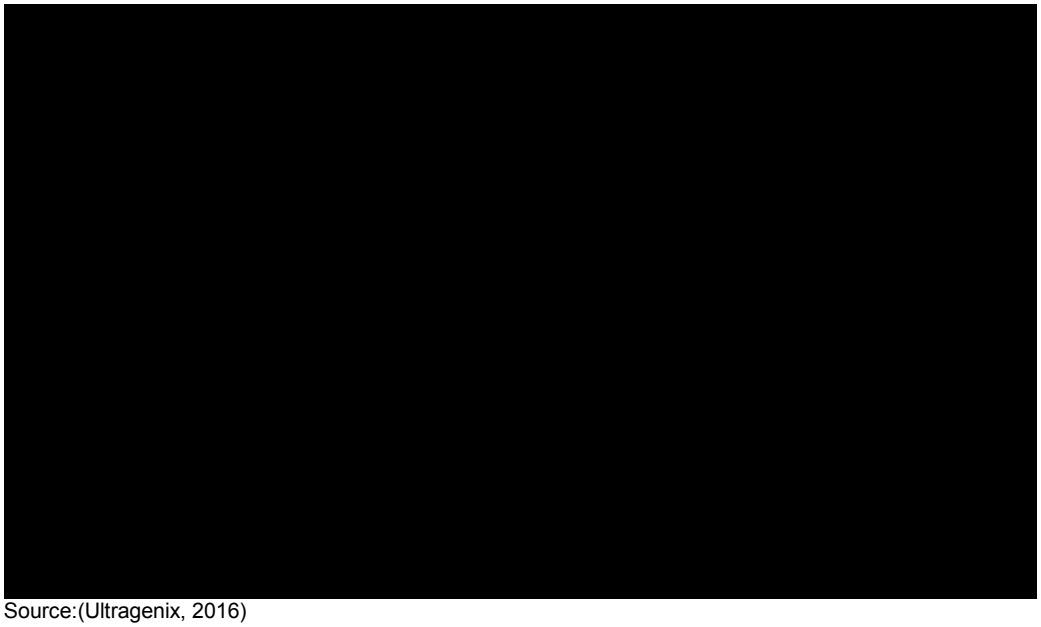
In the burden of illness study, CL001, when asked to list the top three symptoms or complications of XLH that had the greatest impact on their lives, of the [redacted]. These results demonstrate the significant impact of the disease on the lives of children and adults with XLH.

Berndt et al assessed the clinical and psychosocial aspects of the disease in 23 adults using a standardised questionnaire on pain and psychosocial rehabilitation (schooling, vocational training, employment and marital status). The impact of XLH was evident based on the data provided by the 20 patients who responded to the questionnaire. Responders indicated that they were unable to cope with physical and psychological stress as well as their peers and attributed the struggle to the burden of pain, restricted mobility, and a lack of schooling and vocational training resulting from a lifetime of managing disease-related complications (Berndt et al., 1996).

These results are supported by the SF-36 Physical Component Summary (PCS), Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), and General Health

(GH) scores for the 195 adult responders in the burden of illness study, CL001, [redacted]. Scores also suggest a more significant level of impairment in than normative populations with back pain/sciatica and osteoarthritis. Adults with XLH had a mean PCS score [redacted] points below an adult population with back pain/sciatica and [redacted] points below an adult population with osteoarthritis (Figure 4).

Figure 4. SF-36 PCS Scores for XLH and Comparison Groups



Source:(Ultragenix, 2016)

In an early clinical trial for burosumab in adult XLH patients (Ruppe et al, 2014) health-related quality of life (SF-36v2 and WOMAC) was measured at baseline and day 120 among 28 patients and compared to norm scores. At baseline, mean bodily pain, physical functioning, role limitations due to physical health, and Physical component summary (PCS) were far below those of the general USA population.

A UK study (Forestier-Zhang et al., 2016) used cross-sectional data from an ongoing UK-based multi-centre prospective cohort study: RUDY (Rare and Undiagnosed Diseases Study). RUDY is a novel web-based registry and patient-driven research platform designed to improve the understanding of all rare musculoskeletal diseases. Participants completed the EQ-5D-5L questionnaire and for the economic simulation, a hypothetical treatment was considered that would be applied to osteogenesis imperfecta participants in the lower tertile of the health utility score. A total of 109 study participants fully completed the EQ-5D-5L questionnaire (response rate 63%). Pain/discomfort was the most problematic domain for participants with XLH, with over 60% reporting moderate or severe problems.

Decisions around having children are difficult for XLH families. The pattern of transmission with XLH is that a father will always pass the affected gene on to his

daughters but not to his sons; an XLH mother has a 50% chance of passing the affected gene on to a son or daughter. Patients with XLH have described their thoughts about having children (The XLH Network Inc., 2017):

"*The decision to have a second child was complex for us…That experience [of waiting for an XLH diagnosis] made me realise that I did not want to go through that again. I did not want to have any more biological children, partly because of XLH and partly for other reasons… Our daughters are both incredible human beings, and our lives are truly richer because of them. But we all have to weigh both ends and decide what is best for us – for our own families. It is something nobody told me when I was a kid with "rickets" that one day I would have to decide whether to risk passing my condition on to my child.*"

"*I do not have any children. As a young adult, when I had a flicker of a thought about becoming a parent one day, I always reverted back to my childhood beliefs that there didn't need to be another kid in the world like me and that being the mother of a child with my medical challenges would be hard.*"

Furthermore, childbirth may be more complicated for women with XLH. In the UK case note review 26 (76%) children were delivered by caesarean section, with only eight delivered vaginally, of a total of 34 deliveries in 18 women with XLH. This caesarean section rate is much higher than that of the general UK population, in whom 72.9% of deliveries are vaginal and 27.1% by section (Chesher et al., 2018).

Quality of life of families and carers

Having a child with medical needs such as XLH requires full attention, with families and carers providing support and reassurance through the child's life progression. Frequent medication, hospital visits and tests can be overwhelming not only for the patient but for their carer as well. Regular blood tests, ultrasound scans to monitor kidneys, X-rays to check the development and condition of bones, frequent dentist visits and even orthopaedic surgery and osteotomies are required through since an early age of a patient with XLH that only their family and carers can assist with. Emergency situations may also occur periodically as bone fractures or increase in pain severity are common between patients with XLH (XLH Link, 2018a). Parents of children with XLH often suffer from the condition themselves. In a UK survey (Acaster Lloyd Consulting, 2018), [redacted].

The impact on families carries on throughout their lifetime:

"*Parents today still experience fear and worry about their affected children. My parents worry about me even now. I feel for them and for parents today who have children with XLH. We now understand that XLH is not just a childhood disease. We know that there is a progression that goes with us into adulthood and can give parents a lifetime to worry.*" (The XLH Network Inc., 2017)

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

The consistency and magnitude of burosumab treatment across the efficacy endpoints in the clinical studies represent clinically meaningful changes that have a profound effect on the lives of these subjects. In children with XLH, burosumab treatment improved bone disease as evidenced by assessments of rickets, lower extremity deformity, and height. This was accompanied by improvements in the ability to walk and play sports, and a reduction in pain. The ability to improve the skeletal and non-skeletal issues of XLH earlier in life may alter the natural progression of the disease and potentially ameliorate the long-term consequences and clinical complications during adolescence and adulthood, including the need for surgical intervention.

To illustrate this point, below is an example of clinical outcomes in a representative burosumab responder (RGI-C global score of +2.0). [redacted].

The improvements in rickets, patient-reported pain and physical function, and walking ability will enable this child, and other children suffering from XLH, to do activities that are not readily afforded to them with conventional therapy. Earlier treatment is

anticipated to prevent lower extremity deformity and optimise growth potential in younger children. In the example above the patient only started to receive burosumab from the age of 9 years; therefore the potential for transformational outcomes is clear. The improvements with burosumab treatment will allow XLH children to engage in sports and other physical activities typical of a healthy child and allow them to be regular children. These changes are expected to not only improve the patient's overall health-related quality of life, but also the immeasurable quality of life of their family.

Importantly, treatment with burosumab has not been associated with hyperphosphataemia, nephrocalcinosis, hypercalciuria, or secondary/tertiary hyperparathyroidism, that may occur with conventional treatment.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

Kyowa Kirin is not aware of any published NICE, NHS England, other national or expert guidelines for the diagnosis, treatment or management of XLH. XLH is listed amongst Rare Metabolic, Sclerosing and Dysplastic Bone Diseases in the National Health Services England (NHSE) document entitled "A13/S/a 2013/14 NHS STANDARD CONTRACT FOR SPECIALISED RHEUMATOLOGY SERVICES (ADULT)." There is no specialised service specification for Children.

Guidelines on the diagnosis and management of XLH have been produced by a group of clinical experts in the USA (Carpenter et al., 2011; Imel and Carpenter, 2015). These guidelines provide specific recommendations for management of XLH in children and adults (See Section 8.2 for further details).

The above guidance also aligns with the proposals of an expert panel of the Japanese Society for Bone and Mineral Research (Fukumoto et al., 2015) as well as a review by UK clinicians (Pai and Shaw, 2015), that provides guidelines on diagnosis and management of rickets, including a short section on XLH.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Diagnosis

Diagnosis of XLH is typically based on clinical findings, radiographic findings, biochemical testing and family history. Family history remains critically important to the early recognition of inherited forms. Although, genetic testing is increasingly used to confirm the diagnosis of XLH, radiographs have been the gold standard for the diagnosis and evaluation of rickets for several decades (Holick, 2006; Do, 2001; Shore and Chesney, 2013a, 2013b). The radiographic characteristics of rickets include lucency in the metaphyses, physeal widening, fraying and cupping (Shore and Chesney, 2013b; Thacher et al., 2000). These diagnostic radiographic features of rickets typically reflect the impaired mineralisation and ossification affecting the growth plate. Bone manifestations are best seen in the metaphyses of rapidly growing bones, including the distal radius and ulna, distal femur, proximal and distal tibia and proximal humerus (Shore and Chesney, 2013b; Thacher et al., 2000).

Paediatric patients with XLH are managed by paediatric endocrinologists and paediatric nephrologists. There is a limited number of expert clinicians with the necessary training and experience in rare metabolic bone diseases to appropriately manage children with XLH. It is anticipated that treatment would be initiated and monitored by specialist centres and clinicians.

Treatment of children

Treatment aims at alleviating bone or joint pain, preventing skeletal deformities caused by rickets and improving growth. Conventional therapy, consisting of systematic oral administration of phosphate and active Vitamin D analogues (alfacalcidol, once daily), is commonly used. The dose of oral phosphate is divided in aliquots every 4 to 6 hours due to rapid excretion by the kidneys. Patients do not respond to vitamin D supplementation. Use of an active vitamin D analogue (usually alfacalcidol in the UK) helps prevent secondary hyperparathyroidism that can be induced by phosphate administration. Calcitriol is an alternative, however it requires multiple dosing and is available only as a capsule, making it less suitable for infants and young children. Doses of alfacalcidol and phosphate used in practice may vary. Carpenter et al. (Carpenter et al., 2011), recommends an elemental phosphorus dose of 20 to 40 mg/kg/day (in 3-5 divided doses), acknowledging that some children require more, while some do well with less. In the UK, the dose of alfacalcidol used by clinicians for the treatment of XLH is 30 to 50 nanograms/kg/day. According to the BNF, alfacalcidol is recommended for children from one month to 11 years at 25-50 nanograms/kg once daily with the dose to be adjusted as necessary (max 1 microgram/day) and for children 12 to 17 years, 1 microgram/day with the dose to be adjusted as necessary. Changes in body size, growth velocity, and skeletal

mineralisation necessitate regular monitoring and periodic dose adjustments (Carpenter et al., 2011).

Combined treatment with alfacalcidol and phosphate cannot correct the renal handling of phosphate and increases FGF23 production. However, this approach mitigates the impact, providing sufficient minerals to improve osteomalacia in XLH, but often does not result in limb straightening or normal height.

Administration of phosphate and active Vitamin D analogues requires frequent monitoring of height, serum calcium, alkaline phosphatase, parathyroid hormone, phosphate serum concentrations, and urinary calcium and creatinine. UK clinicians stated that the following monitoring is required with conventional therapy:

- Monitor serum calcium, phosphorus, potassium, and creatinine levels monthly until stable and thereafter every three months
- Monitor ALP, PTH and urine calcium and creatinine levels every three months.
- Perform renal ultrasonograms (to monitor nephrocalcinosis) every one to two years.

For children, treatment is initiated at the time of diagnosis and continued until long bone growth is complete. Almost all children with XLH require therapy until growth is complete, although the effectiveness on the skeleton is variable, and surgery is often necessary to correct lower extremity deformities. In Study CL001, many of the children surveyed had already undergone at least one surgical procedure. The most common surgeries reported were [redacted]. The majority of the children (80%) had reportedly experienced bone or joint pain in the previous year with [redacted]% reported needing to use a device to assist with walking.

Linglart et al. (Linglart et al., 2014) provides a comprehensive review of the therapeutic management of hypophosphataemic rickets from infancy to adulthood which very much is aligned with Imel and Carpenter (Imel and Carpenter, 2015) but provides additional commentary on orthopaedic and surgical management in children. Specifically, it is mentioned that surgery during childhood should be avoided, as due to open epiphyses, patients present a significant risk of recurrence of the bowing at the level of osteotomy or secondary to the adjacent epiphysiodesis. If necessary due to major bone deformities, surgery should be combined with adjusted doses of phosphate supplements and vitamin D analogues in order to prevent recurrence as previously evoked. The review also mentions that the actual place of the surgery is the correction of residual deformities at the end of growth. Therefore, avoiding the need for such corrective surgery would be of great value to people with XLH.

Treatment of adults

The goals of treatment in adults are to reduce pain symptoms, the extent of osteomalacia, and/or to improve fracture healing or surgical recovery. There are limited clinical trial data that support the efficacy of conventional therapy for these indications (Carpenter et al., 2011). However, since there are no alternative treatments, therapy with phosphate and active vitamin D therapy is often continued in symptomatic adult patients. Nephrocalcinosis ([redacted]%-42%), hyperparathyroidism ([redacted]%), kidney stones ([redacted]%) and impaired renal function ([redacted]%) are observed as complications of the therapy (Ultragenix, 2016; Chesher et al., 2018); frequent follow-up is therefore necessary. Careful monitoring is required and the frequent follow-up visits and laboratory sampling can be burdensome to patients, sometimes compromising compliance (Carpenter et al., 2011).

Corrective surgery of skeletal deformities is often required in some cases to strengthen limbs and correct orthopaedic problems. Osteotomies with stapling or toggle plate insertion can help straighten legs by allowing bone formation on one side of the growth plate to catch up with the other side. If medical treatment is not continued, bones may regress and bend again. Joint replacement surgery, especially knees and hips, is not uncommon in adults with XLH because of the high frequency of degenerative joint disease and enthesopathy (Carpenter et al., 2011). In Study CL001, lower extremity deformities frequently required corrective surgeries, with [redacted] having undergone corrective osteotomies on at least one occasion. In the UK case-note review 42% of patients had undergone an osteotomy (Chesher et al., 2018). These findings are also supported by a study of 23 adults (mean age at investigation = 29 [19 - 57] years), where Berndt and colleagues found 101 orthopaedic operations had been performed in 13 out of 23 patients (57%) with XLH (Berndt et al., 1996).

Dental disease, particularly root abscess, remains a major problem in adults with XLH, requiring numerous root canals and tooth extractions. Apart from good dental hygiene including regular use of dental floss, no specific therapy has been demonstrated to prevent this debilitating complication (Carpenter et al., 2011).

Burosumab

Burosumab is expected to be used in line with the anticipated marketing authorisation, in children and adolescents with XLH from the age of one year old. Burosumab is a monotherapy: oral phosphate and vitamin D analogues should be discontinued one week prior to initiation of treatment.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

There is no (regulatory) approved therapy specifically for XLH that specifically treats the underlying pathophysiology of elevated FGF23-induced hypophosphataemia. The combination of multiple daily doses of unpalatable oral phosphate and active vitamin D treatment has become the conventional therapy for treatment of XLH in all diagnosed children and a small proportion of adults who continue with active chronic treatment.

The goal of supplementation with phosphate and active vitamin D analogues is to provide sufficient phosphorous to allow mineralisation of bone and improve skeletal outcomes. Conventional treatment with oral phosphate salts and active vitamin D is suboptimal and does not specifically target the underlying cause of the disease (renal phosphate wasting induced by excess FGF23). Rather than addressing the underlying cause of disease, providing a high amount of phosphate to patients might actually stimulate FGF23 production, which, along with the phosphate loading, increases the urinary phosphate wasting. For the majority of paediatric patients with XLH, (98.6%) treatment with conventional therapy (phosphate and vitamin D metabolites) does not adequately heal rickets or other clinical features of XLH (Table 5) and has potential risks such as hypercalciuria, hypercalcemia, nephrocalcinosis and hyperparathyroidism.

Phosphate homeostasis remains an important clinical objective to avoid morbidities associated with hypophosphataemia (Manghat et al., 2014), and as such is a useful endpoint in clinical trials and as a measure of treatment response. However, normalisation of the serum phosphate concentration is not currently a practical therapeutic goal with conventional therapy in children with XLH. With conventional therapy, this strategy may lead to overtreatment and increases the risk for treatment-related complications, such as secondary hyperparathyroidism (Ruppe, 2012; Carpenter et al., 2011). In the UK case note review, three patients (5%) had successful parathyroid gland removal for hyperparathyroidism associated with persistent hypercalcemia (Chesher et al., 2018). Prescribing phosphate intake is a challenge, as a balance in optimal doses must be found, between excessive dosage tending to hyperparathyroidism and insufficient dosage slowing the healing of rickets (Linglart et al., 2014; Carpenter et al., 2011).

With conventional therapy, careful monitoring of plasma calcium, PTH, creatinine, and 24-h urinary calcium excretion is required in order to prevent tertiary hyperparathyroidism, induced by phosphate overdose and hypercalciuria with nephrocalcinosis and renal insufficiency, resulting from vitamin D metabolite overtreatment (Linglart et al., 2014). Frequent monitoring in the first year of treatment is critical because the requirements for alfacalcidol and phosphorus may decrease abruptly as osteomalacia heals. It is important to detect this change early to avoid prolonged hypercalcemia or hypercalciuria (Carpenter et al., 2011).

Whilst liquid or dispersible formulations may be used to allow for more precise dosing and improve adherence, especially in young children (Carpenter et al., 2011), the need for frequent daily dosing and regular monitoring together with the unpalatable nature of the formulations means that persistence/compliance challenges remain and ultimately the therapeutic benefit of conventional therapy is still compromised.

Patients with XLH have a clear unmet medical need, and this is apparent as a proportion of patients remain highly symptomatic despite many years of continued treatment with this conventional therapy approach (Table 5). In addition, due to failure of conventional therapy to attain full growth, human growth hormone therapy is often required. Targeting serum phosphate seems to be the most promising treatment approach in XLH patients. This goal cannot be achieved with the current standard treatment (alfacalcidol and phosphate) due to the high risk of severe side effects. Consequently, new therapeutic measures are required. In order to prevent skeletal deformities, as well as disproportional growth and stunting, these measures should be initiated as early in life as possible (Zivicjak et al., 2011).

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

In general, the overall pathway of care is not expected to change following the introduction of burosumab. Burosumab is expected to replace conventional therapy with oral phosphate and active vitamin D analogues, and as such will reduce or remove the complications seen with conventional therapy. Clinical expert opinion has suggested that patients responding well to burosumab treatment are likely to have a diminishing frequency of consultant visits over the longer term. In addition, burosumab will either prevent or improve skeletal abnormalities, and reduce the need for corrective surgery. Routine treatment with burosumab should also remove the need for additional supplementation with growth hormone in a small subset of patients where this is required.

Discussions with NHS England have suggested that burosumab would only be prescribed by specialist centres that are members of ERN-BOND: European Reference Network on Rare Bone Disorders. It is planned that burosumab will be supplied via a homecare provider once patients have been established on a maintenance dose. During the initial dose titration period burosumab will be supplied directly to designated hospitals where this option is required.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Excess FGF23 causes a severe increase in phosphate wasting, leading to XLH. Burosumab is a first in-class disease-modifying drug that inhibits the action of excess FGF23. Burosumab is a recombinant human IgG monoclonal antibody that binds to the FGF23 protein, neutralising its activity and allowing the kidneys to reabsorb phosphate and restore normal levels of phosphate in the blood. By restoring a more physiological level of phosphate homeostasis it is expected to improve the symptoms of the disease and physical function in patients of all ages. In paediatric patients, treatment with burosumab improves bone mineral metabolism and heals or substantially reduces rickets severity leading to increased growth, mobility and physical functioning. Burosumab has had a significant impact on patients who had previously been receiving oral phosphate and vitamin D from before the age of two years, for an average of approximately seven years up until entry in the performed studies. Burosumab is administered by every two weeks by SC injection. Therefore, for a child with XLH, burosumab has the potential to eliminate the need for multiple daily doses of oral therapy while improving skeletal outcomes and overall mobility, essentially allowing the child and their family to have a more normal daily life while improving long-term outcomes. Burosumab is well tolerated and avoids complications that are associated with conventional therapies.

As such, burosumab is an innovative medicine for the treatment of XLH, with the potential to significantly modify the natural history of the disease, make a substantial impact on the health of children and enable them to reach adulthood with fewer manifestations and deformities. On the 31st January 2017, burosumab received a 'Promising Innovative Medicine' (PIM) designation from the MHRA, confirming its potential to address a high unmet need in children with a seriously debilitating condition [reference EAMS 16508/0001].

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Kyowa Kirin will provide a homecare service in the UK for the administration of maintenance doses of burosumab. There are not expected to be any additional changes to the way current services are organised or delivered as a result of introducing the technology. As mentioned above, in patients responding well to burosumab treatment, clinical expert opinion has suggested that the frequency of consultant visits are likely diminish over the long-term. In addition, burosumab will

either prevent or improve skeletal abnormalities, and reduce the need for corrective surgery.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests are required to select patients for treatment.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every two weeks for the first month of treatment, every four weeks for the following two months and thereafter as appropriate. Fasting serum phosphate should also be measured four weeks after any dose adjustment (Summary of Product Characteristics (Crysvita), 2017). The blood tests can be carried out in line with local arrangements, without the requirement for a visit to the specialist centre.

The following ongoing monitoring is recommended with burosumab (Summary of Product Characteristics (Crysvita), 2017):

- Monitoring for signs and symptoms of nephrocalcinosis, e.g. by renal ultrasonography, is recommended at the start of treatment and every 6 months for the first 12 months of treatment, and annually thereafter.
- Monitoring of plasma alkaline phosphatases, calcium, PTH and creatinine is recommended every 6 months (every 3 months for children 1- 2 years) or as indicated. Monitoring of urine calcium and phosphate is suggested every 3 months. Patient's fasting serum phosphate level should be monitored due to the risk of hyperphosphataemia. To decrease the risk for ectopic mineralisation, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age. Dose interruption and/or dose reduction may be required.
- Increases in serum parathyroid hormone have been observed in some XLH patients during treatment with burosumab. Periodic measurement of serum parathyroid hormone is advised.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

Following initial prescription and dispensing at the specialist centre, burosumab is expected to be provided to patients via a homecare service (to be provided and

funded by the manufacturer). No other additional facilities, technologies or infrastructure will be required.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Concurrent use of oral phosphate and vitamin D analogues is contraindicated with burosumab, therefore use of these is expected to decline following burosumab introduction. The high burden of frequent monitoring when the drug is first introduced will tail off once the patient is on a stable dose, and the overall burden of monitoring is expected to be reduced compared with that required for conventional therapy. In addition, burosumab will either prevent or improve skeletal abnormalities, and reduce the need for corrective surgery.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

A systematic literature review was carried out to identify clinical evidence for treatments for XLH. The review was broad, including both paediatric and adult studies, and was not restricted by intervention or outcomes. Randomised controlled trials (RCTs), cluster RCTs, non-randomised controlled studies and interrupted time series studies were included. However, only studies that are relevant to the scope of this submission have been presented in this section.

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

To identify published literature, an independent reviewer used all identified terms for XLH in a computer-assisted search of MEDLINE and EMBASE starting at the earliest date available for each database and ending in October 2017. A separate search of the Cochrane Library was carried out, including records from inception to December 2017. Further strategies were used to identify studies not identified through database searches, including manual searching of the bibliographies of relevant systematic reviews. A review author independently assessed the publications identified by the literature search strategy for clinical outcomes of treatment strategies of XLH, according to predefined inclusion and exclusion criteria (Table 7). A record of the number of studies included at each stage of the review and the reasons for exclusion

is shown in Figure 5. Data was extracted from included studies using a specially designed data extraction form.

The detailed methodology for the systematic review of clinical effectiveness literature is provided in Appendix 17.1.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

The EU Clinical Trials Register was searched to identify ongoing studies. The U.S. National Institutes of Health clinical trials *registry and results* database (clinicaltrials.gov) was searched to identify ongoing studies or results that may not have been published. Experts and clinical specialists of XLH were consulted for information (e.g. protocols or results) about unpublished or ongoing studies and missing references from the computer-assisted search strategy.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table 7. Selection criteria used for published and unpublished studies (clinical effectiveness in XLH)

Inclusion criteria	
Population	Children or adults with XLH.
Interventions	Any
Outcomes	Reported statistical findings on clinical outcomes (either benefits or adverse effects).
Study design	Studies with a quantitative analytical approach and a study design of case comparison or interventional design (experimental or observational), including: Randomised Control Trials (RCTs), cluster RCTs, non-randomised controlled studies (including controlled before and after studies) and interrupted time series studies (with time points before and after the intervention to establish an underlying trend in the outcome).
Language restrictions	English
Search dates	Database inception to October 31st 2017 (Embase and Medline) and to December 2017 (Cochrane Register of Controlled Trials)
Exclusion criteria	
Population	None
Interventions	None
Outcomes	None
Study design	Animal studies or biochemical or cellular level investigations. Studies with a qualitative design, review articles or articles that investigate the genetic characteristics of XLH.
Language restrictions	Languages other than English.
Search dates	None

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

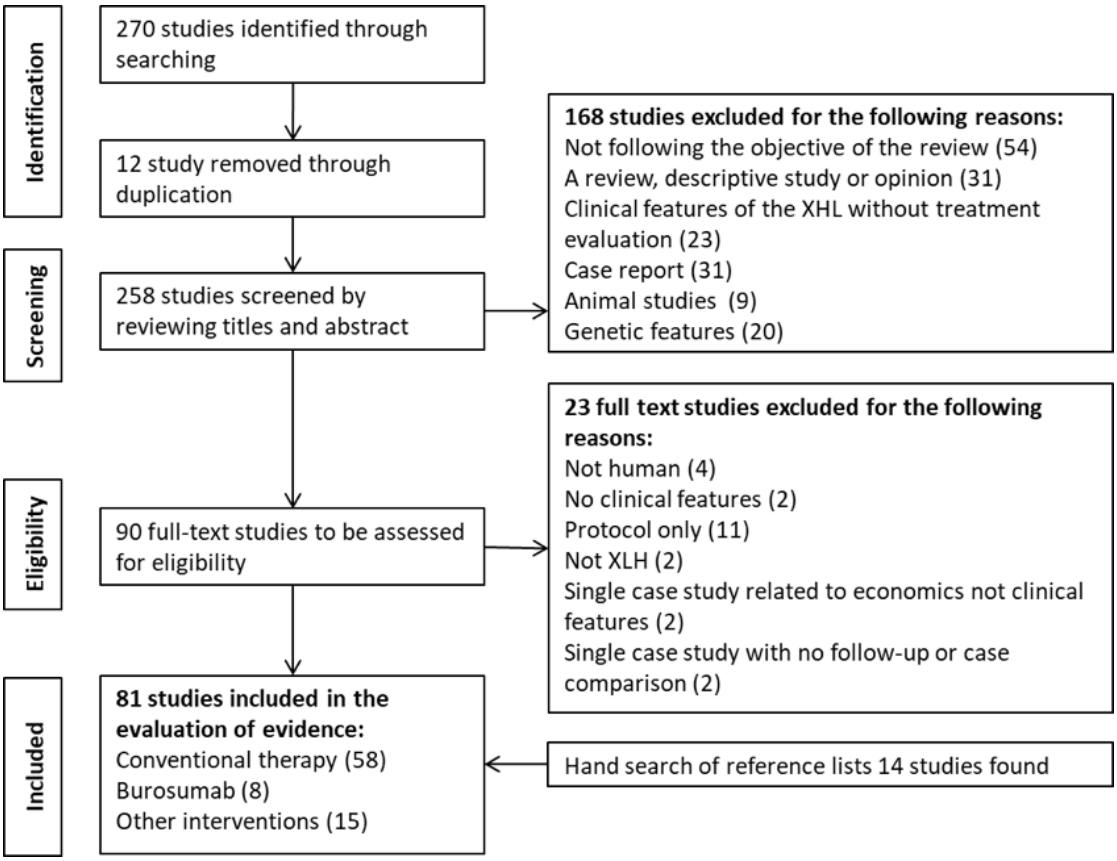
Eighty-one published studies were included in the review:

- A total of 58 published studies report on conventional therapy were identified:
    - 11 studies were in adults
    - 13 studies included both children and adults
    - 29 studies included children (up to 18 years of age)
    - 3 studies did not report the age of participants
- Eight publications reported burosumab treatment. Five of these were in adults with XLH and are not relevant to the scope of this submission. The three publications in paediatric and adolescent patients relate to Study CL201.

(Note: 17 further recent abstracts, presentations and posters were identified. See Appendix 17.5).

- The remaining studies (n=15) were on growth hormones, surgical or other interventions in XLH and are not relevant to the scope of this submission.

Figure 5. PRISMA flowchart: Clinical effectiveness evidence for the treatment of XLH



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

See Table 7.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Three unpublished paediatric studies of burosumab were identified from the ongoing clinical development programme (Table 8). In addition to Study CL201, a further phase 2 study (CL205) has available data and is presented in this submission. A phase 3 study is ongoing: results are expected [redacted]. A further study (UX023-CL207) investigating burosumab in XLH patients less than one year old is planned but is not relevant to the scope (outside indication).

Two studies (CL001 and CL002), were identified that provide data on the burden of illness and natural history of XLH in patients treated with conventional therapy. Study CL001 is a burden of illness study and is described in Section 6.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Paediatric studies of burosumab, identified from the ongoing clinical development programme, are shown in Table 8. Two of the studies have reported data and are included in this submission (UX023-CL201 [CL201]) and (UX023-CL205 [CL205]). Data from Study CL201 has been reported in 20 conference presentations (Appendix 17.5, Table 63). Three were identified in the literature review, an additional 17 presentations from recent conferences have been provided by the manufacturer (Kyowa Kirin).

There are no studies that compare the intervention directly with conventional therapy. Twenty-nine publications reporting on the use of conventional therapy in paediatric and adolescent patients were identified. Except for a single randomised trial, the evidence identified for conventional therapy is based on non-randomised studies. These studies either did not report data on severity of rickets that could be compared to results from the burosumab studies or did not include comparable populations and are therefore not described in detail in this section. A summary of the evidence from these studies is provided in Appendix 17.5 (Table 64).

A historical control study UX023-CL002 (CL002) was conducted to provide reference group data to use for comparative analyses of rickets, growth, and lower extremity deformity in Study CL201, in a similar paediatric XLH population who had received long-term conventional therapy with oral phosphate and active vitamin D. This study was based on a retrospective radiographic and medical chart review of patients with XLH who had repeat historical radiographs when between 5 and 14 years of age.

Table 8. List of burosumab studies

Data Source	Study Number (Status)	Study Title	Patient Population (Type/ Number of Subjects)	Intervention and Comparator
UX023-CL201 Clinical Study report – Week 64 Analysis, May 2017	**UX023-CL201 (ongoing)**	Randomised, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 antibody, burosumab, in Paediatric Patients with XLH	Paediatric patients with XLH, 5 to12 years old 52 initiated treatment	**Multi-dose burosumab** Biweekly or monthly administration of burosumab (doses 0.1 to 2.0 mg/kg) Repeat dose, up to 64 weeks
UX023-CL205 Clinical Study report – Week 40 (Primary) Analysis, Oct 2017	**UX023-CL205 (ongoing)**	An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics and Efficacy of burosumab in Children from 1 to 4 Years Old with XLH	Paediatric patients with XLH, 1 to 4 years old 13 patients enrolled	**Multi-dose burosumab** Biweekly administration of burosumab at a target dose of 0.8 mg/kg. Repeat dose, up to 64 weeks
Data not yet available	**UX023-CL301 (ongoing)**	Randomised, Open-Label, Phase 3 Study to Assess with the Efficacy and Safety of burosumab versus Oral Phosphate and Active Vitamin D Treatment in Paediatric Patients with XLH	Paediatric patients with XLH, 1 to ≤ 12 years old with open growth plates Targeted to enrol 60 patients	**Multi-dose burosumab** Biweekly administration of burosumab at a target dose of 0.8 mg/kg **Control:** Oral phosphate/active vitamin D Repeat Dose, Open label up to 64 weeks

Data Source	Study Number (Status)	Study Title	Patient Population (Type/ Number of Subjects)	Intervention and Comparator
Data not yet available	**UX023-CL207 (planned)**	An Open-Label, Phase 3 Study to Assess the Safety, Pharmacodynamics and Efficacy of the anti-FGF23 antibody, burosumab, in Paediatric Patients under the age of 1 year with XLH	Paediatric patients < 1 year of age Targeted to enrol at least 20 patients	**Multi-dose burosumab** Biweekly administration of burosumab at a starting dose that has yet to be determined (will be based on PK results from UX023-CL205). Repeat dose, Open label, Up to 64 weeks **Control:** None

Table 9: List of relevant studies of conventional therapy in XLH (unpublished)

Data Source	Study Number (Status)	Study Title	Patient Population (Type/ Number of Subjects)	Interventions
UX023-CL002 Clinical Study report, Nov 2016	**UX023-CL002**	A retrospective longitudinal study of skeletal outcomes in children with XLH	Paediatric Patients with XLH, 5 – 14 years old. Images will be collected from up to 100 children	This was not an interventional study; however, study inclusion required the use of conventional therapy (oral phosphate/active vitamin D)

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

No published or unpublished studies have been excluded from this submission.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

Interventional studies

Study CL201

The safety and efficacy of burosumab in the paediatric population with XLH has been evaluated in 52 patients 5-12 years of age in Study UX023-CL201 (CL201), an ongoing, randomised, multicentre, open-label, dose-finding Phase 2 study (Table 10). [redacted] patients were included from three clinical trial centres in the UK.

Subjects discontinued therapies that affect phosphorous metabolism (e.g., oral phosphate, vitamin D metabolite therapy) prior to randomisation and throughout the duration of the study.

In the paediatric XLH population, the requirement for phosphate is higher and may warrant higher burosumab doses or higher frequency of administration. Thus, two dosing regimens, administration every two weeks (Q2W) and every four weeks (Q4W), were evaluated in the paediatric Phase 2 study to determine the most appropriate dose and dose regimen in paediatric patients. Subjects were enrolled sequentially into cohorts defined by the initial dose of burosumab and were randomised (1:1, stratified by sex for pre-expansion subjects) to the Q2W regimen or to the Q4W regimen within each dose cohort. The monthly dose of burosumab was the same for the Q2W or Q4W regimen within each dose cohort, i.e.:

- Dose Cohort 1 received initial doses of 0.1 mg/kg Q2W ([redacted]) or 0.2 mg/kg Q4W ([redacted])
- Dose Cohort 2 received initial doses of 0.2 mg/kg Q2W ([redacted]) or 0.4 mg/kg Q4W ([redacted])
- Dose Cohort 3 received initial doses of 0.3 mg/kg Q2W ([redacted]) or 0.6 mg/kg Q4W ([redacted])

The study consists of two Screening Visits, a 16-week Titration Period, a 48-week Treatment Period, and a 96-week Treatment Extension Period:

- Titration Period (16 weeks): The dose of burosumab was adjusted to achieve the target peak PD effect (fasting serum phosphorus 3.5 to 5.0 mg/dL [1.13 to 1.62 mmol/L]). The dose was adjusted every four weeks in 0.3 mg/kg increments, as needed, based on two-week post-dose (peak) fasting serum phosphorus levels.
- Treatment Period (48 weeks): Each patient continued on the regimen to which they were randomised (Q2W or Q4W) and continued to receive the individually optimised dose of burosumab established during the Titration Period. Dose titration could continue into the Treatment Period, if necessary.
- Treatment Extension Period (96 weeks): All patients receive burosumab Q2W. Subjects initially assigned to the Q2W regimen continue at the individualised dose established during the Dose Titration and Treatment Periods. Subjects initially assigned to the Q4W regimen transition to the Q2W

regimen, and the dose of burosumab is adjusted to maintain serum phosphorus levels in the target range.

Study CL201 examined higher doses (up to 2 mg/kg Q2W) to maximise a stable treatment effect and to drive phosphate levels closer to the normal range, thereby maximising the effect on healing rickets and improving growth.

In addition to PD assessments, clinical efficacy was evaluated based on changes in rickets severity, growth, and bowing, as well as patient-reported outcomes (POSNA-PODCI) and functional assessments (6MWT).

The available clinical data in paediatric patients show burosumab significantly improves rickets severity as measured by two independent methods and suggests Q2W dosing provides greater efficacy. The benefits of treatment are most apparent in those patients with more severe rickets, defined as those with total Rickets Severity Scores (RSS) ≥1.5 at baseline. [redacted]. Burosumab treatment substantially improved physical function and reduced symptoms such as pain. Burosumab has a favourable benefit-risk profile.

Forty-week data (primary efficacy analysis) and 64-week data, the key time points of this study for efficacy analyses are available for the enrolled population (n=52).

Table 10. Summary of methodology for CL201

Study name	**UX023-CL201**
Objectives	• Identify a dose and dosing regimen of burosumab, based on safety and PD effect in paediatric XLH patients • Establish the safety profile of burosumab for the treatment of children with XLH including ectopic mineralisation risk, cardiovascular effects, and immunogenicity profile • Characterise the PK/PD of the burosumab doses tested in the monthly (Q4W) and biweekly (Q2W) dose regimens in paediatric XLH patients • Determine the PD effects of burosumab treatment on markers of bone health in paediatric XLH patients • Obtain a preliminary assessment of the clinical effects of burosumab on bone health and deformity, muscle strength, and motor function • Obtain a preliminary assessment of the effects of burosumab on patient-reported outcomes, including pain, disability, and quality of life in paediatric XLH patients • Evaluate the long-term safety and efficacy of burosumab
Location	This study is being conducted at a total of nine centres: four in the United States, three in the United Kingdom, one in France, and one in the Netherlands
Design	Randomised, multicentre, open-label, dose-finding Phase 2 study assesses the PD, efficacy, and safety of burosumab in prepubescent children (5 to 12 years old) with XLH. The study consists of two Screening Visits, a 16-week Titration Period, a 48-week Treatment Period, and a 96-week Treatment Extension Period.

Duration of study	The planned study duration is 160 weeks (approximately 3 years): 16 weeks in the Titration Period, 48 weeks in the Treatment Period, and 96 weeks in the Treatment Extension Period.
Sample size	Approximately 30 paediatric subjects with XLH and radiographic evidence of bone disease ("pre-expansion subjects") were planned for enrolment under the original study protocol. The study was expanded per amendment 3 of the protocol to include additional subjects ("expansion subjects") who were required to have rickets severity of at least 1.5 at the knee (per the Rickets Severity Score [RSS] method), for a total of approximately 50 subjects planned overall.

Inclusion criteria	• Male or female, aged 5 – 12 years, inclusive, with open growth plates
	• Tanner stage of 2 or less based on breast and testicular development
	• Diagnosis of XLH supported by ONE of the following:
	  ○ Confirmed PHEX mutation in the subject or a directly related family member with appropriate X-linked inheritance
	  ○ Serum FGF23 level > 30 pg/mL by Kainos assay
	• Biochemical findings (based on overnight fasting [minimum 4 hours] values collected at Screening Visit 2) associated with XLH including:
	  ○ Serum phosphorus ≤ 2.8 mg/dL (0.904 mmol/L)
	  ○ Serum creatinine within age-adjusted normal range
	• Standing height < 50th percentile for age and gender using local normative data. (Criterion was changed to "< 50th percentile" [from "< 25th percentile"] per Protocol Amendment 1)
	• Radiographic evidence of active bone disease including rickets in the wrists and/or knees, AND/OR femoral/tibial bowing, OR, for expansion subjects, an RSS score in the knee of at least 1.5 points as determined by central read (The inclusion criterion of RSS ≥ 1.5 for subjects enrolled with the expansion of the study was added per Protocol Amendment 3)
	• Willing to provide access to prior medical records for the collection of historical growth, biochemical and radiographic data, and disease history
	• Provide written or verbal assent (if possible) and written informed consent by a legally authorised representative after the nature of the study has been explained, and prior to any research-related procedures
	• Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule and comply with the assessments
	• Females who have reached menarche must have a negative pregnancy test at Screening and undergo additional pregnancy testing during the study. If sexually active, male and female subjects must be willing to use an acceptable method of contraception for the duration of the study. (This inclusion criterion added per Protocol Amendment 1)

Exclusion criteria	• Use of a pharmacologic vitamin D metabolite or analog (eg, calcitriol, doxercalciferol, alfacalcidol, and paricalcitol) within 14 days prior to Screening Visit 2; washout took place during the Screening Period • Use of oral phosphate within 7 days prior to Screening Visit 2; washout took place during the Screening Period • Use of calcimimetics, aluminium hydroxide antacids, systemic corticosteroids, and thiazides within 7 days prior to Screening Visit 1 • Use of growth hormone therapy within 3 months before Screening Visit 1. (Criterion was changed to "within 3 months" [from "within 12 months"] per Protocol Amendment 2 • Use of bisphosphonates for 6 months or more in the 2 years prior to Screening Visit 1 • Presence of nephrocalcinosis on renal ultrasound graded ≥ 3 based on

	the following scale: ○ 0 = Normal ○ 1 = Faint hyperechogenic rim around the medullary pyramids ○ 2 = More intense echogenic rim with echoes faintly filling the entire pyramid ○ 3 = Uniformly intense echoes throughout the pyramid ○ 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period • Hypocalcaemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits (based on overnight fasting [minimum 4 hours] values collected at Screening Visit 2) • Evidence of tertiary hyperparathyroidism as determined by the Investigator • Use of medication to suppress parathyroid hormone (PTH) within 2 months prior to Screening Visit 1 • Presence or history of any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study • Presence of a concurrent disease or condition that would interfere with study participation or affect safety • Previously diagnosed with human immunodeficiency virus antibody, hepatitis B surface antigen, and/or hepatitis C antibody • History of recurrent infection or predisposition to infection, or of known immunodeficiency • Use of a therapeutic monoclonal antibody within 90 days prior to Screening Visit 1 or history of allergic or anaphylactic reactions to any monoclonal antibody • Presence or history of any hypersensitivity to burosumab excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments
Method of randomisation	Eligible subjects were enrolled sequentially into one of three cohorts defined by the initial dose of burosumab. Within each dose cohort, subjects were randomised to the Q2W or to the Q4W regimen. The dose of burosumab for the Q2W and Q4W regimens was the same on a monthly basis within each dose cohort, ie: • Dose Cohort 1 received initial doses of 0.1 mg/kg Q2W or 0.2 mg/kg Q4W (n = 10 pre-expansion subjects) • Dose Cohort 2 received initial doses of 0.2 mg/kg Q2W or 0.4 mg/kg Q4W (n = 10 pre-expansion subjects) • Dose Cohort 3 received initial doses of 0.3 mg/kg Q2W or 0.6 mg/kg Q4W (n = 30 pre-expansion and expansion subjects) Once the full allotment of subjects had been enrolled into a cohort, the next cohort was enrolled. Additionally, subjects were not randomised for Dose Cohort 2 until the fourth subject in Dose Cohort 1 had completed the Week 4 study visit and a safety review had been completed. Subjects were randomised 1:1 to the Q2W or Q4W regimens within each dose cohort via an Interactive Web Response System (IWRS) based on a randomisation schedule developed by an independent third-party vendor. Randomisation was stratified by gender; no more than 20 subjects of either gender were enrolled in the pre-expansion group. No requirement for gender

	balance was applied in the expansion group.
Method of blinding	This study was designed as an open-label study and hence was not blinded. RSS and RGI-C radiograph assessments were blinded as follows: To obtain the RSS score, the radiographs of the wrists and knees from individual subjects were presented in random order and evaluated separately with the rater blinded to the treatment status of the subject and the timing of the radiograph. Each rating was entered into an electronic data capture (EDC) system at the time of the rating and transferred electronically to a central imaging facility. The scores could not be retrieved from the system by the rater after submission. As a means to further reduce potential bias, additional independent control radiographs were included in the batches reviewed at key assessment points. Three paediatric radiologists not affiliated with the conduct of the study or Ultragenyx performed blinded RGI-C ratings for the wrist, knee, and long leg radiographs. Prior to rating any radiographs, the three raters were trained to perform RGI-C ratings to gain consensus on the terminology used to describe XLH-related radiographic abnormalities and to establish inter-rater reliability. The ratings were performed independently with the raters having no opportunity to discuss images or compare ratings; ratings could not be retrieved or changed by the raters after submission. The raters were not provided access to the protocol, subject identifiers, or information related to burosumab or prior conventional therapy. Radiograph pairs were presented for review in random order. For each RGI-C score (wrist, knee, global and leg), the average of the scores assigned by the three independent raters were used for analysis. To further reduce potential bias, additional radiographs were included in the batches reviewed as described for RSS assessments.
Intervention(s) (n =) and comparator(s) (n =)	Burosumab, n=52: Pre-expansion Subjects • Dose Cohort 1, [redacted] (0.1 mg/kg Q2W [redacted], 0.2 mg/kg Q4W [n[redacted]]) • Dose Cohort 2, n[redacted] (0.2 mg/kg Q2W [redacted], 0.4 mg/kg Q4W [n[redacted]]) • Dose Cohort 3, n[redacted] (0.3 mg/kg Q2W [redacted], 0.6 mg/kg Q4W [n[redacted]]) Expansion Subjects • Dose Cohort 3, n[redacted] (0.3 mg/kg Q2W [redacted], 0.6 mg/kg Q4W [redacted])
Baseline differences	Demographic characteristics were similar for subjects randomised to the Q2W and to the Q4W dose regimens.
Duration of follow-up, lost to follow-up information	All subjects completed at least 64 weeks on study. No subject discontinued from the study, and all subjects are continuing in the study as of the data cut-off date.
Statistical tests	No formal hypothesis was tested to compare treatment groups (Q2W and Q4W) in this study. Changes from baseline in efficacy parameters were tested. Statistical analyses were reported using summary tables, figures, and data listings. Statistical tests were 2-sided at the alpha=0.05 significance level, and 2-sided 95% confidence intervals (CIs) were used. All p-values were presented as nominal p-values. No adjustment on multiplicity was made. For the primary efficacy endpoint of change in RSS total score, the difference between the two dose regimens (Q2W and Q4W) was summarised with 95% CIs. For repeated measures, the generalised estimating equation (GEE) approach was used for assessing the change over time. The GEE model included regimen, study visit and interaction between regimen and study visit as categorical variables. Model-based estimates of changes from Baseline and corresponding 95% CIs were provided along with P-values for assessing

	statistical significance. As exploratory analyses, covariates such as baseline measures, gender, and age were considered for adjustment within GEE models. Continuous variables were summarised with means, standard deviations (SD), standard errors (SE), medians, interquartile ranges (Q1, Q3), minimums, and maximums. Categorical variables were summarised by counts and by percentages of subjects in corresponding categories. No imputation on missing data was made, unless stated otherwise. All data obtained from the Case Report Forms (CRFs) as well as any derived data were included in data listings. Efficacy results were analysed by subgroups defined by RSS total score at Baseline. The "higher RSS" subgroup consisted of subjects with RSS total scores at Baseline ≥ 1.5; the "lower RSS" subgroup consisted of subjects with RSS total scores at Baseline < 1.5. The value of 1.5 was based on the median RSS total score of the study population at the interim analysis of the first 12 subjects. Results also were analysed by subgroups defined by degree of functional impairment: for 6MWT results by percentage of predicted 6MWT (abnormal: < 80%, or normal range: ≥ 80%) at Baseline, and for the POSNA-PODCI questionnaire by Global Functioning scale score (abnormal: < 40, or normal range: ≥ 40) at Baseline.
Primary outcomes (including scoring methods and timings of assessments)	Primary efficacy endpoint: Change from Baseline in severity of rickets as measured by Rickets Severity Score (RSS) total score The primary efficacy analysis was at Week 40. Additional efficacy analysis was carried out at Week 64.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints • Change from Baseline in severity of rickets as measured by RSS knee and wrist scores • Change from Baseline in the radiographic appearance of rickets and bowing as measured by Radiographic Global Impression of Change (RGI-C) global, knee, wrist and long leg scores • Growth (standing height, sitting height, arm length, and leg length) • Walking Ability (Six-minute Walk Test [6MWT]) • Functional disability and pain (Pediatric Orthopedic Society of North America – Pediatric Outcomes Data Collection Instrument [POSNA-PODCI])

Study CL205

UX023-CL205 (CL205) is an ongoing, multicentre, open-label, single-arm, Phase 2 study in 13 children from 1 to 4 years old with XLH who are naive to therapy or have previously received conventional therapy with oral phosphate and active vitamin D to assess the safety, PD, PK, and efficacy of burosumab administered via subcutaneous (SC) injection Q2W for a total of 64 weeks (Table 11).

In CL205 patients received burosumab at a starting dose of 0.8 mg/kg Q2W. The dose can be increased to 1.2 mg/kg Q2W at any time if the patient meets all of the following dose adjustment criteria:

1) Two consecutive serum phosphorus measurements are below the normal range

2) serum phosphorus has increased by < 0.5 mg/dL from Baseline

3) the patient has not missed a dose of study drug that would account for the decrease in serum phosphorus.

The planned duration of treatment in this study is 64 weeks. Patients who complete the study may continue into an extension study. Primary analyses of data to Week 40 for all 13 patients enrolled and additional safety data up to the data cut-off date are available.

Table 11. Summary of methodology for CL205

Study name	**UX023- CL205**
Objectives	Primary objectives: • Establish the safety profile of burosumab for the treatment of XLH in children between 1 and 4 years old • Determine the pharmacodynamic (PD) effects of burosumab treatment on serum phosphorus and other PD markers that reflect the status of phosphate homeostasis in children between 1 and 4 years old with XLH Additional study objectives are to assess the following in children between 1 and 4 years old with XLH: • Effects of burosumab on rickets • Effects of burosumab on growth and lower extremity deformity • Pre-dose burosumab drug concentration levels
Location	This study is being conducted at 3 centres in the USA.
Design	Multi-centre, open-label, single-arm, Phase 2 study in children from 1 to 4 years old with XLH who are naive to therapy or have previously received conventional therapy with oral phosphate and active vitamin D to assess the safety, PD, PK, and efficacy of burosumab administered via subcutaneous (SC) injection Q2W for a total of 64 weeks.
Duration of study	The planned duration of treatment in this study is 64 weeks. Subjects who complete the study may continue into an extension study.
Patient population	Subjects were between 1 and 4 years old, inclusive, with clinical findings consistent with XLH, including hypophosphataemia and radiographic evidence of rickets (at least 5 subjects were required to have a Rickets Severity Score [RSS] at the knee of ≥ 1.5 points at Screening), and a confirmed PHEX mutation or variant of uncertain significance (VUS).
Sample size	Approximately 10 paediatric subjects were planned for enrolment and 13 subjects were enrolled. This submission summarises the planned, primary analyses of data to Week 40 for all 13 subjects and additional safety data available through the data cut-off date.
Inclusion criteria	• Male or female, aged ≥ 1 year and < 5 years • PHEX mutation or VUS in either the patient or a directly related family member with appropriate X-linked inheritance • Biochemical findings associated with XLH including serum phosphorus < 3.0 mg/dL (0.97 mmol/L) and serum creatinine within age-adjusted normal range. (Criteria to be determined based on fasting [minimum 4 hours] values collected at Baseline.) • Radiographic evidence of rickets; at least 5 subjects will be required to have a RSS at the knee of at least 1.5 points as determined by central read • Willing to provide access to prior medical records for the collection of historical growth, biochemical, and radiographic data and disease history

	• Provide written informed consent by a legally authorised representative after the nature of the study has been explained, and prior to any research-related procedures • Must, in the opinion of the Investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule, and comply with the assessments
Exclusion criteria	• Unwilling to stop treatment with oral phosphate and/or pharmacologic vitamin D metabolite or analog (eg, calcitriol, alfacalcidol) during the screening period and for the duration of the study • Presence of nephrocalcinosis on renal ultrasound grade 4 based on the following scale: o 0 = Normal o 1 = Faint hyperechogenic rim around the medullary pyramids o 2 = More intense echogenic rim with echoes faintly filling the entire pyramid o 3 = Uniformly intense echoes throughout the pyramid o 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period • Hypocalcaemia or hypercalcaemia, defined as serum calcium levels outside the age-adjusted normal limits. (Criteria to be determined based on fasting [minimum 4 hours] values collected at Baseline.) • Presence or history of any condition that, in the view of the Investigator, places the subject at high risk of poor treatment compliance or of not completing the study • Presence of a concurrent disease or condition that would interfere with study participation or affect safety • History of recurrent infection or predisposition to infection, or of known immunodeficiency • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments
Intervention(s) (n =) and comparator(s) (n =)	Burosumab, n=13
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	All 13 subjects were included in each analysis set (Efficacy Analysis Set, PK/PD Analysis Set, and Safety Analysis Set). As of the data cut-off date (20 April 2017), all subjects completed Week 40, no subject had discontinued from treatment or from the study, and all subjects continue in the study. Additionally, 9, 7, and 4 subjects have received burosumab through Weeks 42, 44, and 46, respectively, as of the data cut-off date.
Statistical tests	The planned sample size for this study of approximately 10 subjects was considered appropriate to evaluate the burosumab dose and PK/PD relationship in children aged 1 to 4 years to confirm if that relationship is

	similar to that observed in older children (aged 5–12 years; N=52) in Study UX023-CL201. Analyses groups included: the Safety Analysis Set (all subjects who received at least one dose of study drug), the Efficacy Analysis Set (all subjects who received at least one dose of study drug and have at least one post-study drug measurement), and the PK/PD Analysis Set (all subjects who received at least one dose of study drug and have evaluable blood samples). Continuous variables were summarised with means, standard deviations (SDs), standard errors (SEs), medians, interquartile range, minimums, and maximums. Categorical variables were summarised by counts and by percentages of subjects in corresponding categories. No imputation on missing data was made, unless stated otherwise. All data obtained from the case report forms (CRFs) as well as any derived data were included in data listings. Changes from Baseline to post-Baseline time points in PD and efficacy parameters were tested for statistical significance. Statistical tests were 2-sided at the alpha = 0.05 significance level and 2-sided 95% confidence intervals (CIs) were used. All p-values were presented as nominal p-values. No adjustment for multiplicity was made. An analysis of covariance (ANCOVA) model was applied to each RGI-C score (wrist, knee, global and lower limb deformity) and change from Baseline in each RSS score (wrist, knee and total). The ANCOVA model for RSS scores included the change from Baseline in RSS score as the dependent variable and age and RSS score at Baseline as covariates. The ANCOVA model for RGI-C scores included the RGI-C score as the dependent variable and age and RSS at Baseline as covariates. By-visit analyses using the Generalised Estimating Equations (GEE) model was applied for all PD parameters; the GEE model included change from Baseline as the dependent variable, time as the categorical variable and adjusted for Baseline measurement, with exchangeable covariance structure. By-visit analyses using the GEE model also was applied to recumbent length/standing height; the GEE model included the change from Baseline as the dependent variable, visit and gender as factor, age and recumbent length/standing height z-score at Baseline as covariates, with exchangeable covariance structure.
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint is the change from Baseline in serum phosphorus.
Secondary outcomes (including scoring methods and timings of assessments)	• Change in rickets as assessed by the Radiographic Global Impression of Change (RGI-C) global score at Weeks 40 and 64 • Change from Baseline in RSS total score at Weeks 40 and 64 • Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as determined by the RGI-C long leg score at Weeks 40 and 64 • Change in recumbent length/standing height from Baseline to post-treatment study time points in cm, height-for-age z-scores, and percentiles based on age and gender. • Historical growth records may be used to evaluate change in growth velocity • Change and percentage change from Baseline over time in serum alkaline phosphatase (ALP)

Natural History Reference Study

Study CL002

While the ongoing Phase 2 paediatric study CL201 (above) does not directly compare burosumab to conventional therapy, a retrospective reference study, UX023-CL002 (CL002) is being conducted at XLH Centres of Excellence to evaluate the same key outcome measures as CL201 (rickets, growth, and lower leg deformities) in a similar paediatric XLH population who have received long-term therapy with oral phosphate and active vitamin D (Table 12).

CL002 is a retrospective radiographic and medical chart review study designed to evaluate the long-term safety and efficacy of oral phosphate/active vitamin D therapy and to assist with the interpretation of safety and efficacy data from patients treated with burosumab in the CL201 study. All [redacted] subjects who contributed the radiographs for RSS and RGI-C analyses were enrolled at a single US site, Shriners Hospital in St. Louis, Missouri. The study is ongoing and additional data from three other sites in the United States, France, and Canada are anticipated to add to the body of evidence. To maximise the comparability of this retrospective study with Study CL201, patient selection was based on similar entry criteria as in Study CL201 (see Section 9.4.3).

To be eligible for the CL002 study, patients were required to have a confirmed diagnosis of XLH based on a confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance, or a clinical diagnosis of XLH based on biochemical profile and clinical symptoms and have a minimum of two sets of wrist, knee and/or long leg images taken 1-2 years apart (+/- 3 month) when the patient was between 5 and 14 years of age. Subjects were not permitted to have any prior exposure to burosumab treatment.

[redacted]. It is not anticipated that medical care will be significantly different at other XLH centres of excellence, although it should be noted that in the UK, alfacalcidiol, an alternative form of active vitamin D, is generally used instead of calcitriol. Calcitriol is more potent than alfacalcidol but requires multiple daily doses (Imel and Carpenter, 2015).

Data collected included diagnostic, medical and surgical history, a detailed history of treatment with conventional phosphate and calcitriol treatment and historical radiograph, growth and biochemical data, including phosphorus, calcium, iPTH, $1,25(OH)_2D$ and ALP. The outcomes in Study CL002 were predefined to match the endpoints in Study CL201. Endpoints for this study are identical as those in Study CL201, namely change in rickets severity as measured by the RSS and RGI-C, change in lower extremity deformities as measured by the RGI-C, growth as measured by standing height z-score and percentile, and change in biochemical

parameters. Laboratory, phosphate/calcitriol treatment and image collection dates were matched as closely as possible to make this cohort of patients as comparable to the cohort of patients treated with burosumab. The timeframe for analysis was prespecified to capture long-term effects of conventional therapy with a requirement for a minimum of two sets of wrist, knee, and/or long leg images taken 1 to 2 years apart (±3 months) when the subject was between 5 and 14 years of age. This requirement increases the likelihood of collecting meaningful radiographs that will help quantify the effects of conventional therapy on change in rickets and lower extremity deformities. The 1 to 2-year span between radiographs is also intended to match approximately the 40-week and 64-week time points at which radiographs are assessed in Study CL201. To ensure that the central reader and the three radiologists were blinded to the treatment status of the subjects, CL002 x-rays were randomly mixed with CL201 Week 64 x-rays prior to reading, which removes potential bias and ensures that the same readers are applying the same methods across both studies.

Historical images will be collected from up to 100 children. A total of [redacted] children had been enrolled in the CL002 study at the time of the latest data cut (August 2016). One child had not received conventional therapy and was not included in the analysis. The remaining [redacted] children (98%) who met the study inclusion/exclusion criteria and had been treated with conventional therapy were included in the Full Analysis Set (Figure 6). Of these, [redacted] had at least one pair of bilateral wrist and knee radiographs taken one to two years apart from the initial baseline radiographs (Radiographic Analysis Set). The mean duration between baseline and post-baseline radiographs was [redacted]).

Study CL002 represents a valid control for evaluating the treatment effects of burosumab in Study CL201. Both studies had a similar patient population, identical endpoints, and similar timeframe for analysis. Participants in this study had received treatment at XLH centres of excellence to ensure high subject compliance to conventional therapy. The long-term nature of the study provides a robust dataset where patients had received approximately eight years on conventional therapy at the time of the baseline radiograph. Finally, the current study also followed GCP-compliant processes. The sites are well qualified in conducting clinical trials with rigorous processes and quality systems in place for data collection and source verification.

Table 12. Summary of methodology for Study CL002

Study name	**UX023- CL002**
Objectives	To characterise change in rickets severity over time with conventional therapy (oral phosphate/active vitamin D) in children with XLH ages 5 to 14 years.
Location	Two sites in the USA.
Design	Retrospective radiographic and medical chart review of patients with XLH who had longitudinal historical radiographs of the wrist, knee, or long leg

Study name	**UX023- CL002**
	taken between the ages of 5 and 14 years (inclusive).
Duration of study	This is a retrospective study. The mean duration between baseline and post-baseline radiographs was [redacted] ([redacted] [redacted] weeks]).
Patient population	Children with a confirmed diagnosis of XLH who have radiographic images for at least two time points taken between the ages of 5 and 14 years.
Sample size	[redacted] ([redacted] paired wrist and knee images)
Inclusion criteria	• Male or female, with radiographic images from at least two time points taken between the ages of 5 and 14 years, inclusive • Diagnosis of XLH based on a confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance, or a clinical diagnosis of XLH based on biochemical profile and clinical symptoms
Exclusion criteria	• Currently or previously treated with burosumab in Ultragenyx protocol UX023-CL201 (images and data from subjects in the current study were collected as a part of UX023-CL201)
Intervention(s) (n =) and comparator(s) (n =)	Not applicable (patients had been on conventional therapy for approximately 6 years prior to study enrolment).
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were not followed up as this was a retrospective study. The mean duration between baseline and post-baseline radiographs was [redacted] ([redacted] [redacted])
Statistical tests	Retrospective radiographic, biochemical, growth, and conventional therapy data collected from all subjects in this historical cohort were summarised by both event incidence and subject incidence. No formal hypothesis was tested in this study. The primary evaluation in the current study was the change in rickets severity, as evaluated by 2 different methods (RSS and RGI-C). Rickets was assessed based on radiographic changes from radiograph pairs that were 1 to 2 years apart, with the earlier pair considered the baseline radiograph. For each radiograph pair, growth and biochemical data were linked to baseline and post-baseline radiographs by time of measurement and changes in growth and biochemical parameters were summarised. RSS, growth, and biochemical data were also summarised by event incidence in addition to paired incidence; the details of assessment plan for each endpoint are provided in. Subgroups were also prespecified based on rickets severity of the baseline radiographs: baseline radiographs with RSS total score ≥1.5 were referred to as the Higher RSS subgroup and those with RSS total score <1.5 were referred to as the Lower RSS subgroup. For continuous variables, the mean, standard deviation, median, quartiles, minimum, and maximum are provided; 95% confidence intervals (95% CI) on

Study name	**UX023- CL002**
	change from baseline were calculated for paired radiographs by one sample T test. For discrete data, frequency and percent distributions are used. Analysis was performed on the analysis sets by subject incidence, by radiograph incidence, or by paired radiographs.
Outcomes assessed	Conventional therapy endpoints include the following information: • Age at the time of initiating conventional therapy • Total duration of conventional therapy • Conventional therapy treatment status at time of radiographic imaging (Yes/No) • Conventional therapy regimen at time of radiographic image taken, including medication • names, dose and frequency of administration for both phosphate and active vitamin D • Interruptions in conventional therapy of 3 months or more and reason for interruption Radiographic measures of rickets severity were assessed by Rickets Severity Scale (RSS) and Radiographic Global Impression of Change (RGI-C. Growth endpoints include standing height (length) in cm, z-score and percentile (adjusted by gender and age). Biochemical endpoints include change over time in serum or plasma phosphorus, calcium, iPTH, 1,25(OH)2D, and ALP corresponding to dates close to the date radiographic imaging was collected, where available.

Efficacy evaluations

Rickets

Patients with XLH have a spectrum of rickets severity based on varying degrees of phosphorus metabolic defect and degree of prior treatment. To evaluate the spectrum of abnormalities, two radiographic scoring methods, the Thacher Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C), were used in this study. These instruments provide complementary analyses of the severity of rickets. The combination of the absolute score of epiphyseal/distal metaphyseal abnormalities in RSS, with comparative evaluations from baseline to time point of those abnormalities plus deformities in the RGI-C, provides a broader insight into bone disease that any one score alone.

As discussed in Section 6.1, the RSS is a radiographic scoring system that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, lucency, and cupping, as well as the proportion of growth plate affected (Table 6). A single, central, independent rater (Thomas Thacher, MD) performed all RSS ratings for all radiographs for all other studies in the burosumab clinical program, including CL201, CL205 and CL002. A comprehensive evaluation of the intra-rater and inter-rater reliability of the RSS (and RGI-C) scoring systems confirmed the reproducibility of the results using a single or multiple raters. For the RSS assessment, disease improvement is expressed as a negative number, i.e., decreased severity of rickets. The usual range of observed

scores for subjects with XLH is between 0 and 6.5, depending on severity and prior treatment.

The RGI-C utilises a 7-point ordinal scale to evaluate the extent of healing in a radiograph as compared with a radiograph taken at a prior time point. Ratings of -3, -2, and -1 between the two time points assessed indicate severe, moderate, and minimal worsening, respectively, and ratings of +1, +2 and +3, indicate minimal healing, substantial healing, or complete/near complete healing, respectively. Unlike the RSS system, for which radiographs are individually scored independent of any other radiographs, clinical significance is explicit in RGI-C due to the comparison with a previous radiograph. Three paediatric radiologists not affiliated with the study conduct and contracted by a central imaging facility independently evaluated and provided RGI-C scores for pairs of wrist, knee, and long leg radiographs for studies CL201, CL205 and CL002. The average of the scores assigned by the three independent raters were used for analysis. For the RGI-C assessment, in contrast with RSS assessment, disease improvement is expressed as a positive number, i.e., increased healing of rickets.

Growth

Short stature is one of the predominant features in growing children with XLH and is related to serum phosphate levels (Zivicnjak et al. 2011). Growth is measured by changes in standing height or recumbent length (and percentiles) prior to and following treatment.

Walking Ability by 6MWT

Gait disturbance is a common clinical feature in paediatric patients with XLH and is likely due to a combination of bone deformities and bone and joint pain due to rickets as well as the impact of hypophosphataemia on muscle function. The long bone deformity in the lower extremities and mechanical axis defects associated with XLH can manifest clinically as a waddling and inefficient gait and pain with weight bearing. Musculoskeletal impacts of hypophosphataemia can include reduced power, balance, and coordination and increased stiffness that impact walking ability and other gross motor functions. At baseline in CL201, 77% of subjects reported having an unusual gait at some time. The 6MWT distance provides an indicator of mobility and physical functioning, though it alone does not assess the type of gait observed.

Functional Disability and Pain

The POSNA-PODCI questionnaire was used in CL201 to measure the impact of bone and muscle conditions on daily activities and health-related quality of life. The following scales were administered in this study: Upper Extremity and Physical Function, Transfers and Basic Mobility, Sports/ Physical Functioning, Pain/Comfort, and Happiness. Scores from the first four scales, excluding the Happiness domain, are combined to derive a Global Functioning Scale score. Raw scores are scaled to set the mean of the normal population at 50 and one standard deviation in the normal population equal to 10. A score of 40 is therefore considered at the lower boundary of

the normal range for this instrument, and scores in the 30s and 20s imply a significant level of physical impairment and pain.

Based on surveys of XLH children conducted by the sponsor, the two scales most appropriate for the assessment of the impact of XLH are the Sports/Physical Function and Pain/Comfort scales. Children with XLH often experience difficulty performing age-appropriate gross motor activities, such as walking, running, and jumping, due to bowing of the femur, tibia, and/or fibula and the rotation of the tibia that causes the feet to turn in toward each other.

Phosphate homeostasis and bone metabolism

Several PD parameters were used to assess the extent to which burosumab improves phosphate homeostasis and bone metabolism. The key parameters included:

- **Serum phosphorous**
- **Serum 1,25(OH)$_2$D** (a vitamin that enhances intestinal absorption of calcium and phosphate).
- **Serum ALP:** Total and bone-specific alkaline phosphatases are elevated in the presence of rickets, and the magnitude of elevation correlates with the magnitude of rickets (Carpenter et al. 2011). These parameters are commonly used as indicators of the presence and severity of rickets and is one of the primary methods used by physicians managing conventional therapy of XLH as a tool to assess results, since repeated X-rays are not advisable for children.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Data for each study has been derived from one source only (the clinical study reports).

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

The two interventional studies of burosumab and the natural history reference study differ as follows:

Interventions

- CL201 was a dose ranging study that investigated burosumab at starting doses of 0.1, 0.2 and 0.3 mg/kg bi-weekly and 0.2, 0.4 and 0.6 mg/kg bi-monthly. Subsequent doses were adjusted every four weeks in 0.3 mg/kg increments, as needed, based on two-week post-dose (peak) fasting serum phosphorus levels. The study allowed for increases in the dose level as high as 2.0 mg/kg for both the Q2W and Q4W regimens to a maximum dose of 90 mg.
- CL205 investigated bi-weekly burosumab at a starting dose of 0.8 mg/kg that could be increased to 1.2 mg/kg.
- In Study CL002 patients received conventional therapy oral phosphate and calcitriol therapy

Eligibility criteria, demographic and baseline characteristics

To maximise the comparability of the retrospective CL002 study with CL201, patient selection was based on similar entry criteria as in Study CL201. The CL002 study population (ages 5 to 14 years) had a similar age range and characteristics at study entry as that of Study CL201 (ages 5 to 12 years). Similar to Study CL201, eligible subjects in Study CL002 were required to have a diagnosis of XLH based on a confirmed PHEX mutation in the subject or a directly related family member with appropriate X-linked inheritance, or a clinical diagnosis of XLH based on biochemical profile and clinical symptoms.

Study CL205 enrolled a younger population (1 to 4 years of age).

Demographic and baseline characteristics

In CL201 all patients showed signs of XLH disease at baseline by different measures (Table 13 and Table 14).

- [redacted].
- Nearly all had received conventional therapy with oral phosphate and active vitamin D analogues before enrolling in the study. Despite having received conventional therapy and medical care early in life, patients showed substantial evidence of unresolved disease, including rickets, lower extremity bowing, and reduced growth. The enrolled population were diagnosed with multiple symptoms of XLH, [redacted].
- Baseline radiographs showed the presence of rickets (score > 0) in [redacted]

[redacted]

Baseline characteristics in CL002 were similar to Study CL201 [redacted] (Table 13). At baseline, both study cohorts had a [redacted]

In CL205 all subjects showed signs of XLH disease at baseline by multiple measures (Table 13 and Table 15).

- At baseline, biochemical parameters related to XLH [redacted]
- All children had received conventional therapy with oral phosphate and active vitamin D analogues before enrolling in the study. Despite having received conventional therapy and medical care early in life, subjects showed substantial evidence of unresolved rachitic disease: baseline radiographs showed the presence of rickets (score > 0) in all patients at both the knee and the wrists. Growth was impaired at baseline.

Table 13. Demographic and baseline characteristics in studies CL201, CL002 and CL205

	CL201	Study CL002	CL205
	Q2W (n=26)	Radiographic analysis set ([redacted])	(n=13)
Age (years), mean (SD)	8.7 (1.72)	[redacted][a]	2.9 (1.15)
Sex, male n (%)	12 (46.2%)	[redacted]	9 (69.2%)
Race White Black/ African-American Other	 23 (88.5%) 2 (7.7%) 1 (3.8%)	 [redacted] [redacted] [redacted]	12 (92.3%) 1 (7.7%) 0
Weight (kg), mean (SD)	31.87 (7.92)	[redacted]	12.92 (1.81)
Height (percentile for age and gender), mean (SD)	xxx (xxx)	[redacted]	[redacted]
Standing Height (z-score), mean (SD)	-1.72, 1.03	[redacted][a]	-1.38 (1.19)
Renal ultrasound score, (0 – 5 scale) – n (%) 0 1 2	 [redacted] [redacted] [redacted]	[redacted]	NR
Number (%) of Subjects Who Received Prior Conventional Therapy	24 (92.3%)	[redacted]	13 (100%)
Duration of Prior Conventional Therapy, mean (SD)	7.02 (2.14) years	[redacted]	16.7 (14.39) months
Age When Conventional Therapy Was Initiated (years), mean (SD)	[redacted]	[redacted]	[redacted]
Pharmacodynamic parameters, mean (SD) Serum Phosphorus, mg/dL TmP/GFR (mg/dL) Serum 1,25(OH)2 D (pg/mL) ALP (U/L	 [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted]
Rickets Severity RSS Total Score, mean (SD)	 1.92 (1.17)	 [redacted][a]	 2.92 (1.37)

a At baseline paired radiograph (the earlier radiograph pair)

Table 14. XLH Symptoms Diagnosed in Study CL201

	Burosumab Q2W (n=26)
Any Bowing in Limbs	[redacted]
Unusual Gait or Way of Walking	[redacted]
Bowing of Lower Legs	[redacted]
Short Stature/Delayed Growth	[redacted]
Bowing of Upper Legs	[redacted]
Intoeing	[redacted]
Dental Abscesses	[redacted]
Delayed Walking	[redacted]
Nephrocalcinosis	[redacted]
Excessive cavities	[redacted]
Widened/thickened wrists	[redacted]
Knock-knees	[redacted]
Cranial Synostosis	[redacted]
Bowing of the forearms	[redacted]
Irregular-shaped chest	[redacted]
Chiari malformation	[redacted]
Other	[redacted]
Impaired renal function	[redacted]
Hearing loss	[redacted]

Table 15. XLH Symptoms Diagnosed in Study CL205

System Organ Class Preferred Term	**Burosumab (n=13)**
Musculoskeletal and connective tissue disorders	[redacted]
Knee deformity	[redacted]
Bone deformity	[redacted]
Foot deformity	[redacted]
Arthralgia	[redacted]
Lordosis	[redacted]
Pain in extremity	[redacted]
Congenital familial and genetic disorders	[redacted]
Rickets familial hypophosphataemic.	[redacted]
Skull malformation	[redacted]
Tibial torsion	[redacted]
Metaphyseal dysplasia	[redacted]
Investigations	[redacted]
Body height below normal	[redacted]
General disorders and administration site conditions	[redacted]
Gait disturbance	[redacted]
Infections and infestations	[redacted]
Tooth abscess	[redacted]

Outcomes

The method of rickets scoring as measured by the RSS and RGI-C, change in lower extremity deformities as measured by the RGI-C, growth as measured by standing height z-score and percentile, and change in biochemical parameters was identical across the clinical development programme.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Study CL201 (pre-planned analysis): For efficacy analyses, subgroups of subjects were defined based on severity of rachitic disease. The “higher RSS” subgroup consisted of subjects with total RSS scores at baseline ≥ 1.5; the “lower RSS” subgroup consisted of subjects with total RSS scores at baseline < 1.5. The RSS value of 1.5 was based on the median RSS score of the study population at the interim analysis of first 12 subjects. For analysis of 6MWT results, subgroups also were defined based on the Baseline percentage of predicted 6MWT (< 80% [abnormal] or ≥ 80% [normal]). For analysis of POSNA-PODCI questionnaire results, subgroups also were defined based on the Baseline global functioning scale (< 40 or ≥ 40).

Study CL002: Subgroup analysis of rickets, growth, and biochemical endpoints was performed by gender and by baseline radiograph RSS total score (RSS total score < 1.5 (lower RSS) or ≥ 1.5 (higher RSS).

Study CL205: There was no subgroup analysis carried out.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

CL201

A total of 52 paediatric subjects were enrolled into the study and were randomised 1:1 to the Q2W and Q4W dose regimens. Twenty-seven additional patients were screened for the study and were not enrolled because they did not meet one or more entry criteria.

The first 36 subjects were enrolled into three consecutive dose cohorts, starting with the lowest initial dose. Within each dose regimen group (Q2W or Q4W), the consecutive cohorts were enrolled in a staggered fashion. The first cohort of each dose regimen group started on the lowest dose (0.1 mg/kg Q2W or 0.2 mg/kg Q4W).

After establishment of safety of the dose used in the initial cohort, each subsequent cohort received progressively higher starting doses. Within each dose regimen group, [redacted] pre-expansion subjects were enrolled into Dose Cohorts 1, 2, and 3, respectively. All [redacted] expansion subjects were enrolled into Dose Cohort 3, [redacted] to each dose regimen group. A total of 26 subjects were enrolled into each dose regimen group.

Table 16. Distribution of Subjects by Regimen and Dose Cohort

	Number of subjects		
	Regimen		Subtotals by cohorts
	Q2W	Q4W	
Pre-expansion Subjects			
Dose Cohort 1 (0.1 mg/kg Q2W, 0.2 mg/kg Q4W)	[redacted]	[redacted]	[redacted]
Dose Cohort 2 (0.2 mg/kg Q2W, 0.4 mg/kg Q4W)	[redacted]	[redacted]	[redacted]
Dose Cohort 3 (0.3 mg/kg Q2W, 0.6 mg/kg Q4W	[redacted]	[redacted]	[redacted]
Expansion Subjects			
Dose Cohort 3 (0.3 mg/kg Q2W, 0.6 mg/kg Q4W)	[redacted]	[redacted]	[redacted]
Subtotals by regimen	26	26	52

Q2W = every 2 weeks; Q4W = monthly

Per the 1:1 randomisation, 26 subjects were assigned to each regimen (Q2W and Q4W). [redacted].

The ITT, PK/PD, and safety analysis sets were the same, i.e., each comprised all 52 subjects.

CL002

[redacted] subjects had been enrolled in CL002 at the time of the data cut (09 August 2016); however, [redacted]. The remaining [redacted] ([redacted]%) who met the study inclusion/exclusion criteria and had been treated with conventional therapy were included in the Full Analysis Set (Figure 6). No subject withdrew consent during the study. The study is currently enrolling with plans to enrol up to 100 subjects.

Figure 6. Study CL002 patient disposition (Evaluable Data Set)

CL205

A total of 13 paediatric subjects were enrolled into the study.

All 13 subjects were included in each analysis set (Efficacy Analysis Set, PK/PD Analysis Set, and Safety Analysis Set).

in the study as of the data cut-off date (20 April 2017).

The 64-week analysis is expected in .

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

[redacted]. In CL002 the 52 patients who met the study inclusion/exclusion criteria and had been treated with conventional therapy were included in the Full Analysis Set. No patients withdrew consent during the study.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

Study name: CL201		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomised 1:1 to the Q2W or Q4W regimens within each dose cohort via an Interactive Web Response System (IWRS) based on a randomisation schedule developed by an independent third-party vendor. Randomisation was stratified by gender; no more than 20 subjects of either gender were enrolled in the pre-expansion group. No requirement for gender balance was applied in the expansion group.
Was the concealment of treatment allocation adequate?	N/A	This study was designed as an open-label study and hence was not blinded.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The Q2W and Q4W groups were well balanced at the outset. The groups were similar in terms of duration of prior conventional therapy, symptoms diagnosed, pharmacodynamics parameters, and rickets severity.
Were the care providers, participants and outcome assessors	No	This study was designed as an open-label study and hence was not blinded.

blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	There were no dropouts during the study. All patients completed at least 64 weeks of treatment.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	This study is not yet published in a peer-reviewed journal. All outcomes measured are reported in the clinical study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The Intent-to-Treat (ITT) set consisted of all subjects who received at least one dose of study therapy and had at least one post-dose measurement. The safety analysis set consisted of all subjects who received at least one dose of study therapy. The PK/PD analysis set consisted of all subjects who received at least one dose of therapy and had evaluable serum data. In general, missing data were treated as missing, unless otherwise specified. When a change from Baseline was assessed, only subjects with a Baseline and at least one post-baseline measurement were included in the analysis. For repeated measures analyses such as GEE, the model parameters were simultaneously estimated using all of the observed data. Sensitivity analyses were performed using weighted GEE by implementing the inverse probability-weighted method to account for dropouts under the missing at random (MAR) assumption. For scheduled visits, visit numbers were used for analyses, and missing dates were not imputed. Measurements at unscheduled visits were not included in analyses but were provided in the appropriate listings. For

		measurements that were not limited to a particular scheduled visit, i.e., adverse events or concomitant medication use, missing dates were imputed based on the rules outlined in the statistical analysis plan.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: CL002		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	The study was a retrospective chart review. Participants were included in the study using pre-defined inclusion and exclusion criteria. To maximise the comparability of this retrospective study with Study CL201, patient selection was based on similar entry criteria as in Study CL201. To provide a control for Study CL201 with similarly age groups, subjects were required to have a minimum of two sets of bilateral wrist, knee, and/or long leg images taken 1 to 2 years apart (±3 months) when the subject was between 5 and 14 years of age. Patients charts from four XLH centres of excellence were reviewed for inclusion: two in the USA, one in Canada and one in France. The sites chosen are well qualified in conducting clinical trials with rigorous processes and quality systems in place for data collection and source verification.
Was the exposure accurately measured to minimise bias?	Yes	Data extracted from the medical records of consenting subjects included history of treatment with conventional therapy including dose, regimen and complications. The age when therapy was started and compliance to therapy was recorded. Because subjects were treated at an XLH Centre of Excellence, there were no indications that subjects were not compliant with treatment.
Was the outcome accurately measured to minimise bias?	Yes	The study site obtained relevant medical and growth records, and radiographs for eligible subjects who provided informed consent. Radiographs were de-identified at the site or at a central imaging facility at the discretion of the site. De-identified images were processed for rating by the central imaging facility. Study sites reviewed and abstracted demographics, XLH diagnostic and treatment history, growth history, and laboratory results from medical records and

		transcribed them onto the case report forms. The outcomes in Study CL002 were predefined to match the endpoints in Study CL201. Endpoints for this study are identical as those in Study CL201, namely change in rickets severity as measured by the RSS and RGI-C, change in lower extremity deformities as measured by the RGI-C, growth as measured by standing height z-score and percentile, and change in biochemical parameters. Thomas Thacher, MD, the developer of the RSS methodology, served as the single, central, independent rater and performed all RSS scoring for this study, as well as the CL201 study. Laboratory, phosphate/calcitriol treatment and image collection dates were matched as closely as possible to make this cohort of patients as comparable to the cohort of patients treated with burosumab. The timeframe for analysis was prespecified to capture long-term effects of conventional therapy with a requirement for a minimum of two sets of wrist, knee, and/or long leg images taken 1 to 2 years apart (± 3 months) when the subject was between 5 and 14 years of age. This requirement increases the likelihood of collecting meaningful radiographs that will help quantify the effects of conventional therapy on change in rickets and lower extremity deformities. The 1 to 2-year span between radiographs is also intended to match approximately the 40-week and 64-week time points at which radiographs are assessed in Study CL201.
Have the authors identified all important confounding factors?	Unclear	The study is unpublished. Limitations stated in the study report are: • Selection criteria did not specifically exclude radiographs with a close epiphysis. Because the RSS scoring method requires an open epiphysis for evaluation, 13 of the 60 paired radiographs were not evaluable by the RSS method. • All [redacted] subjects who contributed the radiographs for RSS and RGI-C analyses were enrolled at a single US site, Shriners Hospital in St. Louis, Missouri. However, treatment with conventional therapy has become standard over the last several decades and it is not anticipated that medical care at Shriners Hospital in St. Louis, Missouri will be significantly different than care at other XLH centres of excellence It should be noted that use of vitamin D

		analogue differs in the US and UK, since alfacalcidol is commonly used in the UK but is not available in the US.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The study was designed to include a similar population, identical outcomes and similar timeframe for analysis as Study 201. In addition, radiographic images were collected and sent to the same central imaging facility used for x-ray processing in Study UX023-CL201. Radiographs were de-identified either at the site or at BMS at the discretion of the site. It should be noted that the RSS and RGI-C raters scored x-rays from Week 64 of Study UX023-CL201 and x-rays from this study in random order in an effort to keep them blinded to the treatment status of the subject. In addition, Propensity Score Matching methods were used to address imbalances between baseline characteristics in the two studies in analyses of rickets assessments (RSS and RGI-C).
Was the follow-up of patients complete?	N/A	This was a retrospective study.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Study name: CL205		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	This Phase 2 study was designed as an open-label, single-arm clinical trial with no control group included. To ensure that appropriate subjects were selected, eligibility requirements included demonstrated hypophosphatemia, radiographic evidence of rickets (at least 5 subjects were to have a minimum RSS score of 1.5 points at the knee), and genetic evidence consistent with a diagnosis of XLH. PHEX sequence variants were classified according to the joint consensus recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al. 2015). Patients with PHEX mutations classified as pathogenic, likely pathogenic, and possibly pathogenic were included. Patients with PHEX variants of uncertain significance

		were also included, as was recommended by experts in paediatric XLH; there are hundreds of variants of the PHEX gene (PHEXdb) and many of these have not yet been fully characterised. The study was conducted at 3 well qualified centres in the United States (US) with the principle investigators considered specialists in the field of the study.
Was the exposure accurately measured to minimise bias?	Yes	CL205 was a prospective, interventional study with a planned treatment duration of 64 weeks. All patients received treatment for at least 40 weeks (the timepoint for the analysis presented).
Was the outcome accurately measured to minimise bias?	Yes	CL205 was a prospective, interventional study and so the outcomes and analysis were predefined in a statistical analysis plan and subject to limited bias. The primary efficacy outcome was change in serum phosphorous. This is a laboratory measure routinely measured in practice and is not subject to bias. Secondary outcomes included assessment of rickets severity. Two independent, complementary methods were implemented to assess the healing of rickets for this study, the Thacher Rickets Severity Score (RSS) and the Radiographic Global Impression of Change (RGI-C). Change from Baseline in severity of rickets was measured using RSS scores of each radiograph, assessed by an expert reader blinded to the time sequence of the radiographs. Improvements in rickets and lower limb deformities were measured by RGI-C scores, assessed as the mean scores of 3 trained, independent radiologists; RGI-C scores represent a change from an earlier image to later image.
Have the authors identified all important confounding factors?	N/A	The study is unpublished. The study was an open-label phase 2 study designed primarily to investigate the safety and pharmacodynamics of burosumab in younger children. No control arm was included and there is no historical cohort data for comparison. In addition, the study is small (n=13). Please note: the safety and efficacy of burosumab compared to conventional therapy in paediatric patients with XLH aged 1 to ≤12 years will be investigated in a Phase 3 Study, UX023-CL301.
Have the authors	N/A	

taken account of the confounding factors in the design and/or analysis?		
Was the follow-up of patients complete?	N/A	At the interim analysis cut-off, all 13 subjects completed at least 40 weeks on study.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

Interventional studies

CL201

An overview of the results for CL201 are shown in Table 17, alongside results from the historical reference study CL002. CL201 investigated dosing every two weeks (Q2W) and every four weeks. The Q2W regimen is considered the optimal dosing regimen and is the expected licensed dosing frequency. The Q2W regimen showed a more stable increase in pharmacodynamic markers as compared with the Q4W regimen. Moreover, assessments of rickets, growth, and walking ability consistently showed greater improvement with the Q2W regimen as compared with the Q4W regimen, with no increase in AE's. [redacted]

Incidences of TEAEs were similar whether subjects received burosumab Q2W or Q4W.

The recommended starting dose for burosumab [redacted]

Evidence from 26 children 5 to 12 years of age with XLH treated with burosumab Q2W for 64 weeks demonstrates that despite long-term treatment with oral phosphate and active vitamin D, there is considerable residual XLH disease and burosumab treatment substantially improves their condition and addresses the unmet medical need.

Table 17. Outcomes from CL201 and CL002

	Q2W burosumab				Conventional therapy	Conclusions
	Week 40 (n=26)		Week 64 (n=26)		n=[redacted]	
Endpoint	**Effect Size**	**p-value**	**Effect Size**	**p-value**	**Effect Size**	
RSS Total Score % mean change from Baseline[a] (negative is better)	-61%	< 0.0001	-58%	< 0.0001	[redacted]	Burosumab significantly improved rickets and induced substantial healing, [redacted]
RGI-C Global Score Mean (positive is better)	+1.72	< 0.0001	+1.62	< 0.0001	[redacted]	
Substantial Healing by RGI-C % with RGI-C global score ≥+2.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Growth Velocity Mean change, comparing pre- and post-treatment[c] (cm/year)	-	-	[redacted]	[redacted]	[redacted]	Early indicator of increased growth velocity and improvement in z-score with burosumab treatment, [redacted]
Standing Height Z-score LS mean change from Baseline[b]	-	-	[redacted]	[redacted]	[redacted]	
6MWT Distance LS mean change from Baseline[b] (m)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Burosumab significantly improved walking ability
Sports/Physical Functioning Scale (POSNA-PODCI) LS mean change from Baseline[b] (10 = 1 SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Burosumab significantly improved physical functioning, bringing scores up to the levels of healthy children, [redacted]
Pain/Comfort Scale (POSNA-PODCI) LS mean change from Baseline[b] (10 = 1 SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Burosumab significantly improved pain, bringing scores up to the levels of healthy children, [redacted]

NA, Not applicable; NR, not reported 6MWT = 6-minute walk test; GEE = generalised estimation equation; LS = least squares; POSNA-PODCI = Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument; Q2W = every 2 weeks; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score

[a] Percent change based on arithmetic means; p value based on GEE model.

[b] LS mean and p value based on GEE model.

[c] P-value based on one-sample t test on growth velocity change from baseline.

Source: (Whyte et al., 2017)

Effect of burosumab on rickets

RSS Total Score Change from Baseline (Primary Efficacy Endpoint)

Burosumab treatment for 40 weeks and 64 weeks, the key time points of this study for efficacy analyses, substantially reduced rickets severity as assessed by RSS scores (Figure 7). In the primary analysis of the primary efficacy endpoint (overall population), RSS total score at Week 40 was reduced by 50%, a statistically significant ($p < 0.0001$) least squares (LS) mean (SE) change of [redacted]. RSS total score at Week 64 was reduced by 51%, a statistically significant ($p < 0.0001$) LS mean (SE) change of [redacted]. Mean (SD) RSS total scores were [redacted] at Week 40, and [redacted] at Week 64.

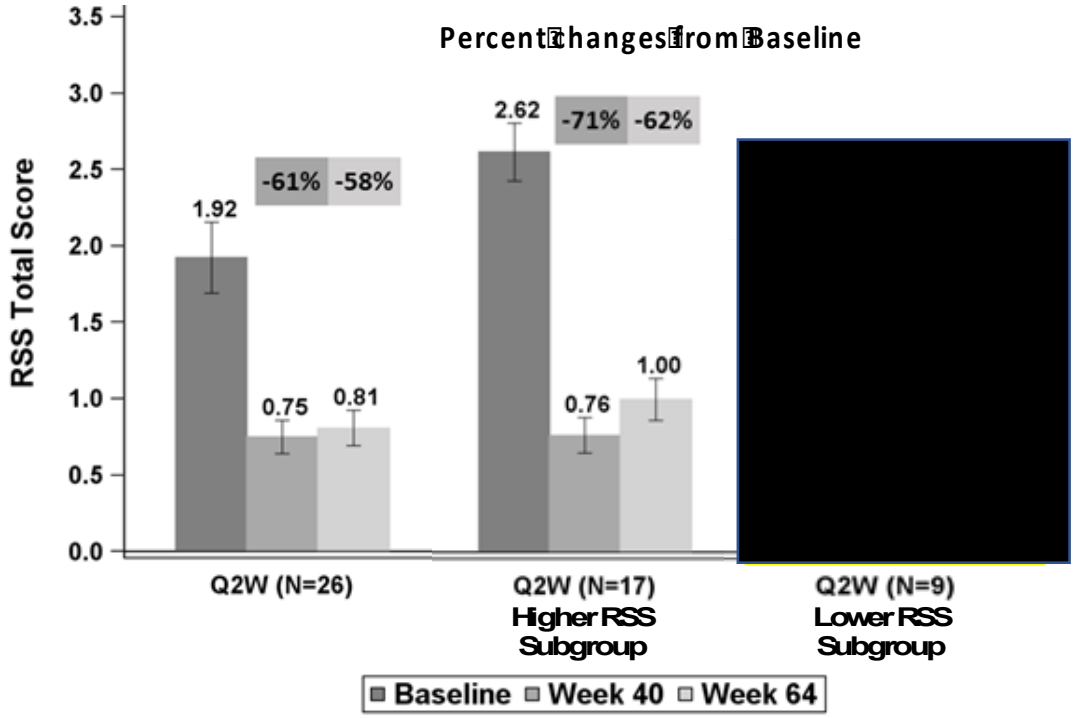
Treatment with burosumab substantially reduced rickets severity within each treatment group. In the Q2W group (N = 26), RSS total scores were reduced by 61% at Week 40 (LS mean [SE] change: [redacted], $p < 0.0001$) and by 58% at Week 64 ([redacted], $p < 0.0001$)(Figure 7 and Table 18). The reduction in RSS Total Score at Week 40 was consistent with that at Week 40 in Study 205 in younger patients (59%; see Figure 15 below).

RSS Scores Change from Baseline by Baseline Rickets Severity Subgroups

In the higher RSS subgroup (Baseline RSS total score ≥ 1.5; N = 34), burosumab treatment for 40 weeks and 64 weeks substantially reduced rickets severity. In the Q2W-treated higher RSS subgroup (N = 17), RSS total score was reduced by 71% at Week 40 (LS mean [SE] change: [redacted], $p < 0.0001$) and by 62% at Week 64 ([redacted], $p < 0.0001$). In the lower RSS subgroup (Baseline RSS total score < 1.5; N = 18), treatment with burosumab for 40 and 64 weeks [redacted].

As expected, greater improvements in RSS scores were observed in subjects with greater disease severity at baseline. [redacted].

Figure 7. RSS Total Scores at Baseline, Week 40, and Week 64 (Mean ± SE)(Q2W, ITT Analysis Set)



Source: (Carpenter et al., 2016; Padidela et al., 2017)
GEE = generalised estimation equation; ITT = intent to treat; Q2W = every 2 weeks; Q4W = monthly; RSS = Rickets Severity Score
Change from Baseline to Week 40 and Week 64, per GEE model: $p < 0.0001$ for All, Q2W, and Q4W

RSS data were analysed using the prespecified responder definition (i.e. reduction in RSS total score from Baseline of at least 1.0 points). In the Q2W group, [redacted]% and [redacted]% of patients were RSS responders at Week 40 and Week 64, respectively. Responder results were similar at Week 40 and Week 64, demonstrating sustained and consistent efficacy through Week 64 of the study.

[redacted]

RSS wrist and knee scores (secondary endpoints)

[redacted]

[redacted] (Table 18).

A supportive analysis of change from baseline in RSS scores was performed using a one-sample t-test. The results of the t-test were similar to the results from the GEE model with regard to statistical significance.

Table 18. RSS Scores and Change from Baseline to Weeks 40 and 64 (Q2W, ITT Analysis Set)

RSS Score	Burosumab Q2W (n = 26)
RSS Wrist Score	
Baseline, mean (SD)	[redacted]
Week 40, mean (SD)	[redacted]
% change in mean observed values	[redacted]
Change to Week 40, LS mean (SE)	[redacted]
p-value[a]	[redacted]
Week 64, mean (SD)	[redacted]
% change in mean observed values	[redacted]
Change to Week 64, LS mean (SE)	[redacted]
p-value[a]	[redacted]
RSS Knee Score	
Baseline, mean (SD)	[redacted]
Week 40, mean (SD)	[redacted]
% change in mean observed values	[redacted]
Change to Week 40, LS mean (SE)	[redacted]
p-value[a]	[redacted]
Week 64, mean (SD)	[redacted]
% change in mean observed values	[redacted]
Change to Week 64, LS mean (SE)	[redacted]
p-value[a]	[redacted]
RSS Total Score	
Baseline, mean (SD)	[redacted]
Week 40, mean (SD)	[redacted]
% change in mean observed values	[redacted]
Change to Week 40[b], LS mean (SE)	[redacted]
p-value[a]	[redacted]
Week 64, mean (SD)	[redacted]
% change in mean observed values	[redacted]
Change to Week 64, LS mean (SE)	[redacted]
p-value[a]	[redacted]

Source:(Ultragenyx, 2017; Carpenter et al., 2016; Padidela et al., 2017)
CI = confidence interval; GEE = generalised estimation equation; ITT = intent to treat; LS = least squares; Q2W = every 2 weeks; RSS = Rickets Severity Score
a LS mean, p value, and CI per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure.
b Primary efficacy endpoint

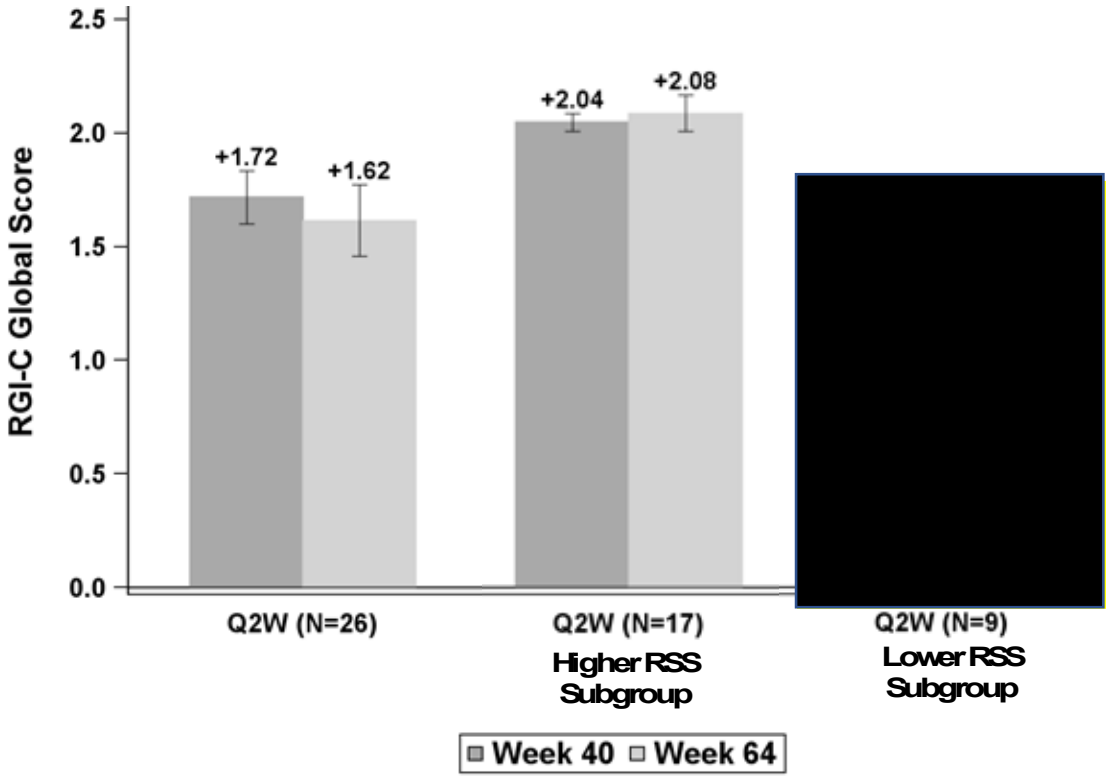
RGI-C Scores

Treatment for 40 weeks and 64 weeks with burosumab, resulted in healing of rickets as assessed by RGI-C scores. Mean global, wrist, and knee RGI-C scores at Weeks 40 and 64 were > +1.4 in the overall group and in both treatment regimens ($p < 0.0001$ [GEE model]). Results for the Q2W dose group are shown in Figure 8 and Table 19.

Burosumab treatment resulted in healing of rickets, as assessed by RGI-C, in both the higher and lower RSS subgroups. In the Q2W dosing group, mean RGI-C Global Score was +2.08 ($p < 0.0001$) in the higher RSS group and [redacted] ($p <$ [redacted]) in the lower RSS group at Week 64.

The RGI-C results complement the RSS results and demonstrate that the greatest improvements in rickets with burosumab treatment were in the subgroup with more severe rickets.

Figure 8. RGI-C Global Scores at Weeks 40 and 64 (Mean ± SE) by Dose Regimen (ITT Analysis Set)



ITT = intent to treat; Q2W = every 2 weeks;; RGI-C = Radiographic Global Impression of Change
Note: Graph presents observed values for mean and SD.

Table 19. RGI-C Scores at Weeks 40 and 64 (Q2W, ITT Analysis Set)

RGI-C Scores[a]	Burosumab Q2W (N = 26)
RGI-C Wrist Score	
Week 40, LS mean (SE)	[redacted]
p-value[b]	[redacted]
Week 64, LS mean (SE)	[redacted]
p-value[b]	[redacted]
RGI-C Knee Score	
Week 40, LS mean (SE)	[redacted]
p-value[b]	[redacted]
Week 64, LS mean (SE)	[redacted]
p-value[b]	[redacted]
RGI-C Total Score	
Week 40, LS mean (SE)	[redacted]
p-value[b]	[redacted]
Week 64, LS mean (SE)	[redacted]
p-value[b]	[redacted]

CI = confidence interval; GEE = generalised estimation equation; ITT = intent to treat; LS = least squares; Q2W = every 2 weeks; RGI-C = Radiographic Global Impression of Change

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

b LS mean and two-sided p value per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure.

Improvements from Baseline in Specific Rickets Radiographic Abnormalities by RGI-C

[redacted]

[redacted]

Lower Extremity Deformity RGI-C Scores

The presence of genu varum (bowing of the legs) and genu valgum (knock knees) was assessed in standing long leg radiographs that were evaluated using the RGI-C method. Changes in these lower extremity deformities from Baseline to Week 64 were assessed using the 7-point RGI-C ordinal scale.

Overall, lower extremity RGI-C score showed [redacted].

Healing and Substantial Healing by RGI-C

Healing and substantial healing of rickets, as assessed by RGI-C, were defined as global scores ≥ +1.0 and ≥ +2.0, respectively. “Healing” in this context indicates improvement in the radiographic abnormalities and does not imply that complete healing was observed.

In the Q2W group, healing of rickets was observed in [redacted]% of subjects at Week 40 and in [redacted]% at Week 64.

- In the higher RSS subgroup, healing of rickets was observed in [redacted].
- In the lower RSS subgroup, healing of rickets was observed in [redacted]% [redacted].

Substantial healing of rickets was observed in [redacted]% of patients in the Q2W dosing group at Week 40 and in [redacted]% of subjects at Week 64.

- In the higher RSS subgroup, substantial healing of rickets was observed [redacted].
- In the lower RSS subgroup, substantial healing of rickets was observed in [redacted].

Impact of burosumab on bone mineral metabolism

Burosumab improved the key PD indicators of XLH.

Serum phosphorus levels increased in all patients and were sustained throughout the study, with mean levels close to or in the low end of the normal range. In the Q2W dosing group, [redacted]% [redacted] ([redacted]) achieved a serum phosphorus level within the normal range (3.2 to 6.1 mg/dL [1.03 to 1.97 mmol/L]). An exaggerated pharmacodynamic effect, i.e., hyperphosphataemia, is a theoretical potential safety concern for burosumab. No patient experienced serum phosphorus levels above the normal range at any time during the study.

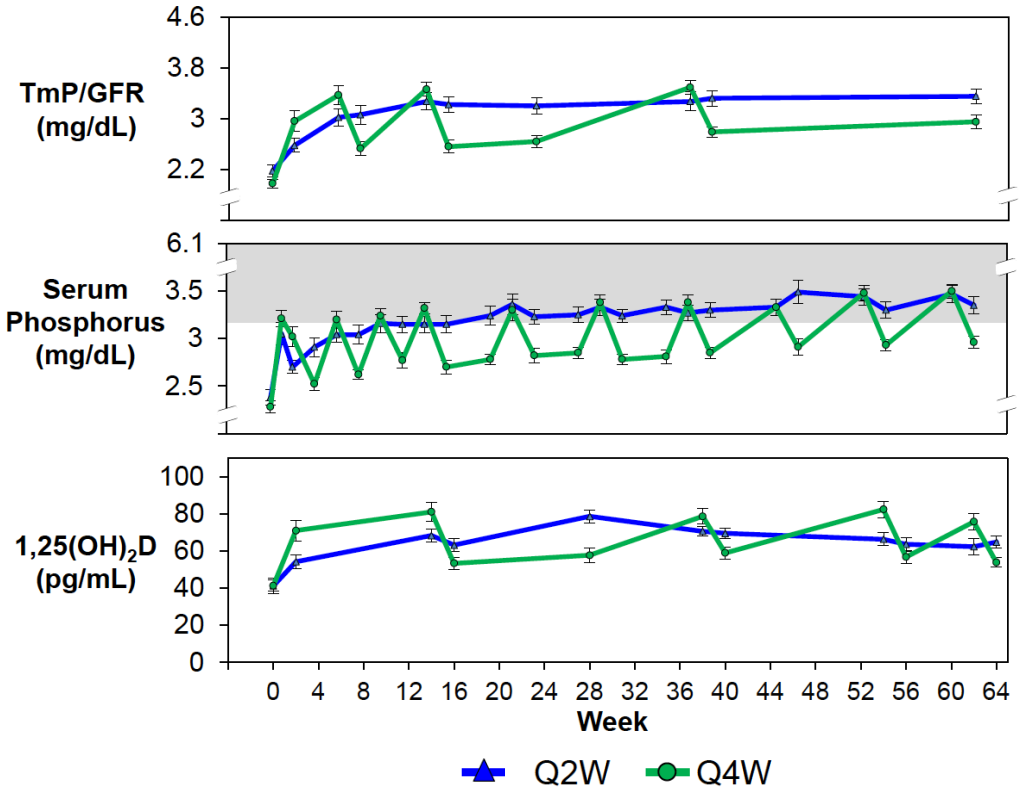
All patients achieved clinically meaningful increases in TmP/GFR: [redacted]% [redacted] had a TmP/GFR value within the reference range (2.6 to 4.4 mg/dL [0.84 to 1.42 mmol/L]). In the Q2W group, [redacted]% [redacted] ([redacted]) [redacted] [redacted] ([redacted]) at Week 64 had TmP/GFR values within the reference range. This is clear evidence of an effect of burosumab on renal phosphate wasting, the main pathophysiologic problem in XLH.

Burosumab treatment increased serum $1,25(OH)_2D$ levels in both the Q2W and Q4W groups. $1,25(OH)_2D$ levels increased from Baseline to Week 64 in the Q2W dose group by [redacted]% ([redacted]). Increases in $1,25(OH)_2D$ from Baseline were statistically significant at each study visit through Week 64 ($p < 0.05$) for both dose groups and overall. Levels of $1,25(OH)_2D$ in children with XLH are generally within normal levels but are low for the degree of hypophosphatemia associated with XLH.

A moderate increase in $1,25(OH)_2D$ is therefore beneficial, but as phosphate-calcium homeostasis improves with burosumab therapy, the regulation and metabolism of $1,25(OH)_2D$ adjusts to the new phosphate-calcium metabolism status. The increases in serum $1,25(OH)_2D$ levels suggest that by blocking FGF23 action, burosumab may restore 25-hydroxyvitamin D 1-alpha hydroxylase activity

Treatment with burosumab did not affect calcium metabolism or serum PTH levels. No clinically meaningful changes in serum or urinary calcium or serum iPTH were observed, consistent with improving the pattern of phosphate-calcium homeostasis while retaining the normal endogenous regulatory feedback pathways for calcium, unlike oral active vitamin D therapy provided with conventional therapy.

Figure 9. Key disease markers of phosphate wasting (Study 201)



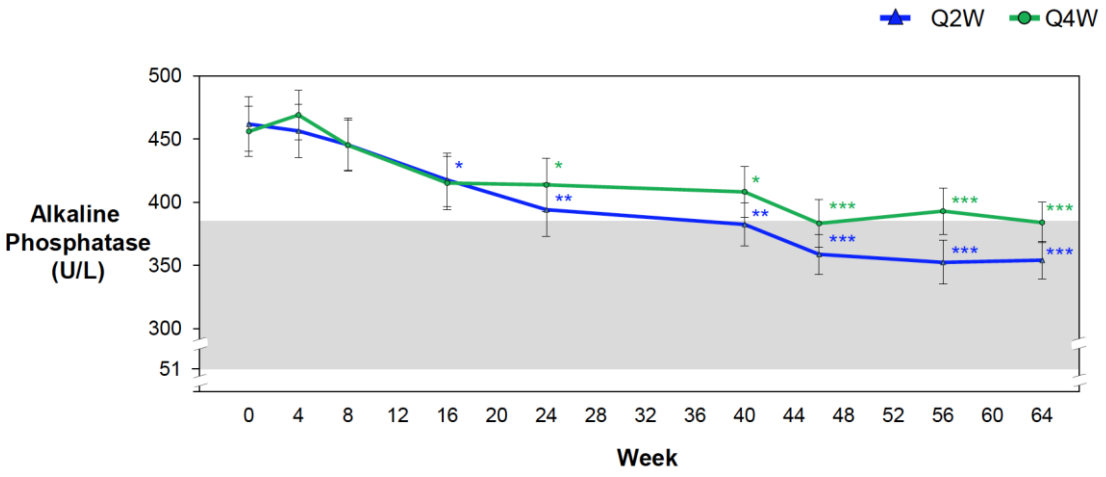
Source: (Whyte et al., 2017)

Serum Markers of Rickets – ALP and BALP

At Baseline, mean (SD) serum ALP levels were [redacted] in the Q2W group, well above the upper limit of the normal ranges for the ages of the children in this study (approximately 297 to 385 U/L, depending on the age and sex of the child). Similarly for BALP, mean (SD) serum levels at Baseline were [redacted], well above the upper limit of the normal ranges for the ages of the children in this study (approximately 23 µg/L). Mean (SD) serum ALP levels at Baseline [redacted].

In the Q2W group, mean (SD) serum ALP levels decreased to [redacted] and to [redacted] (Figure 10). Mean (SD) serum BALP levels decreased to [redacted] at Week 40 (mean change: [redacted]) and to [redacted] µg/L at Week 64 (mean change: [redacted]).

Figure 10. Serum Alkaline Phophatase (Study CL201)



Source: (Whyte et al., 2017)
Mean ±SE; Gray box indicates normal range. ***p ≤ 0.0001 **p ≤ 0.001; *p ≤ 0.01; versus baseline (p-values are presented as nominal p-values, no adjustment on multiplicity)

Effect of burosumab on growth (changes in standing height)

The three measures of change in standing height – velocity (assessed using a model-based approach based on all standing height data obtained during the study), z-score, and percentile for age and gender – demonstrated that burosumab treatment improved growth in children with XLH.

Burosumab treatment for 64 weeks increased growth velocity. In the Q2W group, mean (SD) growth velocity increased, from [redacted] cm/year at Baseline (ie, the 2 years before study entry) to [redacted] cm/year ([redacted], p = [redacted], one sample t-test). Mean (SD) standing height z-score increased from [redacted] at Baseline to [redacted] at Week 64, an LS mean (SE) change of [redacted]. Mean (SD) percentile standing heights were [redacted] at Baseline and [redacted] at Week 64.

In the Q2W-treated higher RSS subgroup, [redacted].

Effect of burosumab on walking ability (six-minute walk test [6MWT])

Burosumab treatment increased mobility as assessed by the 6MWT in the overall population and both dosing groups. In the Q2W group, the distance walked in the

6MWT increased from a mean of [redacted] Table 20). Improvements were noted in the Q2W group at Week 16, the first time point post-baseline at which 6MWT was assessed ([redacted]).

In a planned analysis, 6MWT results were analysed by subgroups based on baseline percentage of predicted 6MWT, < 80% (abnormal) or ≥ 80% (normal range), to assess the effect of burosumab on subjects with, respectively, the greater and lesser impairment in mobility at baseline. In the < 80% baseline predicted 6MWT subgroup, the distance walked in the 6MWT increased in Q2W-treated subjects from a mean of [redacted] at Week 64 ([redacted]; Table 20 and Figure 11). [redacted].

Mean (SD) walking distance at Baseline was [redacted] for the lower RSS subgroup. The proportion of subjects with substantial impairment in walking ability (< 80% of predicted 6MWT based on age, gender, and height) [redacted].

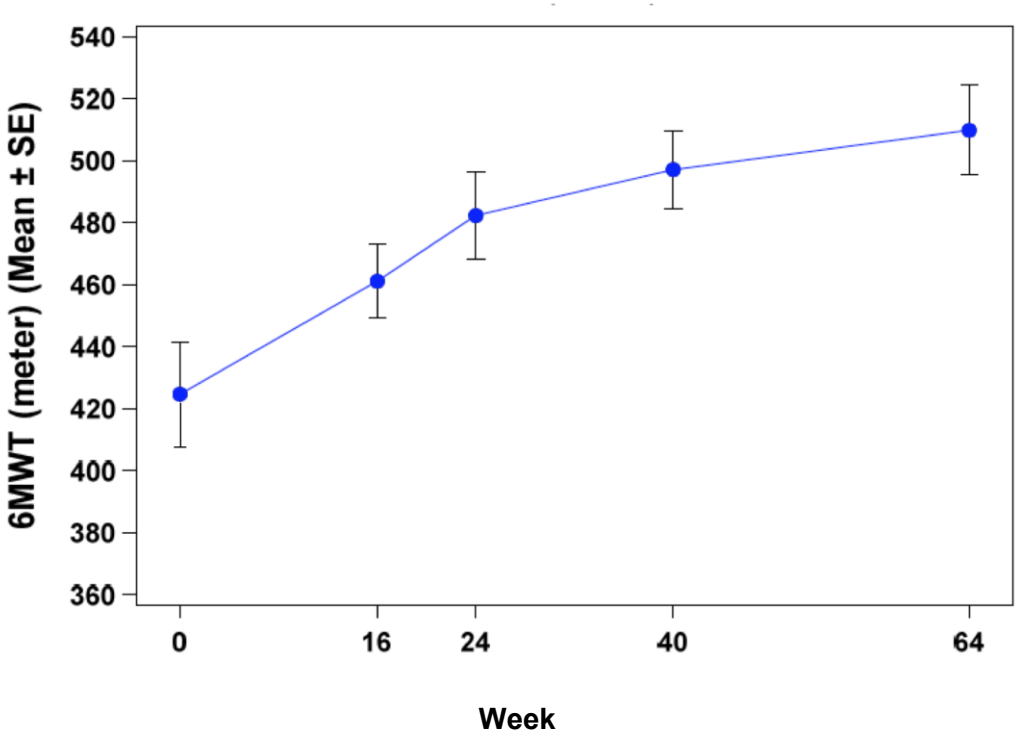
Table 20. 6MWT Distance (m) Change from Baseline to Week 64 (ITT Analysis Set)

6MWT Distance (distance walked [m])	Burosumab Q2W
All subjects	
n	26
Baseline, mean (SD)	[redacted]
Week 64, mean (SD)	[redacted]
Change to Week 64, LS mean (SD)[a]	[redacted]
p-value	[redacted]
Baseline Predicted 6MWT < 80% Subgroup	
n	14
Baseline, mean (SD)	[redacted]
Week 64, mean (SD)	[redacted]
Change to Week 64, LS mean (SD)[a]	[redacted]
p-value	[redacted]

6MWT = 6-minute walk test; GEE = generalised estimating equation; ITT = intent to treat; Q2W = every 2 weeks

[a] The GEE model included change in 6MWT score as the dependent variable; visit, regimen, visit by regimen as factors; and 6MWT at baseline as a covariate, with exchangeable covariance structure. The LS mean, SE, and 2-sided p-value are from the GEE model.

Figure 11. 6MWT Distance (m) (LS Mean ± SE) Change from Baseline to Week 64 (Q2W dosing, <80% of predicted subgroup)



Source: (Imel et al., 2017b)
6MWT = 6-minute walk test; GEE = generalised estimating equation; ITT = intent to treat; LS = least squares
LS mean and SE were calculated from a GEE model, which included visit, regimen, and visit by regimen as factors; and 6MWT at baseline as a covariate, with exchangeable covariance structure.

Effect of burosumab on functional disability and pain (POSNA-PODCI)

Burosumab treatment for 64 weeks improved functional ability and decreased pain as assessed by the POSNA-PODCI.

At Baseline, the greatest deficits in POSNA-PODCI scores were in the scales of Sports/Physical Functioning (mean [SD] score: 33.4 [17.42]), Pain/Comfort (35.0 [15.85]), and Global Functioning (36.6 [15.52]). As the baseline means were more than one standard deviation below the normative value of 50, these results demonstrate that subjects at baseline suffered from significant pain, limited mobility, and inability to participate in sports and other activities despite conventional treatment. Mean scores were within one standard deviation of the normative value of 50 for the other scales. These results are consistent with earlier surveys that indicated that the domains of Sports/Physical Functioning and Pain/Comfort are the most specific and sensitive to XLH disease impact.

Burosumab Q2W treatment resulted in improvement in Sports/Physical Functioning LS mean scores (Week 64: [redacted]; Table 21). In a subset of subjects (N = [redacted]) with impaired physical function (Global Functioning Scale scores at Baseline < 40, regardless of rickets status at baseline) Sports/Physical Functioning LS mean scores improved by [redacted].

Similarly, Pain/Comfort LS mean scores showed improvements following burosumab although this did not reach statistical significance in the Q2W group ([redacted]). Pain/Comfort LS mean scores improved by [redacted] in the above subset of subjects with impaired physical function.

These data suggest that normalisation of phosphate homeostasis and improvement in bone disease and rickets with burosumab is associated with better physical function and reduced pain, and notably in patients with greater rachitic disease or greater functional impairment or both.

Table 21. POSNA-PODCI Sports/Physical Functioning Scale and Pain/Comfort Scale (Normative Score) Change from Baseline to Week 64 (ITT Analysis Set)

	Burosumab Q2W
Sports/Physical Functioning Scale (Normative Score)	
All subjects	
n	26
Baseline, mean (SD)	[redacted]
Week 64, mean (SD)	[redacted]
Change to Week 64, LS mean (SE)[a]	[redacted]
p-value	[redacted]
Baseline Global Functioning Scale Normative Score < 40 Subgroup	
n	[redacted]
Baseline, mean (SD)	[redacted]
Week 64, mean (SD)	[redacted]
Change to Week 64, LS mean (SD)[a]	[redacted]
p-value	[redacted]
Pain/Comfort Scale (Normative Score)	
All subjects	
n	26
Baseline, mean (SD)	[redacted]
Week 64, mean (SD)	[redacted]
Change to Week 64, LS mean (SE)[a]	[redacted]
p-value	[redacted]
Baseline Global Functioning Scale Normative Score < 40 Subgroup	
n	[redacted]
Baseline, mean (SD)	[redacted]
Week 64, mean (SD)	[redacted]
Change to Week 64, LS mean (SD)[a]	[redacted]
p-value	[redacted]

GEE = generalised estimating equation; Q2W = every 2 weeks; ITT = intent to treat;
LS = least squares; POSNA-PODCI = Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument
a The GEE model included change in POSNA-PODCI scale score as the dependent variable; visit, regimen, and visit by regimen as factor; and POSNA-PODCI scale score at baseline as a covariate, with exchangeable covariance structure. The LS mean, SE, and 2-sided p-value are from the GEE model.

POSNA-PODCI scale scores were analysed by predefined subgroups based on RSS total score at Baseline (≥ 1.5 or < 1.5) and by predefined subgroups based on POSNA-PODCI Global Functioning scale score at Baseline (scores < 40 [abnormal] or ≥ 40 [normal range]).

Patients in the higher RSS subgroup had lower scores at Baseline (greater functional disability and pain) [redacted].

CL002

Impact of conventional therapy on bone mineral metabolism

At the time of the baseline radiographs, the mean serum phosphorus level in the overall group was [redacted], below the lower limit of normal (LLN, 3.2 mg/dL [1.03 mmol/L]) for children. At the post-baseline radiographs, mean serum phosphorous level [redacted].

[redacted].

Effect of conventional therapy on rickets

RSS and RGI-C Score Change from Baseline

Prolonged treatment with oral phosphate/calcitriol therapy for a median of [redacted] (Table 22 and Table 23). Changes in RSS total scores (wrist and knee combine) showed a [redacted] with continued treatment with oral phosphate/calcitriol therapy.

For the higher RSS subgroup of the prespecified analysis, mean total RSS decreased (improved) from [redacted] for the post-baseline radiographs. For the lower RSS subgroup, mean total RSS score [redacted].

The RGI-C global score was [redacted] post-baseline for the overall population, [redacted] for the higher RSS subgroup, and [redacted] for the lower RSS subgroup, which translate to [redacted].

RGI-C data were analysed similar to those in Study CL201 based on the categories of healing with a global score of +1.0 indicating minimal healing and a +2.0 score indicating substantial healing. More than [redacted].

Table 22. Change in RSS Scores from Baseline to Post-baseline Radiographs in Overall Group (Radiographic Analysis Set)

RSS Score	N[a]	Conventional therapy
RSS Wrist Score		
Baseline, mean (SD)	[redacted]	[redacted]
Post-baseline radiographs, mean (SD)	[redacted]	[redacted]
Mean Change (SD)	[redacted]	[redacted]
95% CI		[redacted]
RSS Knee Score		
Baseline, mean (SD)	[redacted]	[redacted]
Post-baseline radiographs, mean (SD)	[redacted]	[redacted]
Mean Change (SD)	[redacted]	[redacted]
95% CI		[redacted]
RSS Total Score		
Baseline, mean (SD)	[redacted]	[redacted]
Post-baseline radiographs, mean (SD)	[redacted]	[redacted]
Mean Change (SD)	[redacted]	[redacted]
95% CI		[redacted]

a number of rated radiograph pairs (wrist and knee) from subjects in the Radiograph Analysis Set.
b Thirteen of the 60 evaluable paired radiographs had evidence of fused growth plates and were not included in the RSS evaluation.

Table 23. Mean RGI-C Scores by RSS Subgroups (Radiographic Analysis Set)

RGI-C Scores[a]	Conventional therapy (N =60[b])
Wrist score	
Mean (SD)	[redacted]
95% CI	[redacted]
Knee Score	
Mean (SD)	[redacted]
95% CI	[redacted]
Global Score	
Mean (SD)	[redacted]
95% CI	[redacted]

a The RGI-C score was based on a 7-point ordinal scale rangin from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets)
b number of evaluable radiograph pairs – Radiographic Analysis Set

Markers of Rickets – ALP

Mean alkaline phosphatase (ALP) concentration, a biomarker of rickets, [redacted].

Lower extremity deformity

Of the [redacted] standing long leg baseline radiographs evaluated for anatomical deformities, [redacted]

[redacted]. The mean (SD) time between baseline and post-baseline standing long leg radiographs was [redacted] in the evaluation of lower leg deformities.

After long-term treatment with conventional therapy, the mean RGI-C lower limb deformity score [redacted].

The mean RGI-C lower limb deformity score was [redacted].

Impact of conventional therapy on growth

Observational data corresponding to the [redacted] paired baseline radiographs showed that many subjects in this study had decreased height for age (mean [SD] standing height z-score of -1.89 [0.92]).

After long-term treatment with conventional therapy, [redacted]. As depicted in Figure 12, the data show that conventional therapy [redacted] across age groups from 1 to 17 years.

Figure 12. Mean (SE) Standing Height (cm) from Ages 1 to 17 Years with CDC Percentile Reference Full Analysis Set

CDC, Centers for Disease Control

Comparison with CL201

See Section 9.8.2.

CL205

An overview of the results for CL205 are shown in Table 24.

Table 24. Overview of outcomes from Study CL205

Endpoint	Week 40			Conclusions
	N	Effect Size	p-value	
RSS Total Score % mean change from Baseline[a] (negative is better)	13	-59%	< 0.0001	Burosumab significantly improved rickets and [redacted]
RGI-C Global Score LS mean[b] (positive is better)	13	+2.33	< 0.0001	
Substantial Healing by RGI-C % RGI-C global score ≥ +2.0	13	[redacted]%	-	
ALP % mean change from Baseline[c] (negative is better)	13	-36.3%	< 0.0001	
RGI-C Lower Limb Deformity Score LS mean[b] (positive is better)	13	[redacted]	[redacted]	[redacted]
Recumbent Length/Standing Height Mean change from Baseline (cm)	13	[redacted]	[redacted]	[redacted]
Recumbent Length/Standing Height z-score LS mean change from Baseline[d]	13	[redacted]	[redacted]	

Source: (Imel et al., 2017a)
ALP = alkaline phosphatase; ANCOVA = analysis of covariance; LS = least squares; GEE = Generalised Estimating Equations; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score
a Percent change based on arithmetic means; p value based on ANCOVA model.
b LS mean and p value based on ANCOVA model.
c Percent change based on arithmetic means; p value based on GEE model.
d LS mean and p value based on GEE model.

Impact of burosumab on bone mineral metabolism

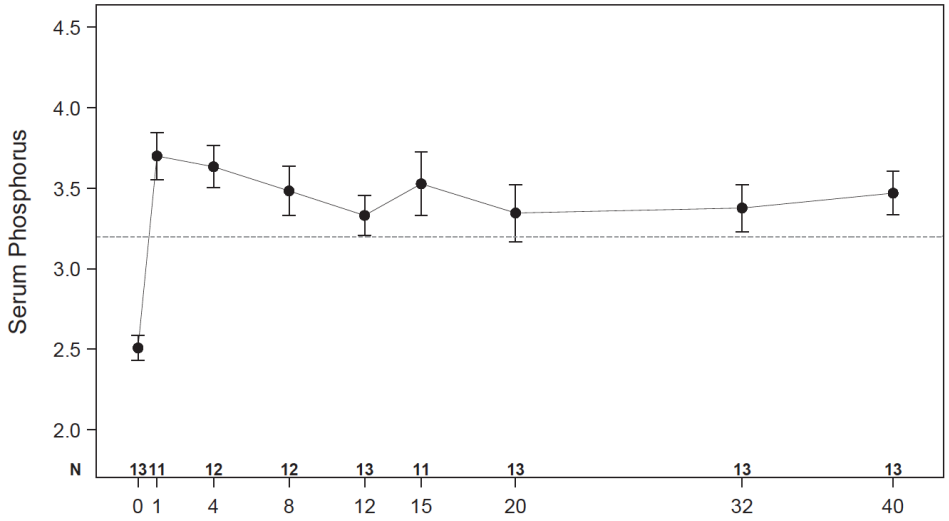
Change in serum phosphorus (primary endpoint)

At Baseline, all subjects had serum phosphorus levels below normal, with a mean (SD) of 2.51 (0.284) mg/dL (0.81 [0.092] mmol/L) compared with the normal range of 3.2 to 6.1 mg/dL (1.03 to 1.97 mmol/L). Burosumab treatment rapidly and

substantially increased mean serum phosphorus levels (Figure 13) with mean concentrations above the lower limit of normal (LLN) at all post-Baseline time points. Increases in serum phosphorus concentration from Baseline were statistically significant at each study visit ($p < 0.0001$, GEE analysis). At Week 40, mean (SD) serum phosphorus concentrations were 3.47 (0.485) mg/dL (1.12 [0.158] mmol/L); change from Baseline to Week 40 was 0.96 (0.439) mg/dL (0.31 [0.143] mmol/L).

All subjects achieved clinically meaningful increases in serum phosphorus. Normal serum phosphorus levels (3.2-6.1 mg/dL) were achieved in 82%, 62%, and 77% of children at Weeks 1, 20, and 40 (Imel et al., 2017a). For individual subjects, the average serum phosphorus concentration for all post-Baseline time points ranged from [redacted].

Figure 13. Serum Phosphorus Concentration over Time (PK/PD Analysis Set)



Source: (Imel et al., 2017a)

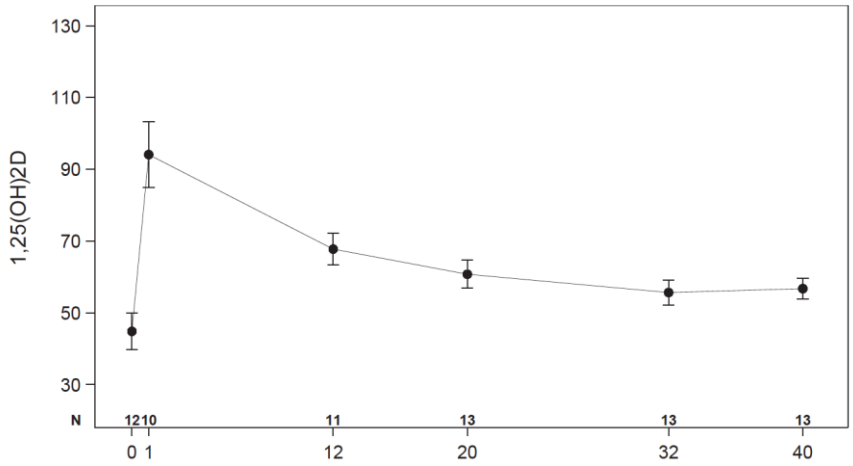
An exaggerated PD effect, i.e., hyperphosphataemia, is a theoretical potential safety concern for burosumab. No subject experienced serum phosphorus levels above the ULN (6.1 mg/dL [1.97 mmol/L]) at any time during the study or experienced TEAEs of hyperphosphataemia (Section 9.7).

Serum 1,25(OH)$_2$D

Burosumab treatment increased serum 1,25(OH)$_2$D levels from [redacted] (Figure 14). Increases in 1,25(OH)$_2$D from Baseline were statistically significant at each study visit through Week 40 ($p < 0.01$, GEE analysis).

Mean serum 1,25(OH)$_2$D levels more than [redacted] from Baseline to Week 1 (mean change: [redacted]). In previous studies in adults with XLH, maximum increases from Baseline in serum 1,25(OH)$_2$D levels were observed at approximately 1 week after the first burosumab dose. Therefore, this pattern of an increase in serum 1,25(OH)$_2$D with a maximum value at Week 1 is consistent with previous findings.

Figure 14. Serum 1,25-Dihydroxyvitamin D Concentration over Time (PK/PD Analysis Set)



Source: (Imel et al., 2017a)

The transitory increase in $1,25(OH)_2D$ was not associated with significant changes in serum or urinary calcium. [redacted].

After the peak at Week 1, and as phosphate homeostasis was restored with burosumab treatment, mean serum $1,25(OH)_2D$ levels declined but remained above Baseline levels, demonstrating the continuing effect of burosumab in blocking excess FGF23 and an appropriate level of $1,25(OH)_2D$ synthesis for low-normal serum phosphorus concentrations.

Assessment of rickets

RSS total score (secondary efficacy outcome)

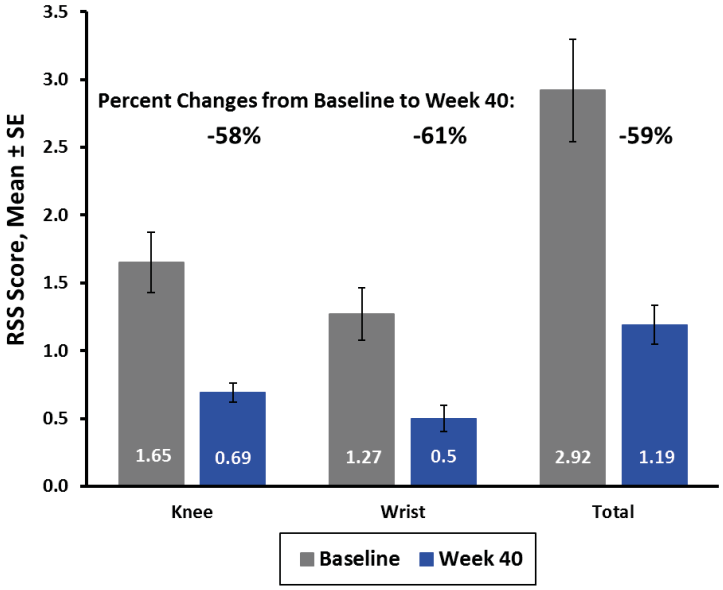
Burosumab treatment for 40 weeks significantly reduced rickets severity as assessed by RSS scores. RSS total score at Week 40 was reduced by 59% ($p < 0.0001$, ANCOVA model) least squares (LS) mean (SE) change of -1.73 (0.132) (Figure 15). Mean (SD) RSS total scores were 2.92 (1.367) at Baseline and 1.19 (0.522) at Week 40.

Similarly, RSS wrist scores and knee scores were reduced at Week 40 by [redacted], respectively. Results of sensitivity analyses using the one-sample t test and the Wilcoxon one-sample signed rank test were consistent with the ANCOVA model with respect to statistical significance.

The improvement in rickets scores from Baseline to Week 40 is also seen in the shift in the distribution of RSS total scores. At Baseline, most subjects [redacted]

[redacted]

Figure 15. Mean (SE) RSS Scores at Baseline and Week 40 (Efficacy Analysis Set)



RGI-C global score (secondary efficacy outcome)

Burosumab treatment for 40 weeks resulted in healing of rickets as assessed by RGI-C scores. [redacted] (Table 25), demonstrating "substantial healing of rickets". LS mean (SE) values at Week 40 were +2.33 (0.080) for RGI-C global scores; +2.26 (0.110) for RGI-C wrist scores; and +2.21 (0.153) for RGI-C knee scores ($p < 0.0001$ for all, ANCOVA model).

Results of sensitivity analyses using the one-sample t test and the Wilcoxon one-sample signed rank test were consistent with the ANCOVA model with respect to statistical significance.

These results demonstrate improvement in radiographic signs of rickets after 40 weeks of burosumab treatment as compared with Baseline. The RGI-C results complement the RSS results in demonstrating the improvement in rickets with burosumab treatment.

Table 25. RGI-C Scores at Week 40 (Efficacy Analysis Set)

	Burosumab (N=13)
RGI-C Wrist Score	
LS mean (SE)[b]	+2.26 (0.110)
p-value	< 0.0001
95% CI	2.01, +2.50
RGI-C Knee Score	
LS mean (SE)[b]	+2.21 (0.153)
p-value	< 0.0001
95% CI	+1.86, +2.55
RGI-C Total Score	
LS mean (SE)[b]	+2.33 (0.080)
p-value	< 0.0001
95% CI	+2.16, +2.51

ANCOVA = analysis of covariance; LS = least squares; RSS = Rickets Severity Score; RGI-C = Radiographic Global Impression of Change

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

[b] LS mean, SE, 95% CI, and 2-sided p-value from the ANCOVA model, which included age and RSS total score at Baseline as covariates.

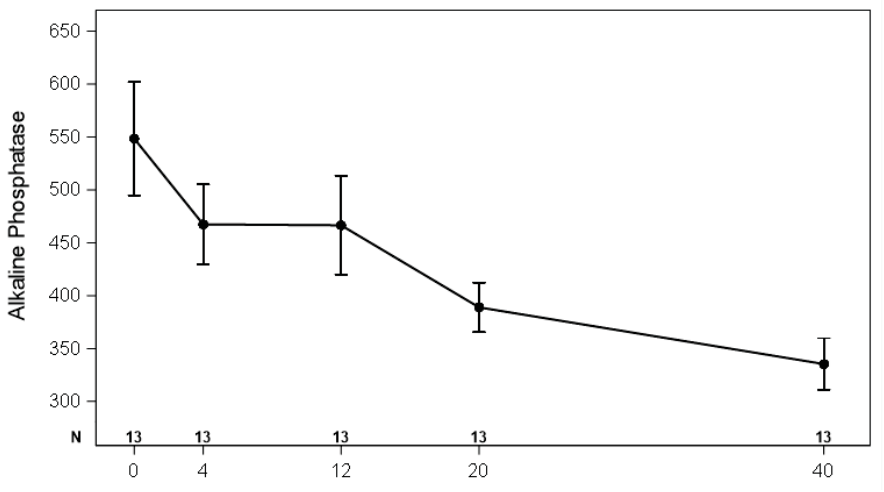
Serum ALP (secondary efficacy outcome)

At Baseline, mean (SD) serum ALP levels were 549 (193.8) U/L, well above the ULN for the children in this study (approximately 297 to 345 U/L, depending on the age and sex of the child). A decrease in mean serum ALP levels was observed at the first post-baseline assessment: at Week 4, mean (SD) levels were [redacted] (Figure 16). Change from Baseline to Week 4 was statistically significant ([redacted], GEE model).

Mean (SD) serum ALP levels decreased further to 389 (84.2) U/L at Week 20 (mean change: -24.8%) and to 335 (87.6) U/L at Week 40 (mean change: -36.3%). Changes from Baseline to Weeks 20 and 40 were statistically significant ($p < 0.0001$).

[redacted]

Figure 16. Serum ALP Level (U/L) (Mean ± SE) over Time (PK/PD Analysis Set)



ALP = alkaline phosphatase; PD = pharmacodynamic; PK = pharmacokinetic
Note: Subject 138-503 had a serum ALP concentration of 908 U/L at Week 12. The subject had no concurrent TEAEs or laboratory values that would be associated with or could explain this highly elevated value; this outlier value reported is presumed to be spurious.

Lower extremity skeletal abnormalities (Secondary Efficacy Outcome)

Burosumab treatment for 40 weeks resulted in [redacted].

[redacted]

Growth

Mean (SD) recumbent length/standing height [redacted].

[redacted].

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

Not applicable.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The search strategy to identify clinical studies relating to burosumab has been described in Section 9.1. Safety data are available from CL201 and CL205.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

CL201

Safety data were evaluated through the data cut-off date of 01 December 2016. Safety data were available for most subjects beyond Week 64. At Week 64, the beginning of the Treatment Extension Period, the dose regimen for subjects in the Q4W group changed to Q2W. The 36 pre-expansion subjects had reached at least the Week 88 visit by the data cut-off date. While all subjects received burosumab Q2W after Week 64, data are reported by the initial regimen to which subjects were randomised.

All Adverse Events

Evaluation of treatment-emergent adverse events (TEAEs) indicated no significant safety concerns. No subject discontinued from the study due to TEAEs or any other reason, and no subject died. One subject experienced serious TEAEs, and [redacted]

[redacted]. All 52 subjects (100%) experienced at least one TEAE during the study (Table 26).

Table 26. Summary of Treatment-emergent Adverse Events in Study CL201 (Safety Analysis Set)

Category	Burosumab Q2W (N = 26)	Burosumab Q4W (N = 26)	Overall (N=52)
All TEAEs	26 (100%)	26 (100%)	52 (100.0%)
Serious TEAEs	0 (0.0%)	1 (3.8%)	1 (1.9%)
Related TEAE	[redacted]	[redacted]	[redacted]
Serious Related TEAE	0 (0.0%)	1 (3.8%)	1 (1.9%)
Grade 3 or 4 TEAE	[redacted]	[redacted]	[redacted]
TEAE leading to study discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAE leading to treatment discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)

Q2W, every 2 weeks; TEAE, treatment-emergent adverse event

The most frequent TEAEs (>30% incidence) were [redacted]. [redacted] Headache, cough, nasopharyngitis, vomiting, upper respiratory tract infection, and pyrexia occur frequently in a paediatric population, and pain in extremity and arthralgia occur frequently in an XLH population. Injection site reactions, which are known to occur with subcutaneously-administered protein therapeutics, [redacted]. The frequency of events of headache observed in this study is consistent with published reviews of epidemiological studies on headache in children and adolescents, which have found a prevalence of headache in this population of approximately 54% to 58% (Wöber-Bingöl, 2013; Abu-Arafeh et al., 2010). Most events of headache [redacted]. Most events of [redacted].

Table 27. Treatment-emergent Adverse Events Occurring in ≥ 3 Subjects Overall by SOC and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Q2W (N = 26)	Q4W (N = 26)	Overall (N = 52)
Subjects with any treatment-emergent adverse events	26 (100.0%)	26 (100.0%)	52 (100.0%)
Infections and infestations	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Pharyngitis streptococcal	[redacted]	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]

System Organ Class Preferred Term	Q2W (N = 26)	Q4W (N = 26)	Overall (N = 52)
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]
Lice infestation	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Injection site rash	[redacted]	[redacted]	[redacted]
Injection site bruising	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]
Respiratory thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]
Sneezing	[redacted]	[redacted]	[redacted]
Wheezing	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]

System Organ Class Preferred Term	Q2W (N = 26)	Q4W (N = 26)	Overall (N = 52)
Arthralgia	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]
Injury poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Skin abrasion	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Procedural pain	[redacted]	[redacted]	[redacted]
Arthropod bite	[redacted]	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]	[redacted]
Thermal burn	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Vitamin D decreased	[redacted]	[redacted]	[redacted]
Blood 25-hydroxycholecalciferol decreased	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]
Ear pain	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]	[redacted]

All TEAEs [redacted].

One subject experienced serious adverse events (SAEs) of [redacted]. [redacted]

[redacted]

All Adverse Events by Relationship to Investigational Product

Overall, [redacted]

Clinical Laboratory Evaluations, Vital signs/physical findings and other observations

No TEAEs with the preferred term “hyperphosphataemia” were reported during the study. One subject experienced a TEAE with the preferred term “blood phosphorous increased” (verbatim term: “serum phosphorous level above target range”); however, the actual serum phosphorus level was 5.2 mg/dL (1.68 mmol/L) and was within normal limits. No TEAEs of hypophosphataemia, or increased or decreased iPTH were reported during the study. While mean serum calcium showed no change from baseline, [redacted]

[redacted]

[redacted]

[redacted]

CL205

All Adverse Events

Evaluation of TEAEs up to the 20th April 2017 (burosumab treatment through Week 40 for all subjects), with maximum duration of exposure up to 46 weeks indicated no

significant safety concerns. No subject discontinued from treatment or from the study due to TEAEs or any other reason, and no subject died. One subject experienced an SAE [redacted] considered unlikely unrelated to study drug. All 13 subjects (100%) experienced at least one TEAE during the study (Table 28). [redacted]

Table 28. Summary of Adverse Events in Study CL205 (Safety Analysis Set)

Category	Burosumab Subjects (N = 13)
AEs starting during screening period	4 (30.8%)
TEAEs	[redacted]
Related TEAEs	[redacted]
Serious TEAEs	1 (7.7%)
Serious Related TEAE	[redacted]
Grade 3 or 4 TEAE	[redacted]
TEAE leading to study discontinuation	0 (0.0%)
TEAE leading to treatment discontinuation	0 (0.0%)
TEAE leading to death	0 (0.0%)

AE = adverse event; TEAE = treatment-emergent adverse event

The most frequent TEAEs (> 30% incidence [four or more of 13 subjects]) were [redacted]

Table 29. Treatment-emergent Adverse Events Occurring in ≥ 2 Subjects by SOC and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Burosumab Subjects (N = 13)
Subjects with any TEAEs	13 (100%)
Infections and infestations	[redacted]
Upper respiratory tract infection	[redacted]
Pharyngitis streptococcal	[redacted]
Tooth abscess	[redacted]
Nasopharyngitis	[redacted]
Viral upper respiratory tract infection	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Cough	[redacted]
Rhinorrhoea	[redacted]
Nasal congestion	[redacted]

Respiratory tract congestion	[redacted]
Gastrointestinal disorders	[redacted]
Vomiting	[redacted]
Diarrhoea	[redacted]
Oral pain	[redacted]
Abdominal discomfort	[redacted]
Abdominal pain upper	[redacted]
Toothache	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
Injury, poisoning and procedural complications	[redacted]
Skin abrasion	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Arthralgia	[redacted]
Pain in extremity	[redacted]
Nervous system disorders	[redacted]
Hypersomnia	[redacted]
Ear and labyrinth disorders	[redacted]
Ear pain	[redacted]

Five subjects (38.5%) experienced nine treatment-related TEAEs (i.e., TEAEs deemed “definitely,” “probably,” or “possibly” related to study drug by the Investigator. Related TEAEs were most frequently in the system organ class (SOC) of General disorders and administration site conditions. Three subjects (23.1%) experienced TEAEs of Injection site reactions; one subject each experienced injection site erythema (three events), injection site pruritus, and injection site reaction. All events were mild in severity and resolved in one or two days without treatment. Injection site reactions were not associated with any severe hypersensitivity reactions and generally represented localised irritation.

Clinical laboratory Evaluations, Vital Signs and Other Observations Related to Safety

There were no clinically meaningful changes from Baseline in clinical chemistry (mean serum calcium or mean serum iPTH), haematology, or urinalysis parameters. Review of four potential hypersensitivity TEAEs (rash, urticaria, swelling face, and hypersensitivity [to “environmental allergies”] – all Grade 1) concluded that these events did not represent hypersensitivity to burosumab because they had alternative aetiologies and were deemed unrelated/unlikely related to study drug. No subject experienced hyperphosphataemia or ectopic calcification. Renal ultrasound scores were 0 for all subjects at Baseline and at Week 40. No clinically meaningful changes from Baseline were noted in ECG parameters or vital signs. All subjects were

negative for anti-burosumab antibodies at a Baseline, Week 4, and Week 12, the last time point assessed by the current assay.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Burosumab has a safety profile appropriate for the treatment of children with XLH:

- Treatment in children showed no adverse impacts on phosphate-calcium metabolism; no adverse events of hyperphosphataemia or clinically meaningful changes in serum or urinary calcium, serum iPTH, or renal ultrasounds (including nephrocalcinosis) were observed.
- No subject died or discontinued from CL201 or CL205 for any reason; all subjects continued treatment on study as of the data cut-off dates.
- Injection site reaction was the most common treatment-related adverse event, [redacted].
- [redacted].
- Other commonly reported TEAEs were [redacted].
- [redacted].

The results of CL201 and CL205 to date indicate that burosumab has no significant safety concerns. Injection site reactions, while frequently reported, [redacted] and did not result in discontinuation.

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

The burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible. A comparison of rickets severity outcomes (RSS and RGI-C) from Study CL201 and Study CL002 is provided here.

Although not a matched control cohort, the change in rickets observed in the patients in CL002 provides an indication of the degree of change in rickets severity that may occur with prolonged phosphate/calcitriol treatment and allows the RSS and RGI-C scores achieved after 64 weeks of burosumab treatment to be put into context.

The findings from CL002, which are consistent with the baseline data collected from Study CL201, confirm that conventional therapy [redacted].

Baseline assessments in Study CL201 and Study CL205 represent the therapeutic effect of conventional therapy during the several months or years before entry into the paediatric studies. In Study CL201 (mean age: 8.5 years), the mean duration of conventional therapy before entering the study was 6.9 years, and in Study CL205 (mean age: 2.9 years), the mean duration of conventional therapy before entering the study was 1.4 years. Comparisons of postbaseline to baseline assessments of rickets therefore serve as comparisons of burosumab treatment to conventional therapy. As shown in Section 9.6, treatment with burosumab significantly improved rickets by multiple measures in Study CL201, suggesting improvement over conventional therapy. This conclusion is supported by comparisons of rickets data from Study CL201 and Study CL002 which showed that the magnitude of improvement in RSS scores, and the magnitude of RGI-C scores, were consistently

greater for those treated with burosumab as compared with those treated with conventional therapy:

- In the analysis of CL201, biweekly burosumab treatment up to Week 64 showed a 58% reduction in the RSS total score, more than [redacted] (Figure 17).
- In Study CL201, the RGI-C score at Week 64 was +1.62 following biweekly burosumab, compared [redacted] with conventional therapy in Study CL002 (median 102 weeks; Figure 18).

Figure 17. RSS Total scores after burosumab Q2W or conventional therapy

Figure 18. RGI-C Total scores after burosumab Q2W or conventional therapy

Comparisons of Rickets Healing with Conventional Therapy (Study CL002) vs Burosumab (Study CL201) Using Propensity Analysis Matching

Propensity Score Matching methods were used to address imbalances between baseline characteristics in the two studies in analyses of rickets assessments (RSS and RGI-C). It should be noted that these analyses were carried out using the whole population of Study 201 and therefore included those who received burosumab at both doses (Q2W and Q4W).

Study CL002 was designed to provide an estimate of the treatment effect of conventional therapy on rickets healing. However, the study has some limitations as a comparator group for Study CL201. It was a retrospective radiograph and chart review study rather than a prospective natural history cohort, [redacted]. In addition, Study CL002 has a [redacted] compared with that of Study CL201. A Propensity Score (PS) approach was used to generate a more comparable sample that would diminish the impact of selection bias on the comparison of the changes in rickets observed with burosumab and conventional therapy in Study CL201 and Study CL002 (Statistical Analysis Plan to Evaluate the Long-term Efficacy of Burosumab [UX023-CL201] Compared to Conventional Therapy [UX023-CL002] using Propensity Score Methodology). PS is defined as the conditional probability of being treated (burosumab) based on observed individual baseline covariates. A logistic regression model with the baseline characteristics and demographic variables RSS total score, age, and sex was used to estimate a PS value for each subject. The PS values were used for weighting or matching as described below. After weighting or matching, an ANCOVA model (with baseline RSS total score as covariate) was used to estimate the difference between groups. The following study populations were assessed:

- Study CL201 (burosumab group): All subjects; rickets data (RSS and RGI-C) collected at baseline and Week 64.
- Study CL002 (conventional therapy group): All subjects; rickets data collected throughout the study. When more than one radiograph pair was available for a subject, the pair with the duration between two radiographs taken closest to 64 weeks was selected. Radiographs deemed as growth plates fused or partially fused were excluded from the analysis.

Three different methods utilising PS were conducted to form comparable populations for the assessment of rickets improvement between the studies:

- Inverse Probability of Treatment Weighting (IPTW): Subjects were weighted by the inverse probability of receiving the treatment that they actually received. Subjects in the burosumab group received a weight equal to 1/PS, and subjects in the conventional therapy group received a weight equal to 1/(1-PS). The weights were then used in a weighted ANCOVA model with

covariates to compare rickets improvement between the studies. The IPTW method included all subjects from Study CL201 and Study CL002.

- Propensity Score Matching (PSM): subjects in the burosumab group and the conventional therapy group were matched based on closest PS values within a maximum tolerated difference (caliper). For the PSM methods, only subjects who were successfully matched were included in the comparison analysis.
    - PSM without replacement in control: subjects in the burosumab group were selected one by one to match to the closest subjects in the conventional therapy group within the caliper. Once matched, the subject in the conventional therapy group was removed from the pool for further possible matching. To account for the matching variability, the order of subjects in the burosumab group to be selected for matching was randomly sorted for 1000 times. The ANCOVA model was applied on each of the matched datasets to compare rickets improvement between the studies, and the results were combined for analyses.
    - PSM with replacement in control: Because the number of subjects in the conventional therapy group was less than in burosumab group, a with-replacement matching was also performed, i.e., a subject in the conventional therapy group could be selected to match multiple subjects in the burosumab group. Subjects in the conventional therapy group who were matched multiple times received higher weights based on the number of times matched. The weights were then used in the weighted ANCOVA model to compare rickets improvement between the studies.

The ANCOVA model included treatment group or study as a factor and baseline RSS total score as a covariate. The PS methods generated populations that were more comparable than the unweighted study populations (Table 30). The baseline RSS total scores for the overall study populations (unweighted) were [redacted] in Study CL201 and [redacted] in Study CL002 while the RSS total scores for the populations weighted by the IPTW approach were [redacted] in both the treatment groups. For the PSM without replacement analysis, RSS total scores for the burosumab and conventional therapy groups were [redacted] and [redacted], respectively; for the PSM with replacement analysis, RSS total scores were [redacted] and [redacted], respectively.

Table 30. Demographics and Baseline Characteristics in Study UX023-CL201 (Burosumab Treatment) vs Study UX023-CL002 (Conventional Therapy) in Propensity Score Analyses

	Study Assessment (not weighted)		Weighted by Inverse Probability of Treatment		Propensity Score Matching Without Replacement in Control		Propensity Score Matching With Replacement in Control	
	UX023-CL201	UX023-CL002	UX023-CL201	UX023-CL002	UX023-CL201	UX023-CL002	UX023-CL201	UX023-CL002
Sample size	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at Baseline (mean [SD] years)	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])
Sex (% female)	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Age when Conventional Therapy Initiated (mean [SD] years	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])
Baseline RSS								
Wrist score (mean [SD])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])
Knee score (mean [SD])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])
Total score (mean [SD])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])

a Burosumab subjects (Study UX023-CL201) receive a weight equal to 1/Propensity Score, and conventional therapy subjects (Study UX023-CL002) receive a weight equal to 1/(1-Propensity Score), where the propensity score is estimated from a logistic regression model with treatment group as response (1 = burosumab, 0 = conventional therapy), baseline RSS total score and age as covariates and sex as a categorical covariate.
b Mean sample size and results based on 1000 iterations of PS matching without replacement.
c A conventional therapy subject could be selected to match multiple treated subjects. Conventional therapy subjects matched multiple times received higher weights based on the number of times matched.
d All subjects from the intent-to-treat (ITT) analysis set were selected.
e All subjects from the radiograph analysis set were selected; when more than one radiograph pair available for a subject, the pair with the duration between two radiographs taken closest to 64 weeks is selected; radiographs that were deemed as growth plates fused or partially fused were excluded from the analysis.

Figure 19. Comparison of RSS Total Scores from Propensity Score Analyses in Study UX023-CL201 (Burosumab Treatment) and Study UX023-CL002 (Conventional Therapy)

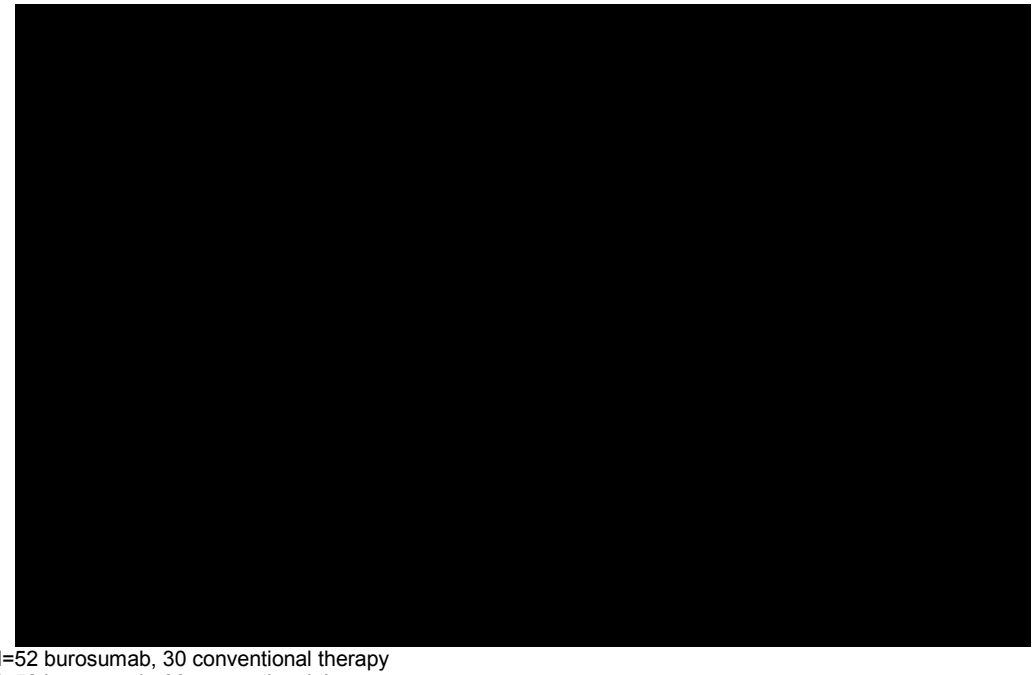
a N=52 burosumab, 30 conventional therapy
b N=52 burosumab, 30 conventional therapy
c N=29.7 burosumab, 29.7 conventional therapy (mean sample sizes based on 1000 iterations of PS matching without replacement)
d N=52 burosumab, 29 conventional therapy

Figure 20. Differences in RSS Total Scores (LS Mean ± SE) Between Study UX023-CL201 (Burosumab Treatment) and Study UX023-CL002 (Conventional Therapy) from Propensity Score Analyses

a N=52 burosumab, 30 conventional therapy
b N=52 burosumab, 30 conventional therapy
c N=29.7 burosumab, 29.7 conventional therapy (mean sample sizes based on 1000 iterations of PS matching without replacement)
d N=52 burosumab, 29 conventional therapy

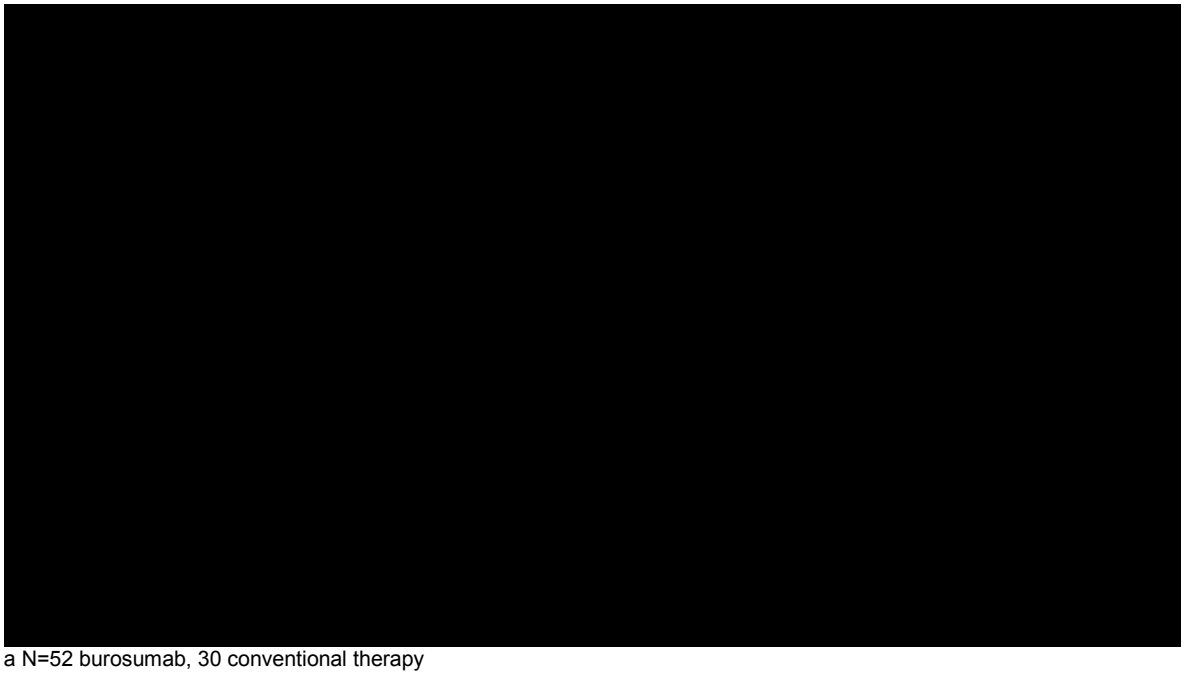
The burosumab group also showed greater increases in estimated RGI-C global scores than did the conventional therapy group in the observed data and for all three PS analyses (Figure 21 and Figure 22). These analyses demonstrate that burosumab treatment provides greater healing of rickets than conventional therapy.

Figure 21. Comparison of RGI-C Global Scores from Propensity Score Analyses in Study UX023-CL201 (Burosumab Treatment) and Study UX023-CL002 (Conventional Therapy)



a N=52 burosumab, 30 conventional therapy
b N=52 burosumab, 30 conventional therapy
c N=29.7 burosumab, 29.7 conventional therapy (mean sample sizes based on 1000 iterations of PS matching without replacement)
d N=52 burosumab, 29 conventional therapy

Figure 22. Differences in RGI-C Global Scores (LS Mean ± SE) Between Study UX023-CL201 (Burosumab Treatment) and Study UX023-CL002 (Conventional Therapy) from Propensity Score Analyses



a N=52 burosumab, 30 conventional therapy
b N=52 burosumab, 30 conventional therapy
c N=29.7 burosumab, 29.7 conventional therapy (mean sample sizes based on 1000 iterations of PS matching without replacement)
d N=52 burosumab, 29 conventional therapy

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The overarching goals of burosumab treatment of XLH are to improve skeletal health, improve functional ability and pain and prevent the immediate and long-term consequences of disease.

The efficacy of burosumab in paediatric subjects was primarily evaluated in Study CL201, a randomised, open-label, Phase 2 study in 52 prepubescent children aged 5 to 12 years old with XLH. An additional open-label paediatric study in 13 children with XLH aged 1 to 4 years (Study CL205) is ongoing to provide pharmacokinetic (PK), pharmacodynamics (PD), efficacy, and safety information in a younger population.

The burosumab clinical development programme in children was designed to specifically evaluate the effects of burosumab treatment on all the important clinical outcomes and manifestations of XLH, including skeletal health, growth, physical function, and patient-reported outcomes such as bone pain and functional disability, e.g., the ability to play sports, through restoration of phosphate homeostasis.

The findings from the historical reference study, CL002, which are consistent with the baseline data collected from Study CL201, [redacted].

Burosumab treatment substantially improves rickets:

- In patients aged 5 to 12 years of age (Study CL201), reduction in rickets severity was demonstrated at Week 40 in the overall study population by a 50% decrease in mean RSS total score, the primary efficacy endpoint ($p < 0.0001$) and was sustained at Week 64 (51% decrease in mean RSS total score, $p < 0.0001$). Rickets severity was reduced in the Q2W dosing group (the licensed dose) at Week 64 by 58% ($p < 0.0001$). This improvement is greater than [redacted] in Study CL002 (Figure 17). Similarly, burosumab treatment for 40 weeks and 64 weeks, the key time points of this study for efficacy analyses, resulted in healing of rickets as

assessed by RGI-C scores. The RGI-C score at Week 64 was +1.62 [redacted] with conventional therapy in Study CL002 (median 102 weeks). At Week 64, 57.7% of patients treated with burosumab Q2W had substantial healing of rickets, compared to [redacted]% treated with conventional therapy in Study CL002 (NNT=[redacted]).

- In XLH there is a continuum of severity as reflected by RSS scores, and this, along with varying degrees of treatment, results in a wide array of bone disease severity in the population studied. In CL201, patients with more severe rickets (higher RSS subgroup) tended to have [redacted].
- As would be expected, the greatest improvements in rickets were observed in the subgroup with more severe rickets at Baseline. In the Q2W higher RSS subgroup (N = 17), the RSS total score was substantially reduced from the Baseline by 71% ($p < 0.0001$) at Week 40 and by 62% ($p < 0.0001$) at Week 64. [redacted].
- Results from CL205 (children aged 1 to 4 years) show that burosumab treatment for 40 weeks substantially reduced rickets severity as assessed by RSS and RGI-C scores. RSS total score at Week 40 was reduced by 59% ($p < 0.0001$), whilst [redacted].

Burosumab treatment improves Growth Velocity

- Growth velocity increased by [redacted]% in the Q2W dosing group in Study CL201 (from [redacted]), with a corresponding LS mean change in standing height z-score of [redacted]. Increased growth velocity is consistent with improvement in rickets: as growth plate development is normalised, growth velocity resumes at the expected rate. The growth rate of children in the reference Study CL002 did not improve.

Burosumab treatment improves Functional Assessments and Patient-Reported Outcomes

- In patients aged 5 to 12 years of age (Study CL201), walking ability, as assessed by the 6MWT, increased with burosumab Q2W by [redacted]

[redacted]. 6MWT distance increased by [redacted] in a subgroup of subjects ([redacted]) with impaired walking ability (walking distance < 80% of predicted normal, regardless of rickets status at baseline). In this subgroup, mean 6MWT distance achieved normal values (≥ 80% of predicted normal).

- Sports/Physical Functioning LS mean scores showed improvements in the overall study population (Week 64: [redacted]). Similarly, Pain/Comfort LS mean scores showed improvements in the overall study population (Week 64: [redacted]).

Bone mineralisation

Burosumab improves serum phosphorus homeostasis in paediatric patients 1 to 12 years of age. Serum phosphorus improved in all patients in both studies, with mean levels close to or in the low end of the normal range. With Q2W burosumab treatment, serum phosphorus remains in or near the normal range for the majority of the dosing interval, thereby giving more physiological control, until a few days before the next subsequent dose. In contrast, oral phosphate is administered 4-5 times daily, with a peak in serum phosphorus after each administration and then a return to baseline levels. These improvements are so transient that physicians do not target any specific level of phosphate increase in their patients, and the overall increases are relatively small.

In Study 201, renal phosphate reabsorption (TmP/GFR) increased in all subjects to levels close to or into the normal range, showing clear evidence of an effect on the main pathophysiologic problem in XLH.

Serum $1,25(OH)_2D$ levels increased substantially. In children with XLH, the chronic low serum phosphorus levels lead to defective bone mineralisation and the two major pathologic consequences, osteomalacia, and rickets. A moderate increase in $1,25(OH)_2D$ is therefore beneficial (by improving intestinal phosphorus absorption), but as phosphate-calcium homeostasis improves with burosumab therapy, the regulation and metabolism of $1,25(OH)_2D$ appears to adjust to the new phosphate-calcium metabolism status. The increases in serum $1,25(OH)_2D$ levels suggest that the blocking action of burosumab on FGF23 restores 25-hydroxyvitamin D 1-alpha hydroxylase activity (Shimada et al. 2004).

Serum calcium, urinary calcium excretion, and iPTH did not show clinically meaningful changes, demonstrating restoration of phosphate homeostasis in a physiologic manner that maintains calcium metabolism.

Safety profile

Burosumab treatment in children was well tolerated and showed no adverse impacts on phosphate-calcium metabolism. No subject died or discontinued from CL201 or CL205 for any reason; all subjects continued treatment on study as of the data cut-off dates. Injection site reaction was the most common treatment-related adverse event, and all events were reported as mild (Grade 1) in severity. Other commonly reported

TEAEs were [redacted].

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The overarching goals of burosumab treatment of XLH are to improve skeletal health, improve functional mobility and pain and prevent the immediate and long-term consequences of disease through restoration of phosphate homeostasis. The clinical development programme in children demonstrated the effect of burosumab treatment on phosphate homeostasis and all the important clinical outcomes and manifestations of XLH, including skeletal health, growth, physical function, and patient-reported outcomes such as bone pain and functional disability, e.g., the ability to play sports.

The burosumab clinical development programme includes a broad patient population with XLH, ranging in age from paediatric patients one year and older to adults. The efficacy of burosumab in paediatric subjects was primarily evaluated in Study CL201, a randomised, open-label, Phase 2 study in 52 prepubescent children aged 5 to 12 years old with XLH. The evidence for burosumab is supported by Study 205 in children aged 1-4 years that showed a consistent effect in improving serum phosphorous, severity of rickets and lower limb deformity.

The efficacy of burosumab in paediatric subjects has, to date, been evaluated in open-label studies. The historical control study CL002 is a retrospective radiographic and medical chart review of subjects with XLH who have repeat historical radiographs when the subject was between 5 and 14 years of age. The study was conducted to provide reference group data to use for comparative analyses of rickets, growth, and lower extremity deformity in Study CL201 in a similar paediatric XLH population who had received long-term conventional therapy with oral phosphate and active vitamin D.

Study CL002 was designed to provide an estimate of the treatment effect of conventional therapy on rickets healing. However, the study has some limitations as a comparator group for Study CL201. It was a retrospective radiograph and chart review study rather than a prospective natural history cohort, and some subjects contributed multiple paired baseline and post-baseline radiographs. In addition, Study CL002 has a lower baseline RSS score compared with that of Study CL201. To address this, a Propensity Score (PS) approach was used to generate a more comparable sample that would diminish the impact of selection bias on the comparison of the changes in rickets observed with burosumab and conventional therapy in Study CL201 and Study CL002 (Section 9.8.2). For the observed data and for all three PSM analyses, the burosumab group showed greater decreases in

estimated RSS total scores and greater increases in estimated RGI-C global scores than did the conventional therapy group (Figure 19 to Figure 22). These analyses support the conclusion that burosumab treatment provides a greater reduction in rickets severity and greater healing of rickets than conventional therapy, within the limitations of these datasets.

The safety and efficacy of burosumab compared to conventional therapy in 60 paediatric patients aged 1 to ≤12 years with XLH who have confirmed evidence of rickets is being evaluated in a Phase III study (UX023-CL301). The primary efficacy and safety analysis is expected to be available [redacted].

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence presented addressed the questions posed in the scope. Burosumab administered at doses up to 2 mg/kg every two weeks for up to 64 weeks induced substantial healing of rickets, and improved lower extremity deformity and growth. These improvements occurred in subjects who had been receiving on average seven years of prior conventional therapy, demonstrating that burosumab can improve bone disease and growth above what was previously achieved in these patients while on long-term conventional therapy.

To better understand the significance of these changes over baseline, the rickets data from Study CL201 were also compared with findings from Study CL002, a retrospective study evaluating the effects of long-term conventional therapy in a comparable population of subjects (ages 5 to 14 years). Burosumab showed a greater effect than conventional therapy on rickets resolution, on improvements in lower extremity deformity as measured by the RGI-C, and on growth as measured by standing height z-score and percentile.

Improvements in bone disease as evidenced by assessments of rickets, lower extremity deformity, and height after burosumab treatment in XLH children were accompanied by improvements in the ability to walk and play sports and a reduction in pain. The ability to improve the skeletal and non-skeletal issues of XLH earlier in life may alter the natural progression of the disease and potentially ameliorate the long-term consequences and clinical complications during adolescence and adulthood. In addition, by improving bone mineralisation, burosumab may reduce the number of fractures and reduce the need for corrective surgery, although the impact on fractures and surgical intervention has not been assessed in the clinical trials to date.

The improvements in rickets, patient-reported pain and physical function, and walking ability will enable children suffering from XLH to do activities that are not readily afforded to them with conventional therapy. The improvements with burosumab

treatment will allow XLH children to engage in sports and other physical activities typical of a healthy child. These changes are expected to not only improve the patient's overall health-related quality of life, but also the quality of life of their family.

Importantly, treatment with burosumab has not been associated with hyperphosphataemia, nephrocalcinosis, hypercalciuria, or secondary/tertiary hyperparathyroidism, that may occur with conventional treatment.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The interventional study CL201 was conducted in nine centres in three countries, including three centres in the UK (Great Ormond Street Hospital, Birmingham Children's Hospital and Manchester) with 10 patients enrolled at these centres. Study 205 was carried out at three centres in the USA. Standards of care in these centres are comparable to those in all other clinical trial centres and are representative of the standard of care available in UK expert centres. However, it should be noted that in the UK, alfacalcidol may be used instead of calcitriol.

Most patients in studies CL201 and CL205 had been exposed to conventional therapy before burosumab i.e. second line use. However, in practice burosumab is also expected to be used as a first line therapy in younger patients who have not yet received treatment with conventional therapy.

[redacted]

[redacted]

Burosumab is expected to be indicated for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children and adolescents one year of age and older with growing skeletons. Patients aged up to around 17 to 18 years of age may therefore be eligible for treatment.

Paediatric studies have assessed burosumab in patients aged up to 12 years, however, there are currently no data in patients initiating burosumab treatment between 13 and 17 years of age. The underlying mechanism of XLH is the same throughout life, characterised by excess levels of circulating FGF23 that lead to increased urinary phosphate excretion, reduced $1,25(OH)_2D$ synthesis, and subsequent hypophosphataemia resulting in defective bone mineralisation. Due to its mechanism of action, it can reasonably be expected that burosumab will have an effect on bone mineralisation and clinical outcomes in all patients. Studies in adults with XLH have shown that burosumab treatment improves phosphate homeostasis, reduces pain and stiffness, and increases physical mobility (Ruppe et al., 2016a; Insogna et al., 2017).

In clinical practice, children will be treated from an early age. Early treatment with burosumab is anticipated to prevent lower extremity deformity and optimise growth potential in younger children. Continuation of treatment until skeletal growth ends at around 16 to 17 years of age would extend these benefits into adolescence and adulthood. Following introduction of burosumab, there will initially be a group of eligible patients that start treatment between 13 and 18 years of age. The extent to which burosumab is able to improve lower extremity deformity and growth in older children (above 12 years of age) with existing impairments has not been shown. However, the number of older children starting treatment with burosumab would steadily decline, and four to five years following introduction it would be expected that most patients would start treatment soon after diagnosis, which in most cases occurs under five years of age.

The recommended starting dose is 0.4 mg/kg of body weight and the normal maintenance dose is 0.8 mg/kg burosumab given every two weeks (maximum dose is 90 mg). As described in Section 9.6.1, the Q2W regimen is considered the optimal dosing regimen for burosumab. The dose of burosumab was titrated in Study 201 based on serum phosphorus levels. In the Q2W group, the curve of mean dose vs study visit plateaus at approximately 0.8 mg/kg starting at approximately Week 24. This dose of burosumab increased serum phosphorus in all subjects and resulted in meaningful improvements in rickets as well as growth, walking ability, physical functioning, and pain. Importantly, even at the highest doses administered (2.0 mg/kg Q2W or Q4W), burosumab has shown no off-target, dose-related risks in children with XLH. No hyperphosphatemia was observed at any time point with any burosumab dose (up to 2.0 mg/kg).

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable. It is expected that children and adolescents will be eligible as per the licensed indication.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

X-linked hypophosphatemia (XLH) is a rare, lifelong, chronically debilitating and deformative bone disease that profoundly impacts the affected individual's day to day functioning and health-related quality of life (HRQL).

Rickets, the hallmark of XLH in children, is associated with substantial skeletal deformities that can profoundly impact quality of life in the short and longer term. Skeletal deformities are associated with bone pain, joint pain, and joint stiffness that restrict range of motion, impair gait and diminish physical health status in children with XLH (Linglart et al., 2015b). The severity of rickets is associated with the level of disability and pain; in Study CL201 children with more severe rickets at baseline had, as assessed by POSNA-PODCI scores, greater impairment in sports and physical functioning, and experienced greater pain, than those with less severe rickets (Ultragenyx, 2017). Impaired walking ability was also associated with more severe rickets (the mean distance walked in the 6MWT at baseline was 33 metres less in a subgroup of children with a higher RSS group compared to children in a lower RSS group)(Ultragenyx, 2017). Impaired functionality and mobility, pain and ongoing health service utilisation from an early age can inhibit a child's participation in physical, educational and social activities.

People affected by XLH suffer lifelong disability and pain as the deformities developed in childhood become permanent. Bone and joint pain, that can be localised or diffuse, are the chief symptoms reported by adult XLH patients (Reid et al., 1989). Joint pain is frequently reported as being polyarticular and predominantly located in the hips, knees, and ankles. In adults, osteomalacia and skeletal deformities lead to development of early osteoarthritis and enthesopathy that also cause pain and continue to limit physical function, and have been shown to be associated with worse quality of life (Che et al., 2016). In adults with XLH, reduced bone quality increases the risk for non-traumatic pseudofractures (Shore et al. 2013a) that may impact on quality of life.

In a study of adults with XLH (n=24, aged 22 to 78 years) (Forestier-Zhang et al., 2016), 46% had moderate, severe or extreme problems with mobility and 67% had moderate, severe or extreme problems with pain or discomfort (as measured using the EQ-5D-5L). Similar results were observed in a larger study (n=150, aged 18 to 73 years), where most complained of joint and bone pain (97%), restricted range of motion (93%) and gait disturbance (83%). Significant pain was reported on all three outcome measures, [Mean SF-36 Bodily Pain score = 39.2), BPI (Mean Pain Severity

Score = 3.6), and WOMAC (Mean Pain Severity Score = 7.9)] and led to pain medication use by 70%, including 18% taking narcotics (Skrinar et al., 2015). A high proportion of adults also experience fatigue which is detrimental to HRQL (Che et al., 2016).

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

There are no studies that describe HRQL over the disease course of XLH. As described above, children with XLH are mainly affected by loss of mobility and pain due to skeletal deformities. The severity of skeletal deformities is associated with the degree of HRQL impairment. Skeletal deformities persist through adulthood. Adult patients with XLH have significant morbidity and complications with aging as a result of the continued weight bearing on lower extremities that have mechanical axis defects from childhood, including joint stiffness and mineralisation of tendons/ligaments (enthesopathy) (Carpenter et al., 2011; Beck-Nielsen et al., 2010; Reid et al., 1989). The combination of pain and stiffness resulting from enthesopathy substantially impair patient mobility and impact daily function. In the study by Che et al, increasing age was associated with worse quality of life (Che et al., 2016). Adults with XLH are likely to have both a lower quality-of-life and a sharper decline in quality-of-life associated with accelerated skeletal ageing process.

Treatment during childhood and the potential avoidance or reduction of skeletal deformities during a child's growth development period (before growth plates close) and represents a window of opportunity to prevent or minimise lifelong impairment. Hence the value of any treatment effect is not only manifest in the improvement of childhood quality of life but also in creating a better platform of bone health for adulthood, once the growth plates are closed.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.

- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The HRQL data captured in clinical trials does not meet the reference case for cost-effectiveness analysis.

The (POSNA-PODCI) was used in CL201 to measure the impact of bone and muscle conditions on daily activities and health-related quality of life. The SF-10 was also used in CL201. There is no valuation set for the POSNA-PODCI or the SF-10 to be able to derive utilities.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was conducted.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

The systematic literature review reported for the cost-effectiveness covered HRQL studies that would applicable to the economic analysis. See section 11 and section 17.3.

The search terms included QALY and utility which is not necessarily exhaustive, which may be a limitation of the search. However, given the rarity of XLH and the small body of literature, it is unlikely that the search has missed relevant studies reporting utilities in XLH patients.

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

Eight publications consisting of six studies were included in the review. An overview of the six studies are given below. None of the studies provided adequate data that could be used to inform the economic model because utilities were not presented, or could not be calculated, or because the data was reported by a mean utility rather than by severity.

1. As detailed in Section 7.1 and 10.1.1, a UK study measured quality of life using the EQ-5D-5L in 109 UK XLH adults. However, the study reported only a mean utility (0.648) with standard deviation (0.290) and a kernel density estimation demonstrating the utilities were bi-modal at around 0.1 and 0.8 (Forestier-Zhang et al., 2016). Therefore, the study could not be used to estimate utilities by health state for the model of interest. The authors noted that the utility scores were relatively high for adult XLH patients, and that they were higher than VAS scores, suggesting that the health utility estimated through the EQ-5D-5L instrument may be over-estimating HRQL and failing to capture the negative effects of these rare chronic conditions (Forestier-Zhang et al., 2016).
2. Zhang et al. reported EQ-5D-5L utilities across 82 patients with osteogenesis imperfecta, fibrous dysplasia and XLH from which utility scores for XLH patients were not reported (Zhang et al., 2016).

3. Ruppe et al. assessed and validated the use of the SF-36 questionnaire and McMaster Osteoarthritis Index in 26 US patients with XLH. No estimates of utilities by health state or severity were reported (Ruppe et al., 2014, 2016b).
4. Che et al. assessed quality of life using HAQ, RAPID3 and SF-36 in 52 XLH patients but results were not reported by severity; only mean values were presented. The authors noted that none of the utility instruments used are validated in XLH, and the utility scores were obtained 15-20 years ago and without recent normative values they may be invalid (Che et al., 2015, 2016).
5. Pinedo-Villanueva et al. assessed quality of life of UK patients using the SF-36 compared to patients with osteoarthritis and the general UK population. No data were collected according to disease severity or health state (Pinedo-Villanueva et al., 2017).
6. A cross sectional study of 32 adult XLH patients with PHEX mutations in France by Briot et al. assessed quality of life using HAQ, RAPID3 and SF-36. No estimates of utilities by health states were reported (Briot et al., 2014).

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

As detailed in section 9.7.2, most of the commonly reported treatment emergent adverse events in the clinical trials were typical for a paediatric population (e.g. nasopharyngitis, headache, vomiting, cough, pyrexia, upper respiratory tract infection) or frequent manifestations of XLH (e.g., arthralgia and pain in extremity). The adverse event which is likely to differ to standard of care is injection site reactions, which was the most common treatment-related adverse event. Injection site reactions are known to occur with subcutaneously administered protein therapeutics. However, all injection site reactions with burosumab were reported as mild (Grade 1) in severity and are therefore not expected to significantly impact HRQL.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Measuring HRQL in XLH presents some challenges because the condition is rare and many of the people affected are children whose parents and siblings may also be affected by the condition. It is possible that existing generic measures of HRQL may lack validity when used with XLH patients, and there are no validated condition specific measures in XLH. To generate utilities for the model, a study was conducted to describe patients with different severities of XLH and to use a standardised measure to estimate patients' HRQL, using the vignette methodology.

The vignette methodology involves developing vignette descriptions of the relevant health states based upon clinical data, literature review and/or interviews with clinical experts and patients (Lloyd et al., 2006). These vignettes can then be valued by members of the general public in a standard gamble or time trade-off exercise. However, it is difficult to determine the accuracy of the vignettes themselves and the general public rating the states may not fully recognise the relevance of aspects of the disease burden or may over emphasise the impact of certain issues. Therefore, as an alternative, to generate utilities for the model, the vignettes were used as a starting point and physicians were asked to imagine such a patient and consider their clinical experience to rate the impact of the health state on HRQL using the EQ-5D-5L.

Several steps were taken to avoid some of the limitations of previous vignette studies:

- The manifestation of XLH is heterogeneous and therefore not easily summarised in simple vignettes. Therefore, the clinical experts were encouraged to incorporate their own clinical experience to interpret the burden of the states. A series of detailed case studies were developed which included some clinical information as well as general information about functioning and symptoms. Physicians were permitted to provide a range of responses when they rated patients' HRQL, so they could indicate that a patient may have no problems or some problems on an EQ-5D dimension.
- It was decided that it would be preferable to derive the HRQL weights (or utilities) using standardised sets of preference weights from the EQ-5D. This means that the data are much more closely aligned with NICE requirements. Therefore, the study elicited preference weights using the EQ-5D-5L (Herdman et al., 2011) rather than undertaking time trade-off interviews.

Full details of the study are available in a report (Lloyd et al., 2018). The case histories describing XLH with different levels of functioning defined in terms of RSS and age were developed based on qualitative published studies and a series of five

interviews with experts. Twelve case histories were developed, including four severities of rickets (healed, mild, moderate and severe defined by RSS in line with the cost-effectiveness model) and three age bands (1-4 years, 5-12 years, 13 years and older). Validation and valuation of the chosen health states was conducted through another series of interviews with six UK clinical experts, including five clinical consultants and one endocrine bone nurse specialist. All the experts had over six years of experience in treating XLH patients and an average, each unit was treating about 15 children with XLH.

Each participant reviewed every case study. They were asked to imagine a child in the specified age range with that level or severity of XLH with the problems described. The description of very young children being in pain was queried with some experts indicating that very young children may have difficulties in recognising and expressing pain, therefore pain is not often reported in this age group. One expert also suggested that very young people with XLH may not feel any frustration or sadness as a result of XLH. For each age group, the physicians were asked to consider each state and were allowed to include the changes that they recommended when making their judgements i.e. the case study description was treated as a starting point for imagining such patients. For each case study, the physician was asked to judge the impact of disease on different aspects of HRQL as assessed by the EQ-5D-5L. The NICE preferred mapping was used to score the EQ-5D-5L data to generate EQ-5D-3L utilities (Van Hout et al., 2012). Two experts did not assess the severe state because they said that they never saw patients who were that bad.

The derived utilities (Table 31) showed a stepwise decline in HRQL with increasing severity of rickets. This decline is slightly greater for the older children (especially the teenagers). This is very much in line with the findings of the interviews where experts described how teenagers experience greater psychological and social impacts of the disease as well as the physical impacts.

Given the small sample of clinical experts that valued the health states, there is significant variation around the mean values. When considering how to account for this uncertainty in probabilistic and deterministic sensitivity analysis, it was considered that using the mean and standard deviations directly would lead to implausible simulations since ‘better’ health states could have lower utilities than ‘worse’ health states. To ensure the variation was accounted for whilst generating plausible simulated utilities, the moderate health state was used as an anchor and the values for other health states were calculated based on differences to the moderate state. The moderate health state was chosen since not all clinical experts valued the healed and severe health states.

The derived utilities for adolescents aged 13 and over have been assumed to also be applicable to adults. Since XLH is not associated with mortality, the derived utilities are used over the lifetime of the patient. Given utilities in the general population decline with age (Janssen and Szende, 2014), utilities multipliers by age have been

incorporated such that the healed health state is associated with a utility of 0.862 for a 18 year old and 0.765 for a 50 year old.

As detailed in Section 10.1.6, a UK study measuring quality of life using the EQ-5D-5L in 109 UK XLH adults of mean age 46 reported a mean utility of 0.648 (Forestier-Zhang et al., 2016). The model results indicate that patients treated with conventional therapy in the UK typically have severe, moderate or mild RSS scores. Applying the age-related utility multipliers gives an estimated utility for a 46-year-old of 0.511 for moderate patients. Thus, the derived utilities or the use of age-related utility multipliers may be underestimating the utilities of adults with XLH.

Table 31. Summary of quality-of-life values for cost-effectiveness analysis

Health state	Utility value	Standard deviation	Justification
Age 1-4			
Healed rickets	0.872	0.097*	In the absence of utilities from clinical trials or the published literature, a de novo analysis was conducted to identify utilities.
Mild rickets	0.774	0.094**	
Moderate rickets	0.685	0.175	
Severe rickets	0.545	0.065***	
Age 5-12			
Healed rickets	0.969	0.072*	In the absence of utilities from clinical trials or the published literature, a de novo analysis was conducted to identify utilities.
Mild rickets	0.757	0.119**	
Moderate rickets	0.613	0.170	
Severe rickets	0.521	0.084***	
Age 13 and over			
Healed rickets	0.862	0.105*	In the absence of utilities from clinical trials or the published literature, a de novo analysis was conducted to identify utilities.
Mild rickets	0.671	0.110**	
Moderate rickets	0.575	0.094	
Severe rickets	0.462	0.161***	
Utility multipliers			
Age 18-24	1.000	-	Utilities in the general population decline with age (Janssen and Szende, 2014), so the lifetime utilities were adjusted by age. The utility multipliers have been calculated from the general population mean utility by age.
Age 25-34	0.992	-	
Age 35-44	0.966	-	
Age 45-54	0.930	-	
Age 55-64	0.888	-	
Age 65-74	0.851	-	
Age 75+	0.781	-	
Adverse events	**Disutility value**	**Confidence interval**	**Justification**
Injection site reaction	None	None	See Section 10.1.8; in the clinical trials, all injection site reactions with burosumab were reported as mild (Grade 1) in severity and are therefore not expected to significantly impact HRQL.

*This is the standard deviation around the difference between the healed and mild states
**This is the standard deviation around the difference between the mild and moderate states
***This is the standard deviation around the difference between the moderate and severe states

It is acknowledged that the method used here to develop states and capture utilities is not the optimal source of evidence. The study was undertaken in the context that the best resource available at the time of submission was the expertise of clinical experts, who could draw on their experience of treating people with XLH. A more appropriate proxy for assessing HRQL would be a parent or primary carer because they know the patient better and spend more time with them. Consequently, to validate the utilities derived using clinical experts, an ongoing study will report

findings from a survey of parents of children affected by XLH. Results of this subsequent study will be reported during the NICE appraisal of burosumab and will be made available to the committee at the earliest convenience.

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

See Section 10.1.9.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

During derivation of utilities, clinical experts indicated that the variability of patient experience by health state is correlated with age. Consequently, during the derivation of utilities, HRQL was categorised into three age groups for each health state. Age-related utility multipliers based on the general population have been included for adult patients to reflect the diminishing HRQL by age.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

As a heterogeneous condition, it is likely that the simplification of the health states does not capture the variability of the patient experience at each severity. However, the use of mean utilities derived from clinical experts considering their range of patients should account for this to some extent.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The clinical trials did not capture HRQL that could be used in the analysis. Two studies conducted by the company have included SF-36, but neither included RSS or other measures of severity, so health state utilities could not be generated (Linglart et al., 2015b; Ruppe et al., 2014). No HRQL data was identified in the literature that could be utilised for the model.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable - quality of life values were determined by health state only.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Utilities have been generated for three age groups. After the age of 13, HRQL is assumed to decline at the same rate as the general population. However, in practice, the manifestations and impact of XLH in adulthood might be greater, particularly if the patient had severe rickets / manifestations carrying over from childhood as this would have a greater impact on the ageing skeleton. Therefore, patients' HRQL might decline faster in the more severe health states as the skeleton is subject to early aging.

A prospective tertiary centre study evaluating HRQL associated with skeletal symptoms in 57 XLH patients identified that aging was strongly associated with an increased prevalence of skeletal deformities (Che et al., 2016). If a patient had more skeletal deformities in childhood, this may result in further problems in adulthood which would imply a reduced HRQL. Given that burosumab reduces skeletal deformities in childhood, then it may be expected that by assuming HRQL remains constant over time may be underestimating the number of incremental QALYs associated with burosumab.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

No.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The anticipated indication for burosumab is for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with *growing skeletons*. UK growth charts indicate that growth plateaus at age 16 years old in females and 17 years old in males which correlates with closure of the epiphyses in the long bones and (Royal College of Paediatrics and

Child Health, 2013b, 2013a) which provides a reasonable estimation of the age at which treatment is likely to be stopped. Based on this UK growth data, in the cost-effectiveness model, girls are assumed to remain on treatment up to 16 years of age (inclusive) and boys are assumed to remain on treatment until 17 years of age (inclusive).

This stopping rule will not require any additional monitoring.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

A systematic literature review of the economic and health economic evidence of XLH was conducted.

Details of the databases searched are provided in Appendix 17.3.

Studies in 'grey literature' such as conference abstracts, presentations, research posters, letters, online posts, magazine or newspaper articles were considered provided that the foundation for the reported findings is a study with a publicly available research protocol or is a study published in full manuscript form as an academic resource (Working Paper, Peer-Review Journal or in a book).

A review author independently assessed the titles and abstracts of all citations identified by the literature search strategy. All irrelevant titles were excluded, and full-text papers were obtained where titles were deemed to be relevant. Where there was uncertainty as to the eligibility based on title and abstract alone, the full text was reviewed. If more information was required to determine the articles eligibility the reviewer sought to identify any additional associated articles. If there were no such articles available, the author was contacted for additional information. Where there was uncertainty as to the relevance of the information presented in the articles, a second independent researcher reviewed it in a duplicate, independent and unblinded manner and a consensus was arrived at.

Data extracted for such economic studies included data on the participants in the sample (e.g. cohort age), location of patients (e.g. North America, Europe), sample size and research design (e.g. prospective or retrospective, whether controlled, method of recruiting participants), type and frequency of treatment, health and cost outcomes, how these were established or validated (e.g. statistical tests), the

perspective taken for costing (whether from the patient's, provider's, organisation's or society's) and the justification for the cost perspective if one was provided.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

A broad inclusion criterion was used for patient inclusion, leaving the definition of XLH and method of establishing a diagnosis (e.g. physician or different medical professional with an objective diagnostic criterion) to be defined by the authors of each article. However, for research reports involving multiple cases or families the studies must state an exact diagnostic criterion of establishing XLH to be included. There were no restrictions on participant demographics (e.g. age, sex), geographic characteristics (e.g. where they live or work), social factors (e.g. education level, 'at-risk' groups), population characteristics and research settings (e.g. counties where the research took place, University or clinical settings) or method of recruiting participants (e.g. XLH patients chosen at random or have volunteered to be study participations).

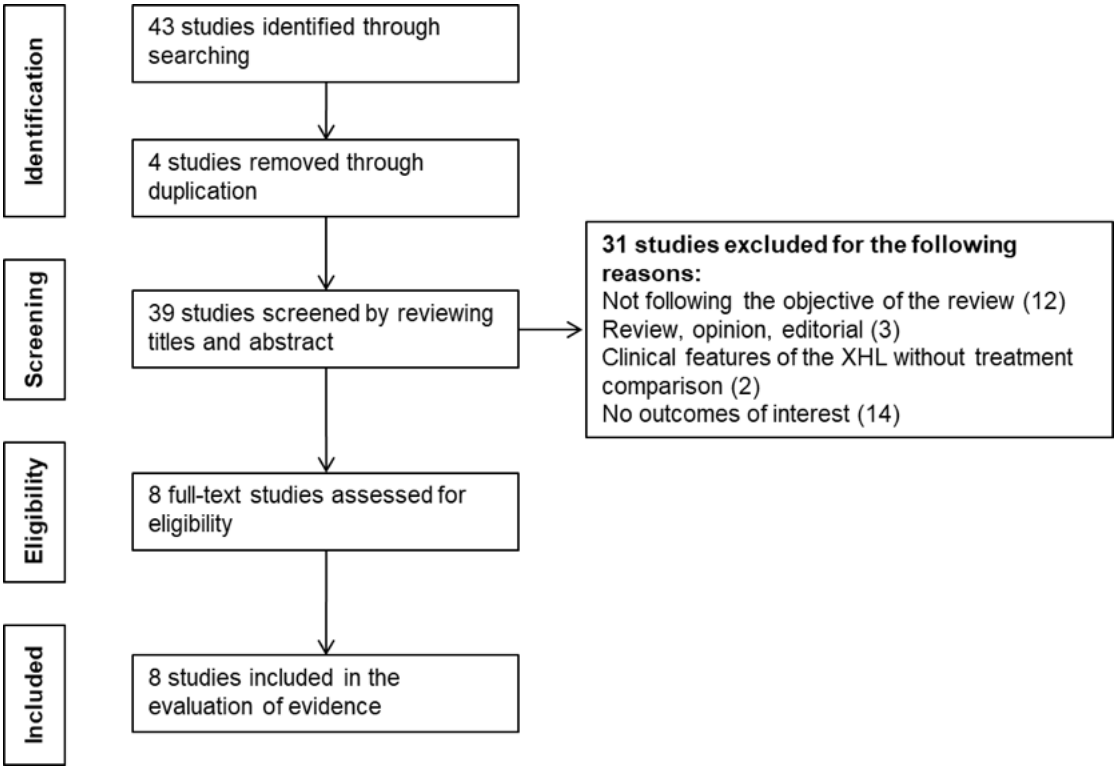
Table D11.1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Child or adult subjects with XLH
Interventions	Any
Outcomes	Cost-effectiveness, cost-utility, unit costs, resource use, utilities, generic measures of quality of life
Study design	Cost-effectiveness, cost utility, cost-benefit, cost consequences, cost of illness, or budget impact
Language restrictions	English
Search dates	Up to October 2017
Exclusion criteria	
Population	Populations other than XLH
Interventions	No restriction
Outcomes	No restriction
Study design	No restriction
Language restrictions	Not in English
Search dates	No restriction

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

A PRISMA diagram is presented in Figure 23.

Figure 23: PRISMA diagram of economic SLR



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

One economic study was identified in the review (Forestier-Zhang et al., 2016). This study reported a UK cost-utility simulation of 109 patients which included 24 UK XLH patients, examining various scenarios for the maximum willingness to pay threshold based on observed utility values. The study was not an economic evaluation in the sense that it was not an economic model and did not consider resources other than hypothetical treatment costs. Consequently, the evaluation is not relevant to the burosumab analysis and cannot be used to inform the cost-effectiveness evaluation.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Not applicable.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The patient population in the cost effectiveness analysis is consistent with the licensed indication for burosumab and NICE scope. That is, patients with XLH with radiographic evidence of bone disease, aged one year and older with growing skeletons. The distribution of ages in the patient cohort at baseline is aligned to the clinical trials for burosumab.

Treatment with burosumab is expected to be continued throughout growth of the skeleton. UK growth charts indicate that growth plateaus at age 16 years old in females and 17 years old in males (Royal College of Paediatrics and Child Health, 2013b, 2013a). Thus, the modelled duration of treatment is to age 16 years in females and 17 years in males (inclusive).

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

In line with the scope, the comparator is established clinical management, referred to as standard of care (SoC).

As detailed in Section 8.2, current treatment aims at improving growth, bone or joint pain, and preventing skeletal deformities caused by rickets. Conventional therapy consists of systematic phosphate supplements and active Vitamin D analogues. Phosphate is administered using oral phosphate supplements, while vitamin D is given in the form of alfacalcidol A or calcitriol oral or injectable therapies.

Doses of Vitamin D analogues and phosphate used in practice may vary. Carpenter et al., recommend a calcitriol dosage of 20 to 30 ng/kg/day in 2-3 divided doses, and an elemental phosphorus dose of 20 to 40 mg/kg/day (in 3-5 divided doses), acknowledging that some children require more, while some do well with less (Carpenter et al., 2011). Generally, in clinical practice, alfacalcidol is used rather than calcitriol. Clinical expert opinion indicates that alfacalcidol is given at approximately double the dose recommended for calcitriol due to the difference in half-life.

For children, treatment is initiated at the time of diagnosis and continued until long bone growth is complete. Almost all children with XLH require therapy until growth is complete, although the effectiveness on the skeleton is variable, and surgery may be necessary to correct lower extremity deformities.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

A Markov model has been constructed on the basis of the primary end point of the CL201 clinical trial – rickets severity, which is the hallmark clinical manifestation of XLH. Rickets is a major pathologic consequence in the bone and commonly manifests as limb deformities and short stature.

Based on the natural history of XLH disease progression and variation in resource utilisation, the Markov model tracks patients as they progress through the series of mutually exclusive health states graded on the Rickets Severity Score (RSS) (Figure 24):

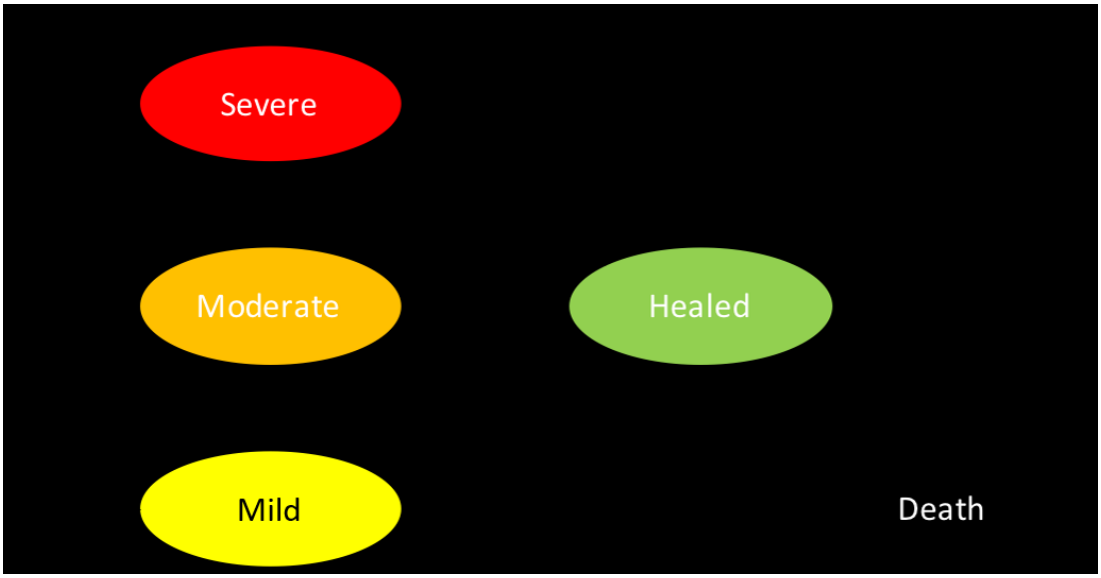
- Mild rickets (RSS of 0.5 or 1.0)
- Moderate rickets (RSS of 1.5 or 2.0)
- Severe rickets (RSS of 2.5 or more)
- Healed rickets (RSS of 0)

To calculate age-related treatment and health state costs, 12 tunnel states were included for each state to track patients by age.

Death is an additional absorbing health state within the model. Since XLH is not associated with premature death, only age-specific background mortality was included. The background mortality rates were derived from the national life tables for England, 2014-16 (Office for National Statistics, 2017).

Patients can move freely between health states. The simulated cohort transition between health states over a fixed 1-year cycle period including half-cycle correction.

Figure 24. Markov model state structure



All health states can result in death

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The spectrum of disease severity is expressed in the RSS scores, and associated health states. No cost-effectiveness model has been published previously on XLH. Therefore, *a de novo* Markov model structure was developed in Microsoft Excel, where the clinical pathway and the subsequent long-term outcomes of patients with XLH was simulated.

A Markov model was deemed appropriate since XLH is a progressive heterogeneous disease, it seemed fit to adapt multiple Markov model health states that would simulate patients' worsening of XLH.

As radiographic severity can be related to clinical manifestations, Makitie et al assumed that the disease could be stratified by different degrees of severity (Mäkitie et al., 2003). The degree of rickets was graded by Makitie et al as normal,

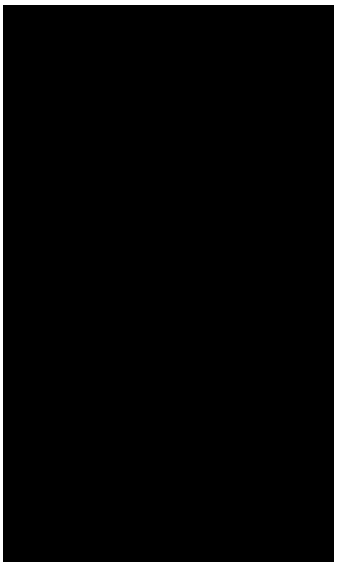
normal/mild, mild, mild/moderate, moderate, moderate/severe, or severe rickets. This would indicate 7 health states. However, clinical expert opinion indicated that these seven different states did not necessarily have different economic or HRQL consequences. To better define patients with different clinical manifestations that require different healthcare utilisation, the health states were simplified to healed, mild, moderate, or severe based on RSS scores.

In valuation of patients HRQL, there was a consensus from clinical experts that stratifying patients according to these definitions of healed/ mild/ moderate/ severe was reasonable and that a worse severity (as defined by the health state) reflected the reduced quality of life of the patient. Thus, the health states chosen correlate with HRQL.

In addition, patients residing in the healed rickets health state generally accrue costs for surveillance and drug treatment. Patients with mild rickets experience additional pain and mobility problems, and associated costs. In the moderate and severe health states, orthopaedic intervention costs are seen in addition to costs from less severe health states. Thus, the model health states also generally correlate with cost.

Within the model, a patient's change in RSS was used as a proxy for the change in their overall XLH health status. For example, a RSS of 0.5, classified in the model structure as mild rickets, would imply the patient has mild XLH. Whilst rickets is the hallmark manifestation of XLH, given the heterogeneity of the condition there is a chance that someone with mild rickets may have more severe additional manifestations. [redacted]. Thus, rickets and the RSS do not necessarily capture all aspects of XLH symptoms and progression, but the RSS measure provides a reasonable indication of patients' health status which is why rickets severity was also the primary endpoint of the CL201 study. It is acknowledged that basing a model structure on the RSS is a limitation of the analysis.

Figure 25: Leg bowing in a subject with baseline RSS Score of zero in CL201



RSS provides an indication of patients' status at any one time and is therefore an appropriate basis for health states. However, it is scored independently (not compared to previous x-rays) which may result in inconsistencies in RSS scores between time points that are used to generate transition probabilities. The RSS is complemented in CL201 by the RGI-C which provides a comparison to baseline (previous x-rays). RGI-C scores are positive if there is an improvement (+3 if healed, -3 if worsening) compared to baseline. Whilst the RGI-C gives an indication of change in status, it does not indicate the patient status so cannot be used to generate health states.

During CL201, no patients' rickets worsened according to the definitions of healed/ mild/ moderate/ severe using the RSS scores. In addition, no patients' rickets worsened at Week 64 in the study, as all RGI-C scores were positive (Table 32). Therefore, whilst the RSS is a limited measure, it captures the treatment effect as also measured by the RGI-C.

Table 32. Comparing RSS and RGI-C between Week 0 and 64 in CL201

RSS change	n	RGI-C mean	RGI-C min	RGI-C max
Healed > Healed	1	[redacted]	[redacted]	[redacted]
Mild > Healed	4	[redacted]	[redacted]	[redacted]
Mild > Mild	4	[redacted]	[redacted]	[redacted]
Moderate > Healed	1	[redacted]	[redacted]	[redacted]
Moderate > Mild	3	[redacted]	[redacted]	[redacted]
Moderate > Moderate	3	[redacted]	[redacted]	[redacted]
Severe > Healed	1	[redacted]	[redacted]	[redacted]
Severe > Mild	6	[redacted]	[redacted]	[redacted]
Severe > Moderate	3	[redacted]	[redacted]	[redacted]

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Assumptions made in the model are listed below:

- After age 17 (the closure of a patient's growth plates), the patient will stay in the same health state (mild/moderate/severe/healed) lifelong on the assumption that if the patients' skeleton has stopped growing, they are likely to not have further significant skeletal changes.
- Only patients in the moderate or severe health state are eligible to receive orthopaedic treatment. In the absence of data for each health state, the orthopaedic intervention frequency was assumed to be the same for moderate and severe.
- Only patients in the mild, moderate or severe health states receive pain and mobility costs (consisting of physiotherapy). In the absence of data for each health state, the proportion of patients receiving physiotherapy was assumed to be the same for the mild, moderate and severe health states.
- All patients receive the same surveillance costs regardless of health status.
- Background mortality is assumed to be the same as in the general population.
- In the absence of clinical data for 13 to 17-year olds, transition probabilities for 5 to 17-year olds are based on clinical data on 5 to 12-year olds (CL201).
- One-year transition probabilities based on 64-week clinical data for 5-12-year olds have been extrapolated up to age 17.
- One-year transition probabilities based on 40-week clinical data for 1-4-year olds have been extrapolated up to the age of four.
- The weight of children with XLH is assumed to the same as the median weight of UK general population. This may be a conservative assumption given the typical short stature of children with XLH.

12.1.6 Define what the model's health states are intended to capture.

The model tracks patients as they progress through the series of mutually exclusive health states based on the disease model of rickets. While severity of rickets doesn't necessarily capture all aspects of XLH symptoms and progression, the RSS measure provides a reasonable indication of patients' status which is why it was also the primary endpoint of Study CL201.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Table 33. Key features of model not previously reported

Factor	Chosen values	Justification
Time horizon of model	Lifetime	As per the reference case, the lifetime horizon was chosen to capture all future consequences of treatment with burosumab. The impact of changing skeletal deformities with burosumab is likely to benefit an XLH patient's quality of life throughout the rest of their lifespan.
Discount rate	1.5%	The NICE methods guide indicates that in cases when treatment restores people who would have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered. Following treatment with burosumab, the model indicates that most patients remain in the healed health state for life. Consequently, these patients are expected to have a near-normal full health. Therefore, a discount rate of 1.5% is used for costs and outcomes in the base case analysis. Discount rates of 3.5% are explored in sensitivity analysis.
Perspective (NHS/PSS)	NHS and PSS	As per the reference case.
Cycle length	1 year	Clinical data was reported at 40 weeks and 64 weeks, so a midpoint of 52 weeks was used.
Half-cycle correction	Included	A half-cycle correction is included to account for the imprecision in the cost and outcomes as a consequence of using one-year cycle length.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

As detailed in section 9, the clinical evidence for burosumab consists of:

- CL205 – 40 weeks: Treatment of burosumab in 1-4-year olds with XLH (n=13)
- CL201 – 64 weeks: Treatment of burosumab in 5-12-year olds with XLH (n=52 with all doses, n=26 with the licensed bi-weekly administration regime)

- UK chart review: RSS data from three of the largest UK XLH centres with median follow-up of approximately 5 years (n=34)
- CL002 – 2 years, on average: Case record survey that acts as a comparison cohort for CL201 (n=[redacted])

The following sections outline how these data were used for demographics, the baseline health state distribution, transition probabilities and adverse events.

Gender and weight

The gender of patients in the model is derived from the CL205 and CL201 studies. Note that CL201 included two doses of burosumab of which only one is expected to receive marketing authorisation. However, all CL201 data was used for baseline characteristics in the model because the patient population was the same; from baseline the patients were randomly allocated to a treatment dose. Four of the 13 patients included in CL205 were female. Twenty eight of the 52 patients in CL201 were female. Thus, overall, 49.2% of the population was female.

Weight estimates are required to calculate the intervention and comparator dosage for children and adolescents. The weight by age and gender for ages 1 to 17 years was taken from UK growth charts (Royal College of Paediatrics and Child Health, 2013b, 2013a) (Table 34). In the base case analysis, the median (50^{th} percentile) weight for children is used. However, given the typical short stature of patients with XLH, the 25^{th} percentile weight data is explored in sensitivity analysis.

Table 34. UK weights by age group and gender

	Percentile Weight (kg)			
	Males		Females	
Age	25th	50th (base case)	25th	50th (base case)
1	9.0	9.8	8.2	8.9
2	11.2	12.2	10.5	11.4
3	13.2	14.4	12.8	13.8
4	15.0	16.2	14.7	16.0
5	17.1	18.8	16.9	18.2
6	19.0	20.8	18.8	20.5
7	21.0	23.0	21.0	23.0
8	23.2	25.8	23.2	26.0
9	25.8	28.4	26.0	29.0
10	28.2	31.5	28.8	32.1
11	31.0	35.0	32.0	36.0
12	34.0	38.2	35.8	40.0
13	38.2	43.0	40.2	45.1
14	43.9	49.2	45.0	50.0
15	49.2	55.2	48.2	53.2
16	54.8	61.0	50.3	55.3
17	58.8	64.5	51.9	56.8

Baseline age and health state distribution

This distribution of the patients over the health states at baseline at the start of the model was matched to the baseline distribution of patients upon enrolment to study CL201 and study CL205 (Table 35). All CL201 data was used for baseline characteristics in the model; it was not limited to the 26 patients that received the dose expected to be licensed. The associated distribution of patients at model baseline is shown in Table 36. Most patients (>70%) had moderate or severe rickets at baseline according to the RSS.

Table 35. Numbers of patients in each health state, by age, at model baseline using CL205 and CL201

Age	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**
Severe	2	2	4	0	0	0	0	7	4	5	3	1	28
Moderate	1	1	0	2	2	3	2	1	3	2	1	0	18
Mild	0	1	0	0	3	2	1	1	5	1	1	1	16
Healed	0	0	0	0	0	0	0	1	2	0	0	0	3
Total	**3**	**4**	**4**	**2**	**5**	**5**	**3**	**10**	**14**	**8**	**5**	**2**	**65**

Table 36. Distribution of patients in each health state, by age, at model baseline using CL205 and CL201

AGE	1	2	3	4	5	6	7	8	9	10	11	12	Total
Severe	3%	3%	6%	0%	0%	0%	0%	11%	6%	8%	5%	2%	43%
Moderate	2%	2%	0%	3%	3%	5%	3%	2%	5%	3%	2%	0%	28%
Mild	0%	2%	0%	0%	5%	3%	2%	2%	8%	2%	2%	2%	25%
Healed	0%	0%	0%	0%	0%	0%	0%	2%	3%	0%	0%	0%	5%
Distribution	**5%**	**6%**	**6%**	**3%**	**8%**	**8%**	**5%**	**15%**	**22%**	**12%**	**8%**	**3%**	**100%**

Transition probabilities

Transition probabilities for burosumab treated patients are calculated from RSS data from the Phase II clinical trials (Study CL201 and CL205). Transition probabilities for SoC were derived from the UK chart review in the base case and Study CL002 in sensitivity analysis.

For patients aged 1-4 years old, transition probabilities for burosumab are based on the 0 to 40-week RSS progression data from patients in the study CL205 (Table 37). There were no observations for patients healed at baseline so probabilities of transition out of the healed state could not be derived. However, since no patients aged 1-4 transitioned to the healed state, the lack of data for the healed state does not impact the model.

For patients aged over five years, transition probabilities are based on the 0 to 64-week RSS progression data from patients in the CL201 study (Table 39). In this study, 50% of the cohort were treated with a licensed dose of burosumab once every 2 weeks, the other 50% of the cohort received a once monthly licensed dose of burosumab. Only the data for patients receiving the bi-weekly dose were used to generate transition probabilities since this is the expected licensed dose.

Transition probabilities for the control group were calculated from a review of patient charts in three leading UK centres. This data provides many more observations and is more representative UK cohort than Study CL002 (which included all US patients). However, it was not matched to exactly the same inclusion and exclusion criteria as Study CL201 and therefore it is uncertain if it matches the burosumab-treated population as well. The UK data is real world data with observations with inconsistent time points. Observations more than 3 years part were excluded, and two approaches were used to account for missing data:

- Rounding time points to the nearest year and imputing missing years (Table 43). For example, if RSS=1 at Year 1 and RSS=2 at Year 3, then it was estimated that at Year 2 RSS=1.5.
- Rounding time points to the nearest year at assuming last observation carried forwards (LOCF) for missing years (Table 41). For example, if RSS=1 at Year 1 and RSS=2 at Year 3, then it was estimated that at Year 2 RSS=1.

LOCF is considered to be the more conservative approach so this is used in the base case analysis. Two-year RSS progression data taken from Study CL002 with patients aged 5-12 was considered in sensitivity analysis (Table 45).

From the 40-week / 64-week / 2-year / 3-year observations, one-year transition probabilities have been derived using the following four steps:

1. Generate 40-week, 64-week, two-year and three-year transition probability matrix
2. Convert the probabilities to rates and annualise, using

   rate = – ln(1 – probability) / time
3. Convert the annualised rates back to transition probabilities, using

   probability = 1 – exp(– annualised rate)
4. Proportionally adjust the probabilities such that each row of the transition probability matrix equates to one.

The calculated transition probabilities used in the model for burosumab are displayed in Table 38 (burosumab 1-4 years old), Table 40 (burosumab 5 years and older), Table 42 (standard of care, base case), Table 44 (standard of care, scenario 1) and Table 46 (standard of care, scenario 2).

Patients transition between health states until they stop growing i.e. reach adulthood. In the model patients are therefore bound to their current health-state from the age of 18 for the remainder of their lifespan.

Table 37. Observation matrix for burosumab, age 1 to 4 years old (Study CL205, baseline to week 40)

Week 40 / Baseline	Mild	Moderate	Severe	Healed	Total
Mild	1	0	0	0	1
Moderate	2	2	0	0	4
Severe	4	4	0	0	8
Healed	0	0	0	0	0

Table 38. Transition matrix for burosumab, age 1 to 4 years old using Study CL205 data

	Mild	Moderate	Severe	Healed
Mild	100%	0%	0%	0%
Moderate	50%	50%	0%	0%
Severe	50%	50%	0%	0%
Healed	0%	0%	0%	0%

Table 39. Observation matrix for burosumab, age 5 to 12 years old (Study CL201, baseline to week 64)

Week 64 / Baseline	Mild	Moderate	Severe	Healed	Total
Mild	4	0	0	4	8
Moderate	3	3	0	1	7
Severe	6	3	0	1	10
Healed	0	0	0	1	1

Table 40. Transition probability matrix for burosumab, age 5 and older using Study CL201 data

	Mild	Moderate	Severe	Healed
Mild	50%	0%	0%	50%
Moderate	43%	43%	0%	14%
Severe	60%	30%	0%	10%
Healed	0%	0%	0%	100%

Table 41. Observation matrix for standard of care (UK chart review, 1-year observations assuming LOCF for missing data)

Year n+1 / Year n	Mild	Moderate	Severe	Healed	Total
Mild	31	5	4	4	44
Moderate	9	35	5	2	51
Severe	5	11	75	4	95
Healed	1	1	2	10	14

Table 42. Transition probability matrix for standard of care using UK chart review (assuming LOCF for missing data)

	Mild	Moderate	Severe	Healed
Mild	70%	11%	9%	9%
Moderate	18%	69%	10%	4%
Severe	5%	12%	79%	4%
Healed	7%	7%	14%	71%

Table 43. Observation matrix for standard of care (UK chart review, 1-year observations with missing data imputed assuming linear change)

Year n+1 / Year n	Mild	Moderate	Severe	Healed	Total
Mild	12	5	4	3	24
Moderate	7	14	5	2	28
Severe	4	10	33	3	50
Healed	1	1	2	1	5

Table 44. Transition probability matrix for standard of care using UK chart review (missing data imputed assuming linear change)

	Mild	Moderate	Severe	Healed
Mild	51%	21%	16%	12%
Moderate	24%	52%	17%	7%
Severe	7%	19%	68%	6%
Healed	20%	20%	40%	20%

Table 45. Observation matrix for standard of care (Study CL002, baseline to Year 2)

Year 2 / Baseline	Mild	Moderate	Severe	Healed	Total
Mild	8	2	1	3	14
Moderate	5	7	1	0	13
Severe	0	2	0	0	2
Healed	1	1	0	0	2

Table 46. Transition probability matrix for standard of care using Study CL002 data

	Mild	Moderate	Severe	Healed
Mild	61%	13%	6%	20%
Moderate	37%	56%	7%	0%
Severe	0%	100%	0%	0%
Healed	50%	50%	0%	0%

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Yes, costs and clinical outcomes extrapolated beyond the study follow-up period. Data collected up to 40 weeks in Study CL205 has been used to generate transition

probabilities for patients aged between 1 and 4. Such that, if a patient starts at age 1 in the model, the 40-week data are extrapolated for 4 years until they reach 5 years old. Data collected up to 64 weeks in Study CL201 were used to generate transition probabilities which are extrapolated up to the end of growth.

The primary objective of burosumab therapy in XLH patients is to improve serum phosphate, which is expected to improve physical function in patients at all ages, healing or substantially reducing rickets severity leading to increased growth, improved quality of life and mobility through the restoration of normal or near-normal phosphate homeostasis. The normalisation of serum phosphate is sustained on burosumab. Consequently, it is reasonable to assume that healing rickets will be sustained over the long term.

As well as healing rickets will improve bone quality during childhood which will mean adults will have improve bone quality with lower chance of complications such as fractures and pseudo fractures and the resulting disabilities.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No, intermediate outcome measures were not used in the model.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

As discussed in 10.1.8, most of the commonly reported treatment emergent adverse events in the clinical trials were typical for a paediatric population or were frequent manifestations of XLH, with the exception of injection site reactions. Injection site reactions are known to occur with subcutaneously administered protein therapeutics. Treatment-related injection site reactions occurred in 10 of 26 patients in CL201 and 1 of 13 patients in CL205. Thus, the overall incidence was 11 in 39 patients (28.2% patients). The duration of most injection site reactions was approximately 1 to 2 days and the majority of subjects that experienced an injection site reaction had only one or two occurrences. In addition to the short duration, all injection site reactions were reported as mild in severity and are therefore not expected to significantly impact costs or HRQL. Thus, adverse events are included in the model but no costs or disutilities are applied in the base case analysis. In sensitivity analysis, the impact of

including costs and disutilities associated with adverse events are explored, using an incidence rate of 28.2%.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Clinical experts that provided or validated resource use inputs (see Section 12.3.3) were given an overview of the model structure and invited to comment on the appropriateness of the chosen structure. The clinical experts deemed that the model structure was reasonable in light of the clinical data available. Further external validation is ongoing.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission.

Table 47. Summary of variables applied in the cost-effectiveness model

Variable	Value	Range and distribution	Source
Baseline age and severity distribution	See Table 36	Dirichlet distribution using observed values in Table 35.	Pooled baseline distribution from CL201 (all doses) and CL205
% male	50.77%	An arbitrary 10% variation is explored in one-way sensitivity analysis.	Pooled data from CL201 (all doses) and CL205
Weight	Median weight of the general population in Table 34	A lower weight at the 25% percentile (also Table 34) is tested in sensitivity analysis	(Royal College of Paediatrics and Child Health, 2013b, 2013a)
Transition probabilities – treated group, age 1-4 years	See Table 38	Dirichlet distribution using observed values in Table 37.	CL205 study
Transition probabilities – treated group, age 5 years and older	See Table 40	Dirichlet distribution using observed values in Table 39.	CL201 study
Transition probabilities – control group, all ages	See Table 42	Dirichlet distribution using observed values in Table 41. An alternative approach to missing data imputation is used in a scenario analysis. A further scenario analysis uses data from Study CL002.	UK chart review

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There is no specific healthcare resource group (HRG) or payment by results (PbR) code for XLH. Relevant HRG codes and PbR codes have been estimated below.

In the PbR 2016/17 tariff, outpatient attendances may include:

- Orthopaedic adult first attendance £129

- Orthopaedic adult follow-up £77
- Paediatric orthopaedic outpatient first attendance £145
- Paediatric orthopaedic outpatient follow-up attendance £94

In NHS reference costs 2015-16, outpatient appointments may include:

- Consultant-led (WF01A) paediatric endocrinology (service code 252) £270
- Consultant-led (WF01A) paediatric nephrology (service code 259) £229
- Consultant-led (WF01A) endocrinology (service code 302) £97
- Consultant-led (WF01A) nephrology (service code 361) £108
- Paediatric dentistry (service code 142) £125
- Maxillo-facial surgery (service code 144) £126

Bone deformities caused by rickets or osteomalacia may require surgical intervention. It is difficult to attribute the hospital therapy to a specific HRG code within the PbR tariff. In NHS reference costs 2015-16, outpatient procedures may include:

- Major dental procedures, 18 years and under (CD01B) £1,048
- Intermediate dental procedures, 18 years and under (CD02B) £189
- Minor dental procedures, 18 years and under (CD03B) £127
- Major dental procedures, over 18 years (CD01B) £679
- Intermediate dental procedures, over 18 years (CD02B) £307
- Minor dental procedures, over 18 years (CD03B) £165
- Stapling of growth plates (insertion of 8-plates): Trauma & Orthopaedics, Intermediate Knee Procedures for Non-Trauma, between 6 and 18 years, with CC Score 0 (HN24E) £171
- Hip arthroplasty: Very Major Hip Procedures for Non-Trauma with CC Score 0-1 (HN12F) £5,992
- Knee arthroplasty: Very Major Knee Procedures for Non-Trauma with CC Score 0-1 (HN22E) £5,653

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria and consider published and unpublished studies.

The systematic literature review reported for the cost-effectiveness covered resource data that would applicable to the economic analysis. See section 11 and section 17.3 for the search strategy. No studies were identified that contained resource data.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

The following clinical experts were consulted during the development of the cost utility model for Burosumab:

- Dr William G Van't Hoff, Consultant Paediatric Nephrologist, Great Ormond Street Hospital
- Dr Jeremy Allgrove, Consultant Paediatric Endocrinologist, Great Ormond Street Hospital

The clinical experts provided ratification of the frequencies and costs (surveillance, drugs, pain and mobility, and orthopaedic interventions) from two perspectives: endocrinology and nephrology. Both departments manage XLH patients across the country. These interviews confirmed that the clinical practice of nephrologists and endocrinologists do not significantly differ. The experts were provided with an overview of the proposed costs and resource use in a document in advance of one-hour telephone interviews.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

In accordance with the SPC, the starting titration dose for burosumab is 0.4 mg/kg with a maintenance dose of 0.8 mg/kg administered every 2 weeks. It is assumed that in the first year of treatment, patients commence treatment on recommended starting dose of 0.4 mg/kg with a stepwise increase up to 0.8 mg/kg over 3 months. Thus, for the purposes of estimating treatment costs, in the first 3 months the mean dose is 0.6 mg/kg and in the subsequent 9 months the mean dose is 0.8 mg/kg. The first-year dose is therefore estimated to be 0.752 mg/kg, which equates to 94% of the maintenance treatment dose.

The SPC indicates that all doses should be rounded to the nearest 10 mg. A scenario analysis explores the impact of rounding up to the nearest dose, rather than to the nearest as recommended in the SPC. The cost per vial (Table 48) has been applied to give an annual cost per patient in Table 49.

Table 48. Dosage and cost of burosumab

	Vial size	Cost per vial	Dose per infusion (mg per kg)
Burosumab	10 mg	£2,992	0.752mg/kg in the first 12 months of therapy, then the full dose of 0.8mg/kg
	20 mg	£5,984	
	30 mg	£8,976	

Table 49. Summary of acquisition treatment costs by age/weight

Age (years)	Weight (kg)	Dose (mg)	Rounded dose (mg)	Vials (10mg)	Vials (20mg)	Vials (30mg)	Annual cost
1	9.4	7.5	10.0	1	0	0	£ 77,792.00
2	11.8	9.4	10.0	1	0	0	£ 77,792.00
3	14.1	11.3	10.0	1	0	0	£ 77,792.00
4	16.1	12.9	10.0	1	0	0	£ 77,792.00
5	18.5	14.8	10.0	1	0	0	£ 77,792.00
6	20.7	16.5	20.0	0	1	0	£ 155,584.00
7	23.0	18.4	20.0	0	1	0	£ 155,584.00
8	25.9	20.7	20.0	0	1	0	£ 155,584.00
9	28.7	23.0	20.0	0	1	0	£ 155,584.00
10	31.8	25.4	30.0	0	0	1	£ 233,376.00
11	35.5	28.4	30.0	0	0	1	£ 233,376.00
12	39.1	31.3	30.0	0	0	1	£ 233,376.00
13	44.0	35.2	40.0	1	0	1	£ 311,168.00
14	49.6	39.7	40.0	1	0	1	£ 311,168.00
15	54.2	43.4	40.0	1	0	1	£ 311,168.00
16	58.2	46.6	50.0	0	1	1	£ 388,960.00
17	60.7	48.6	50.0	0	1	1	£ 388,960.00

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

The list price is used in the analysis. [redacted].

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables

D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Monitoring costs

Monitoring costs described in Table 50 account for dose adjustments in the first year of treatment with burosumab. After initiation of treatment with burosumab, in the first month of treatment fasting serum phosphate is monitored fortnightly, followed by every 4 weeks for the subsequent 2 months and thereafter as appropriate. If fasting serum phosphate is within the reference range for age, the same dose should be maintained. Thus, it is expected that costs of up to 5 additional serum phosphate measures may be incurred.

In the first year of treatment, patients are therefore assumed to require five additional blood tests and 15-minute consultations with nurses to take the blood tests to support dose titrations over the course of 3 months. This equates to a total monitoring cost of £126.55 per patient.

Table 50. Summary of monitoring costs

Monitoring Items	Unit cost	Resource use	Total cost	Source
Nurse visit	£22.25	5	£111.25	PSSRU (2017): Cost of Band 5 nurse per hour of patient contact. Assuming 15 minutes contact time.
Blood test	£3.06	5	£15.30	NHS reference costs 2016/17: DAPS05 (Haematology)
Total			**£126.55**	

Comparator acquisition costs

The costs of alfacalcidol and oral phosphate were taken from the BNF (British National Formulary, September 2017) and are shown in Table 51.

Alfacalcidol is dosed based on weight. A mean dose of 40 nanogram/kg/day is used, based on clinical expert opinion which indicates that the usual dose of alfacalcidol is 30-50 nanogram/kg/day. This is almost double the recommended dose for another vitamin D analogue, calcitriol, due to the difference in half-life between the two formulations (Carpenter et al., 2011). Due to the computational complexity of modelling treatment costs by age and the relatively low costs of the comparator, a

mean of the cost of treatment across 1-to-17 year olds was used to estimate the average annual cost of alfacalcidol.

For oral phosphate, Carpenter et al. recommended dosing in 3-5 divided doses, therefore the mean is assumed to be one tablet four times per day (Carpenter et al., 2011).

Table 51. Dosage and cost of oral phosphate and alfacalcidol

Treatment	Pack size	Cost per Pack	Dose per treatment	Annual cost
Alfacalcidol	500 nanogram capsules (30)	£9.27	40 nanogram per kg per day	1-year-old £112.79 17-year-old £425.23 Assuming an average across ages of £252.69
Oral Phosphate (Phosphate Sandoz)	Effervescent tablets (100)	£16.43	Four tablets per day	£239.88
Total comparator drug costs per year				**£492.57**

Health-state costs

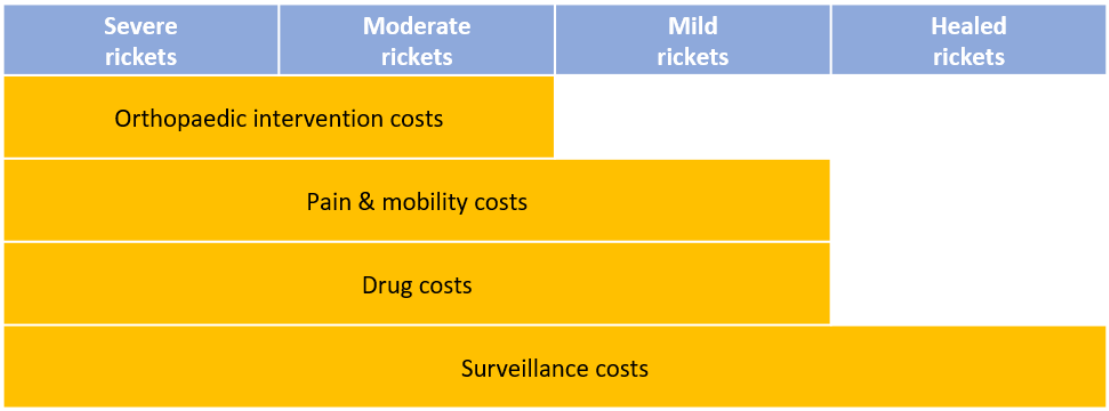
12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost-effectiveness model.

Follow-up costs for XLH disease management have been categorised in four groups as outlined in Figure 26: surveillance, pain and mobility, orthopaedic intervention and drugs (adults only).

Only patients in the moderate or severe health state are eligible to receive orthopaedic treatment. Only patients in the mild, moderate or severe health states receive pain and mobility costs (consisting of physiotherapy). All patients receive the same surveillance costs regardless of health status. Only patients that have rickets in childhood are assumed to receive the cost of vitamin D analogues and phosphate supplements in adulthood.

Unit costs and resource use for all health state costs are detailed in Table 52, with summary annual costs presented in Table 53.

Figure 26. Costs categorised by health state



Surveillance costs

Surveillance costs are the current costs of clinical management in the UK, to monitor and manage treatment in patients. These are assumed to be the same costs for all health states and the same in both arms and therefore do not impact on the base case results. A scenario analysis is conducted in which patients that are healed at the end of childhood do not require ongoing clinical reviews in adulthood. Since patients are not usually healed with current treatment, clinical experts could not estimate how often they would see patients if they appeared to be healed but suggested that may change in the future when healing occurs.

Surveillance costs consist of:

- Laboratory monitoring costs consisted of costs required to test serum calcium, phosphorus, potassium, and creatinine levels, ALP, PTH and urine calcium and creatinine levels.
- A specialist consultation consists of the costs for outpatient visits for specialist reviews.
- Radiography, the gold standard for the diagnostic and efficacy of rickets, is necessary to track the efficacy of treatment and to identify bone malformations at an early stage.
- During renal ultrasonography in XLH patients their kidneys are screened for signs of nephrocalcinosis, a clinical indicator for worsening XLH severity.
- At risk of dental problems, XLH patients attend dental outpatient appointments once every 2 years for dental examinations or minor interventions.

Full details of surveillance costs are provided in Table 52.

Drug costs

In childhood, the goal of treatment is to correct serum deficiencies and minimise rickets, osteomalacia, radiographic abnormalities and skeletal deformities to maintain

growth velocity and improvement in skeletal deformities. In adults on the other hand, the primary goals of treatment are to reduce pain symptoms, extent of osteomalacia and/or improve fracture healing. A French study indicated that 64.6% of adult patients receive phosphate supplements and 59.2% of adults receive a vitamin D analogue (Che et al., 2016). This is consistent with a larger US study which indicated that 62% of the surveyed population received phosphate / Vitamin D treatment (Skrinar et al., 2015).

The Summary of Product Characteristics for Phosphate Sandoz effervescent tablets recommends 4-6 tablets per day for vitamin D resistant rickets, so a mean of 5 tablets per day was used. Guidelines by Carpenter at al. recommend a dose of 0.5-0.75 micrograms per day for calcitriol, but clinical expert opinion indicates that double the dose is required for alfacalcidol, so a mean of 1.125 micrograms is used (Carpenter et al., 2011). Costs were obtained from the British National Formulary.

Pain and mobility costs

Many children and adults take frequent painkillers to manage their XLH. Clinical expert opinion indicates that painkillers are usually over-the-counter medicines and therefore would not be relevant to the NHS & PSS perspective. A UK parent survey indicated that some children may receive prescription pain relief (Acaster Lloyd Consulting, 2018) but the proportion that need prescription pain relief is unknown, so it has been conservatively assumed that patients do not receive pain management costs.

The parent survey also indicated that patients require visits to their GP (Acaster Lloyd Consulting, 2018) but it is not clear what symptoms of XLH require GP visits so these costs have not been included.

Pain and mobility costs therefore consist of physiotherapy costs only. Clinical expert opinion indicated that 5% of children may request physiotherapy. It has been assumed that these children would receive one session per month. A French study of adult XLH patients found that 57.4% of adults with XLH require physiotherapy. It has been assumed that adults that receive physiotherapy have one hour per month.

Orthopaedic intervention costs

In some patients, orthopaedic intervention is necessary, including osteotomy, stapling of growth plates, hip and knee arthroplasties and surgeries for dental abnormalities. Osteotomy and stapling of the growth plates is only effective in children with XLH, while hip arthroplasty and knee arthroplasty is only possible in adult patients.

Resource use from dental abnormalities were approximated from the proportion of patients with a medical history of tooth abscess in CL201 clinical study report. The costs of the procedures were obtained from an average of dental procedures and

weighted number of major/intermediate/minor procedures on the NHS in the UK (see Table 52).

Patients that have an osteotomy procedure are assumed to require two during childhood, which is applied by assuming the cost occurs every 8 years as a child. The same assumption is made regarding stapling of growth plates.

It has been assumed that if patients require a hip arthroplasty, they will have only one in their lifetime to calculate the average annual costs. A hip arthroplasty will usually last around 20 years, so it is possible people with XLH may require another during their lifetime; therefore this assumption may be an underestimate. Given the costs apply to adults only, the cost of a hip arthroplasty has been divided by 60 years to estimate annual cost. The same calculation applies to knee arthroplasty.

Table 52. Unit costs and resource use for health states

	Age group	% of patients	Unit cost	Resource use	Total cost	Unit Cost Source	Resource Use Source
Surveillance Costs							
Specialist Consultation	Children	100%	£ 249.31	4	£ 997.22	NHS reference costs 2016/17. Using an average of consultant-led (WF01A) paediatric endocrinology (service code 252) and nephrology (service code 259) as patients are managed by both.	Clinical expert opinion
	Adults	100%	£ 102.33	1	£ 102.33	NHS reference costs 2016/17. Using an average of consultant-led (WF01A) endocrinology (service code 302) and nephrology (service code 361) as patients are managed by both.	Assumption
Laboratory Monitoring	Children	100%	£ 4.19	4	£ 16.76	NHS reference costs 2016/17: DAPS05 (Haematology) and DAPSS04 (Clinical biochemistry).	Clinical expert opinion
	Adults	100%	£ 4.19	1	£ 4.19		
Radiography	All	100%	£ 29.78	0.50	£ 14.89	NHS reference costs 2016/17: DAPF (Direct Access Plain Film).	Clinical expert opinion
Renal Ultrasono-graphy	All	100%	£ 51.36	1	£ 51.36	NHS reference costs 2016/17: IMAGDA RD40Z (Direct access ultrasound scan with duration of less than 20 minutes, without contrast).	Clinical expert opinion

Dental Check up	Children	100%	£125.39	0.50	£ 62.70	NHS reference costs 2016/17: Outpatient attendance 142 (Paediatric dentistry).	Clinical expert opinion
	Adults	100%	£ 126.26	0.50	£ 63.13	NHS reference costs 2016/17: Outpatient attendance 144 (Maxillo-facial surgery).	Clinical expert opinion
Drug Costs							
Oral Phosphate	Adults	65%	£ 0.16 per tablet	5 tablets per day	£ 193.70	Cost from BNF 20th December 2017: Phosphate Sandoz effervescent tablets (100).	The summary of product characteristics recommends 4-6 tablets per day (using 5 average) for vitamin D resistant rickets; Che et al indicated 64.6% of adult patients receive phosphate supplements (Che et al., 2016).
Alfacalcidol	Adults	59%	£ 0.31 per 500ng capsule	Dose of 1,125 ng per day	£ 200.31	Cost from BNF 16th January 2018: Alfacalcitrol 500nanogram capsules (30).	Guidelines by Carpenter at al recommend a dose of 0.5-0.75 mcg per day for Calcitriol (another Vit D not used in UK), but KOL opinion indicates that double the dose is required for alfacalcidol, so a mean of 1.125 mg is used. Che et al indicated 59.2% of adults receive a vitamin D (Che et al., 2016).
Pain and Mobility Costs							
Physiotherapy	Children	5.00%	£87 per session	1 session per month	£ 52.20	Cost from PSSRU 2016 (6.1).	Clinical expert opinion indicated that 5% patients may request physiotherapy. Assuming one session per month.

	Adults	57.40%	£45 per hour	1 hour per month	£ 309.96	Cost from PSSRU 2016 (section 13). Assuming Physiotherapist specialist which is a band 8.	Resource use from Che et al (Che et al., 2016). Assuming one hourly session per month.
Orthopaedic Intervention Costs							
Dental Abnormalities	Children	19.20%	£ 154.60	1	£ 29.68	NHS reference costs 2016/17: average of dental procedures in 18 years and under, weighted by the number of major/intermediate/minor procedures on the NHS (CD01B, CD02B, CD03B).	Resource use is approximated from the proportion of children with a medical history of tooth abscess in CL201 clinical study report. We assume one procedure per year.
	Adults	62.50%	£169.52	1	£271.24	NHS reference costs 2016/17: average of adult dental procedures, weighted by the number of major/intermediate/minor procedures on the NHS (CD01A, CD02A, CD03A).	The proportion of adults with dental abnormalities is sourced from Che et al (Che et al., 2016). We assume one procedure per year.
Osteotomy	Children	7.7%	£3,914	Twice in childhood	£37.67	(Smith Ii et al., 2015)	Resource use is approximated from the proportion of patients with a medical history of osteotomy in CL201 clinical study report. We assume patients have two osteotomy procedures during childhood which is applied by assuming the cost occurs every 8 years as a child.
Stapling of Growth Plates	Children	17.5%	£171	Twice in childhood	£3.74	NHS reference costs 2016/17: HN24E Trauma & Orthopaedics (Intermediate Knee Procedures for Non-Trauma, between 6 and 18 years, with CC	Resource use from clinical expert opinion. We assume patients' growth plates are stapled twice during childhood which is applied by assuming the cost

						Score 0).	occurs every 8 years as a child.
Hip Arthroplasty	Adult	8%	£5,992	0.017%	£ 7.99	Unit cost from NHS reference costs 2015-16 using the most frequent major hip procedure code (HN12F: Very Major Hip Procedures for Non-Trauma with CC Score 0-1).	Resource use from Skrinar et al (Skrinar et al., 2015). Assuming one per lifetime (60 years, adulthood at approximately 20 and life expectancy approximately 80).
Knee Arthroplasty	Adult	12%	£5,653	0.017%	£ 11.31	Unit cost from NHS reference costs 2015-16 using the most frequent major knee procedure code (HN22E: Very Major Knee Procedures for Non-Trauma with CC Score 0-1).	Resource use from Skrinar et al (Skrinar et al., 2015). Assuming one per lifetime (60 years, adulthood at approximately 20 and life expectancy approximately 80).

Table 53. Total costs per health state in the cost- effectiveness model

Health states	Items	Value	
		Children	**Adults**
Rickets Healed	Surveillance cost	£ 1,142.93	£ 235.90
	Drug cost	N/A	£ 0.00
	Total	**£ 1,142.93**	**£ 235.90**
Mild	Surveillance cost	£ 1,142.93	£ 235.90
	Drug cost	N/A	£ 394.01
	Pain and mobility cost	£ 52.20	£ 309.96
	Total	**£ 1,195.13**	**£ 939.86**
Moderate	Surveillance cost	£ 1,142.93	£ 235.90
	Drug cost	N/A	£ 394.01
	Pain and mobility cost	£ 52.20	£ 309.96
	Orthopaedic cost	£ 71.10	£ 188.82
	Total	**£ 1,266.23**	**£ 1,128.68**
Severe	Surveillance cost	£ 1,142.93	£ 235.90
	Drug cost	N/A	£ 394.01
	Pain and mobility cost	£ 52.20	£ 309.96
	Orthopaedic cost	£ 71.10	£ 188.82
	Total	**£ 1,266.23**	**£ 1,128.68**

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

As discussed in 10.1.8 and 12.2.4, no costs associated with adverse events were applied in the base case analysis as it was observed that the impact of adverse events on the cost effectiveness was not significant. In sensitivity analysis, the impact of including costs and disutilities associated with adverse events are explored, using an incidence rate of 28.2% for injection site reactions based on Study CL201 and Study CL205.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Out of pocket costs have not been included in the analysis. These are likely to be incurred for pain medications associated with bone pain, joint pain, and joint stiffness that restrict range of motion, impair gait and diminish physical health status. It has been reported that pain medication is taken by 70% of patients with severe pain, including 18% taking narcotics (Skrinar et al., 2015).

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It is challenging to quantify the burden associated with XLH. All known costs resources have been considered.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Scenario analysis has been conducted to investigate model assumptions as follows:

1. Applying a discount rate for costs and effects at 3.5% as per NICE reference case
2. Considering a cohort of XLH patients with an even age distribution between 1-12 years, rather that the age distribution from the clinical studies
3. Health state severity baseline distribution using only patients from Study CL201 that received the expected licensed dose of burosumab

4. Using 40-week observations for transition probabilities in patients aged 0 to 4 years, rather than 40-week data extrapolated to one year
5. Using 64-week observations for transition probabilities in patients aged 5 years and over, rather than 64-week data extrapolated to one year
6. Using UK chart-review data for SoC transition probabilities with missing data imputed using linear interpolation (Table 44)
7. Using Study CL002 data for SoC transition probabilities (Table 46)
8. Alternative ages for stopping treatment in both genders: 15 years, 16 years and 17 years
9. Using a mean dose to 1.05 mg/kg in line with the mean dose observed in the dose finding study CL201 rather than the recommendation from the summary of product characteristics
10. Rounding up the dosage of burosumab required, rather than rounding to the nearest 10mg as recommended in the SPC.
11. Using the 25th percentile weight distribution to calculate treatment and comparator costs
12. Including drug treatment (vitamin D and phosphates) in adults with healed rickets
13. Assuming patients that have healed rickets in childhood no longer require surveillance in adulthood

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

One-way deterministic sensitivity analysis (DSA) was conducted to sensitivity of the results to individual parameters. Variables included in the DSA are shown in Table 54.

Probabilistic sensitivity analysis (PSA) was run using 5,000 Monte Carlo simulations. With the exception of utilities, for which standard errors were available, the standard error of each parameter was assumed to be 25% of the mean value.

Costs and resource use were sampled from a gamma distribution. The proportion of patients receiving drugs, receiving physiotherapy and having orthopaedic interventions were sampled from a beta distribution. A Dirichlet distribution was used to generate probabilistic transition probabilities, which utilities the number of observations.

A beta distribution was used for utilities, since utility values in patients with XLH are not expected to be lower than 0. Reported standard errors were used (Table 31). To ensure that plausible utilities were obtained in the simulation, the utilities are bounded such that they do not exceed one and:

- The utilities for the moderate health state are bounded to not be lower than severe health state utilities
- The utilities for the mild health state are bounded to not be lower than moderate health state utilities
- The utilities for the healed health state would not be lower than the mild health state utilities.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table 54. Variables used in one-way deterministic sensitivity analysis

Parameter	Source of variation	Base-case value	Lower	Upper
Proportion Female (%)	Arbitrary	49.23	0	100
Specialist Consult cost – children (£)	Base case is an average of the national average unit cost of endocrinology and nephrology specialist consultations. Lower bound is endocrinology, upper bound is nephrology.	249.31	228.68	269.93
Specialist Consult cost – adults (£)		103.33	96.88	107.77
Laboratory Monitoring cost (£)	±25%	4.19	3.1425	5.2375
Radiography cost (£)	±25%	29.78	22.34	37.23
Renal Ultrasonography cost (£)	±25%	51.36	38.52	64.20
Dental Check Up cost - children (£)	±25%	125.39	94.04	156.74
Dental Check Up cost - adults (£)	±25%	126.26	94.70	157.83
Specialist Consult resource use – children (visit/year)	±25%	4	3	5
Laboratory Monitoring resource use – children (visit/year)	±25%	4	3	5
Radiography resource use – children (visit/year)	±25%	0.5	0.375	0.625
Renal Ultrasonography resource use – children (visit/year)	±25%	1	0.75	1.25
Dental Check Up resource use – children (visit/year)	±25%	0.5	0.375	0.625
Specialist Consult	±25%	1	0.75	1.25

resource use – adults (visit/year)				
Laboratory Monitoring resource use – adults (visit/year)	±25%	1	0.75	1.25
Radiography resource use – adults (visit/year)	±25%	0.5	0.375	0.625
Renal Ultrasonography resource use – adults (visit/year)	±25%	1	0.75	1.25
Dental Check Up resource use – adults (visit/year)	±25%	0.5	0.375	0.625
Oral Phosphate cost (£)	±25%	0.16	0.12	0.21
Alfacalcidol cost – 500 nanogram (£)	±25%	0.31	0.23	0.39
Alfacalcidol cost – 1 microgram (£)	±25%	0.43	0.32	0.54
Oral Phosphate dose – children (tablet/day)	Guidelines recommend 3 to 5 divided daily doses (Carpenter et al., 2011)	4	3	5
Alfacalcidol dose – children (nanogram/kg/day)	Clinical expert opinion	40	30	50
Oral Phosphate dose – adults (tablet/day)	±25%	5.00	3.75	6.25
Alfacalcidol dose – adults (nanogram/kg/day)	±25%	1125	843.75	1406.25
Nurse visit cost (£)	±25%	22.75	16.69	27.81
Blood test cost (£)	±25%	3.06	2.30	3.83
Nurse visit frequency (visit/year)	±25%	5.00	3.75	6.25
Blood test frequency (visit/year)	±25%	5.00	3.75	6.25
Physiotherapy cost child (£)	±25%	1044.00	783.00	1305.00
Physiotherapy cost adult (£)	±25%	540.00	405.00	675.00
Physiotherapy resource child (%)	±25%	5.00	3.75	6.25
Physiotherapy resource adult (%)	±25%	57.40	43.05	71.75
Dental Abnormalities cost - child (£)	±25%	154.60	115.95	193.25
Osteotomy cost (£)	±25%	3914.00	2935.50	4892.50
Stapling of Growth Plates cost (£)	±25%	171.01	128.26	213.76
Dental Abnormalities resource use – child (%)	±25%	19.20	14.40	24.00
Osteotomy resource use (%)	±25%	0.96	0.72	1.20
Stapling of Growth Plates resource use (%)	±25%	2.19	1.64	2.73
Dental Abnormalities cost - adult (£)	±25%	271.24	203.43	339.04
Hip Arthroplasty cost (£)	±25%	5992.16	4494.12	7490.20

Knee Arthroplasty cost (£)	±25%	5653.29	4239.97	7066.61
Dental Abnormalities resource use - adult (%)	±25%	62.50	46.88	78.13
Hip Arthroplasty resource use (%)	±25%	0.13	0.10	0.17
Knee Arthroplasty resource use (%)	±25%	0.20	0.15	0.25
Injection site reaction cost (£)	±25%	0.00	0.00	5.00
Injection site reaction resource use (%)	±25%	28.20	21.15	35.25
Utilities				
Severe (age 1-4)	± 1 standard deviation	0.545	0.480	0.610
Moderate (age 1-4)	± 1 standard deviation	0.685	0.510	0.860
Mild (age 1-4)	± 1 standard deviation	0.774	0.685	0.868
Healed (age 1-4)	± 1 standard deviation	0.872	0.775	0.968
Severe (age 5-12)	± 1 standard deviation	0.521	0.437	0.605
Moderate (age 5-12)	± 1 standard deviation	0.613	0.443	0.783
Mild (age 5-12)	± 1 standard deviation	0.757	0.639	0.876
Healed (age 5-12)	± 1 standard deviation	0.969	0.897	1.000
Severe (age 13+)	± 1 standard deviation	0.462	0.301	0.575
Moderate (age 13+)	± 1 standard deviation	0.575	0.481	0.669
Mild (age 13+)	± 1 standard deviation	0.671	0.575	0.781
Healed (age 13+)	± 1 standard deviation	0.862	0.756	0.967

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

All relevant parameters have been included in the sensitivity analysis.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme.

Burosumab is associated with 10.414 more discounted QALYs than SoC and £[redacted] more costs over a lifetime, resulting in a cost per QALY of £[redacted] (Table 55). These results indicate that burosumab offers significant benefit to patients. The key driver for the QALY gain with burosumab is from improving the skeletal and non-skeletal manifestations of XLH in childhood, altering the natural progression of the disease with lifelong improvements in functional outcomes and quality of life.

Table 55. Base case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard of care	[redacted]	25.989			
Burosumab	[redacted]	36.402	[redacted]	10.414	[redacted]

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

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The only outcome in the decision problem that is relevant to the model is 'severity of rickets'. The model inputs are derived from the clinical trials so an explicit comparison here is not required.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The Markov trace for SoC and burosumab are illustrated in Figure 27 and Figure 28, respectively. The greatest proportion of SoC patients that remain in a health state is those with severe rickets (approximately 35% of patients), followed by those with mild or moderate rickets (approximately 25% of patients each). Very few patients (approximately 15%) typically spend most of their lives in the healed health state. Comparatively, most patients treated with burosumab are expected to spend their lives in the healed rickets health state.

Figure 27. Markov trace: standard of care

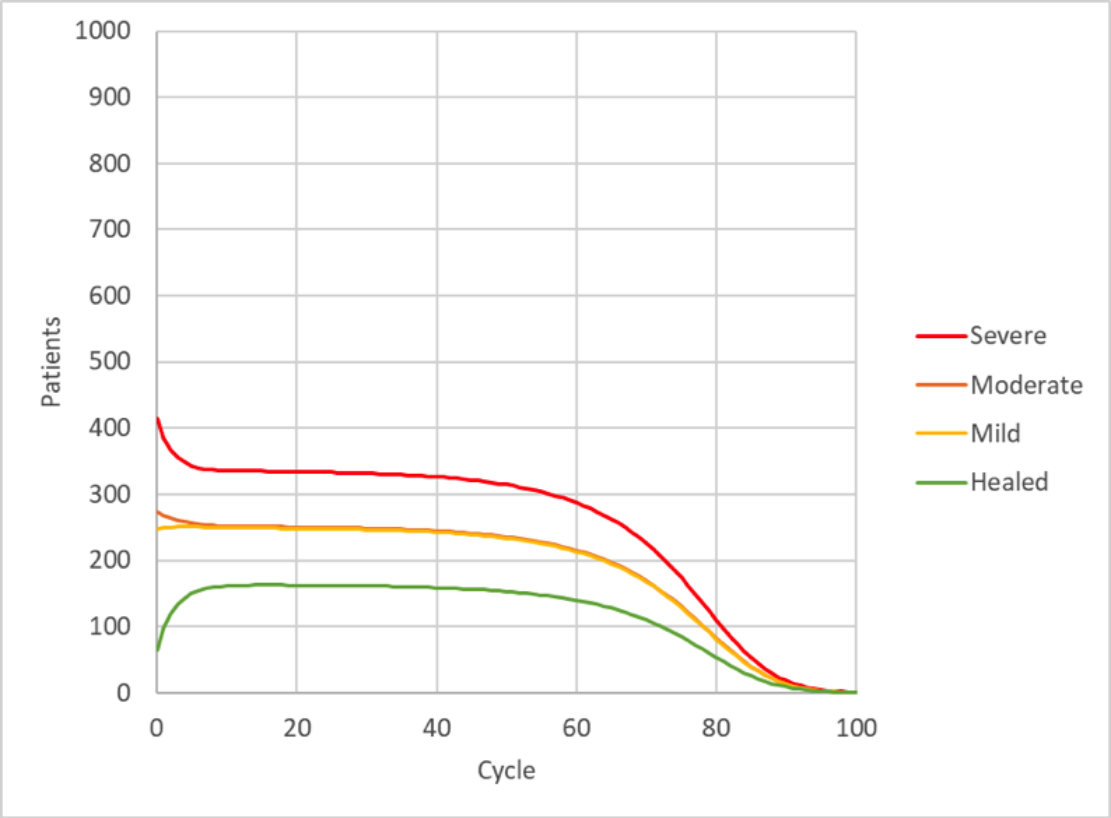
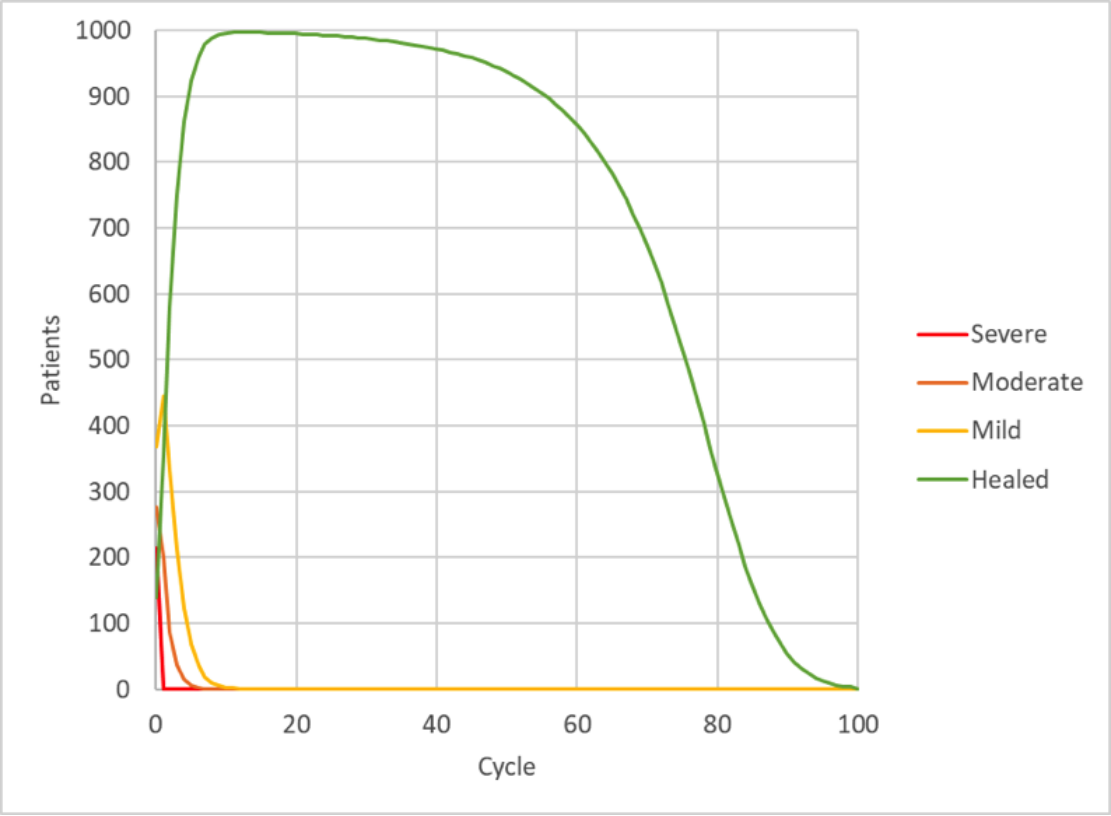


Figure 28. Markov trace: burosumab



12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The Markov traces illustrating accrual of QALYs for SoC and burosumab are provided in Figure 29 and Figure 30, respectively.

Figure 29. QALY accrual: standard of care

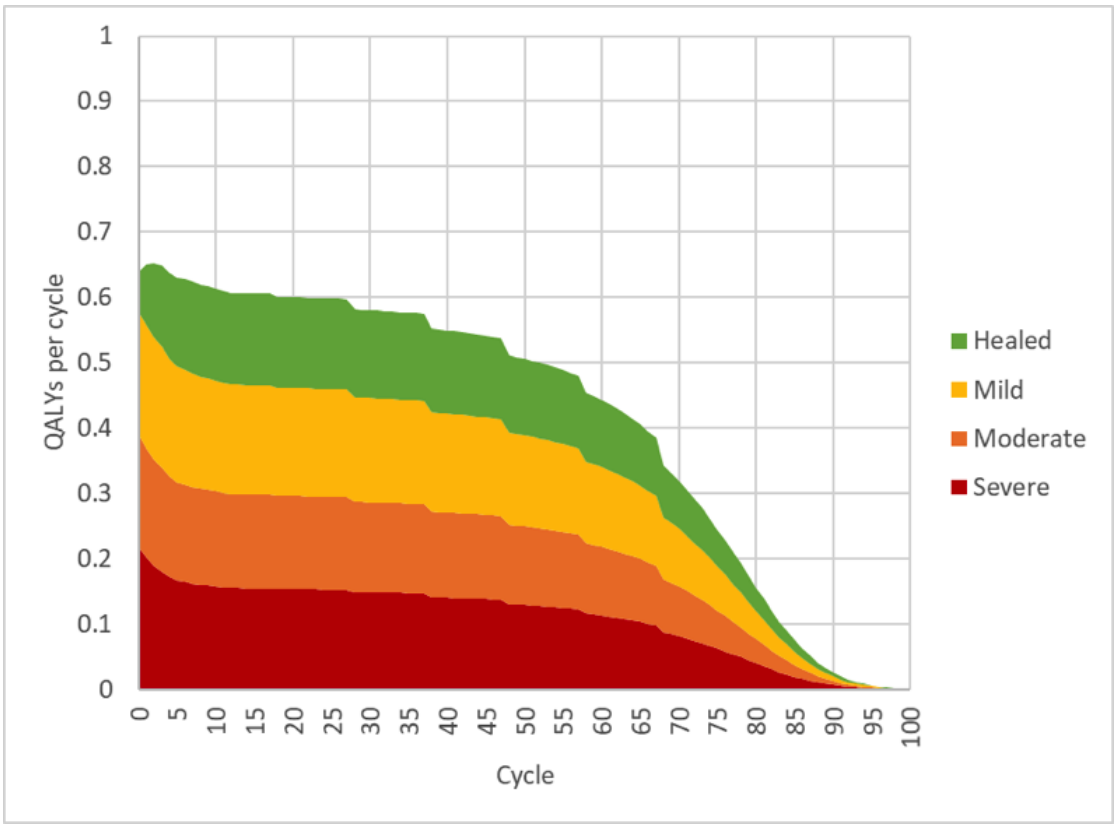
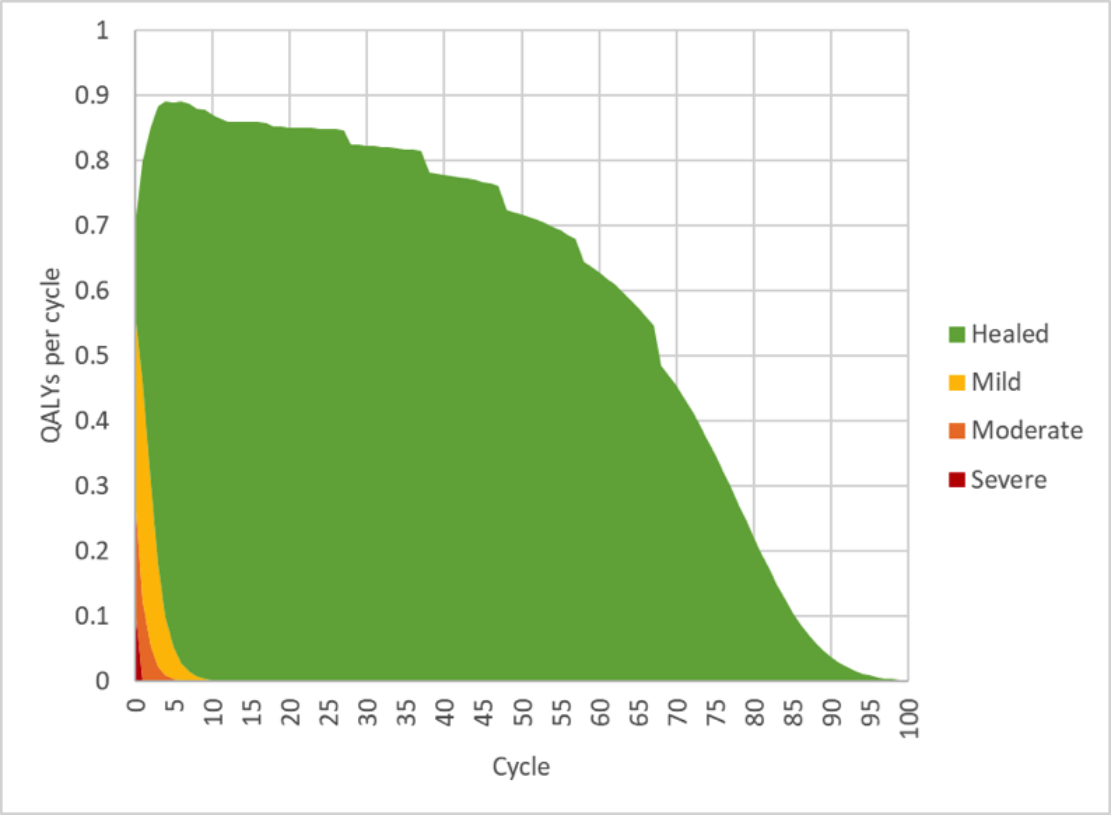


Figure 30. QALY accrual: burosumab



12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Not applicable.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Disaggregated incremental QALYs by health state are provided in Table 56.

Table 56. Summary of QALY gain by health state

Health state	QALY burosumab	QALY SoC	Increment	Absolute increment	% absolute increment
Healed rickets	34.723	5.770	28.952	28.952	61%
Mild rickets	1.181	7.210	-6.029	6.029	13%
Moderate rickets	0.385	6.230	-5.845	5.845	12%
Severe rickets	0.113	6.778	-6.665	6.665	14%
Total	36.402	25.989	10.414	54.675	100%

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

The comparator (standard of care) is associated with 41.786 undiscounted QALYs whilst the intervention (burosumab) is associated with 58.793 undiscounted QALYs, giving an undiscounted QALY gain of 17.008.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

A breakdown of the costs indicates that the greatest cost driver of the analysis is the cost of burosumab (Table 57).

Table 57. Summary of costs by category of cost

Item	Cost burosumab	Cost SoC	Increment	Absolute increment	% absolute increment
Burosumab treatment costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	99%
Drug costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	1%
Monitoring costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	0%
Surveillance Costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	0%
Pain & Mobility costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	0%
Orthopaedic Intervention costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	0%
Adverse Event costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	0%
Total	£[redacted]	£[redacted]	£[redacted]	£[redacted]	**100%**

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Not applicable.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event.

Not applicable.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

The results of the DSA are detailed in Appendix 17.6 (Table 65) and illustrated in Figure 31. The greatest drivers of the cost-effectiveness analysis are utilities, particularly those for adolescents and adults. Results are sensitive to the gender distribution since growth plates, and therefore treatment, stops earlier in females. Results are insensitive to all other costing inputs included.

Figure 31. Tornado diagram illustrating results of top 20 most sensitive parameters in one-way sensitivity analysis

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

The results of the scenario analysis are detailed in Table 58.

As expected, the results are sensitive to applying a discount rate of 3.5% for costs and effects, resulting in an ICER of £[redacted]. Results are insensitive to changes in the baseline age and severity distribution and the burosumab transition probabilities. Applying an alternative method of handling missing data in the UK chart review data used for SoC transition probabilities results in an 11% improvement in incremental QALYs and an ICER of £[redacted]. Using Study CL002 data for SoC transition probabilities results in a significant increase to the ICER, resulting in a cost per QALY

of £[redacted], which is driven by a 14% reduction in incremental QALYs. This is a plausible scenario as the data is the best match to Study CL201 which has been used for burosumab transition probabilities for those aged 5 years and over.

Results are sensitive to the age of stopping treatment, with ICERs ranging between £[redacted] and £[redacted]. Results are sensitive to all scenarios that relate to the cost of burosumab: weight, dosage and dose rounding. In these scenarios, the ICER ranges between £[redacted] and £[redacted].

The two scenarios that test structural assumptions in the model result in negligible impact on the results:

- Continuing conventional drug therapy in adults with healed rickets
- Terminating surveillance in XLH patients who enter adulthood with healed rickets.

Table 58. Results of scenario analyses

Scenario	Total costs (£)		Total QALYs		Incremental costs (£)	Difference in incremental costs	Incremental QALYs	Difference in incremental QALYs	ICER (£)
	Burosumab	SoC	Burosumab	SoC					
Base case analysis	[redacted]	[redacted]	36.402	25.989	[redacted]		10.414		[redacted]
Discount rate (3.5%)	[redacted]	[redacted]	22.420	16.121	[redacted]	-10%	6.299	-40%	[redacted]
Even age distribution of cohort aged 1-12 years	[redacted]	[redacted]	36.686	26.215	[redacted]	2%	10.470	1%	[redacted]
Baseline age and severity distribution: using only patients that were randomised to the bi-weekly burosumab dose	[redacted]	[redacted]	36.668	26.187	[redacted]	2%	10.481	1%	[redacted]
Transition probabilities, aged 1-4 years: 40-week observations	[redacted]	[redacted]	36.402	25.989	[redacted]	0%	10.414	0%	[redacted]
Transition probabilities, aged 5 years and over: 64-week observations	[redacted]	[redacted]	36.400	25.989	[redacted]	0%	10.412	0%	[redacted]
UK chart-review data for SoC transition probabilities with missing data using linear interpolation	[redacted]	[redacted]	36.402	24.825	[redacted]	0%	11.577	11%	[redacted]
Study CL002 data for SoC transition probabilities	[redacted]	[redacted]	36.402	27.434	[redacted]	0%	8.969	-14%	[redacted]

Treatment stops at 15 years, both genders	[redacted]	[redacted]	36.402	25.989	[redacted]	-22%	10.414	0%	[redacted]
Treatment stops at 16 years, both genders	[redacted]	[redacted]	36.402	25.989	[redacted]	-7%	10.414	0%	[redacted]
Treatment stops at 17 years, both genders	[redacted]	[redacted]	36.402	25.989	[redacted]	7%	10.414	0%	[redacted]
Mean burosumab dose 1.05 mg/kg	[redacted]	[redacted]	36.402	25.989	[redacted]	29%	10.414	0%	[redacted]
Rounding up the dosage of burosumab required, rather than rounding to the nearest 10mg	[redacted]	[redacted]	36.402	25.989	[redacted]	12%	10.414	0%	[redacted]
25th percentile children weight distribution	[redacted]	[redacted]	36.402	25.989	[redacted]	-10%	10.414	0%	[redacted]
Continuing SoC drug treatment in adults with healed rickets	[redacted]	[redacted]	36.402	25.989	[redacted]	0%	10.414	0%	[redacted]
Children with healed rickets no longer require surveillance in adulthood	[redacted]	[redacted]	36.402	25.989	[redacted]	0%	10.414	0%	[redacted]

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Mean probabilistic sensitivity analysis results are presented in Table 59. The mean probabilistic ICER is higher than the deterministic ICER due to a difference in QALYs. As illustrated in the cost-effectiveness plane (Figure 32), some simulations resulted in negative QALYs. Small numbers of observations in transition probabilities meant that the Dirichlet distribution resulted in extreme scenarios where patients treated with burosumab were in the same or worse states than SoC, meaning no incremental QALYs or fewer incremental QALYs. The frequency of this extreme result was uncommon, with only 5 of the 5,000 simulations in north-west quadrant of the ICER plane. In addition, the nature of utilities means they have an upper bound of 1 but no lower bound as they can be negative. Thus, sampling from a utility distribution is skewed. This could be the cause of the incremental QALYs being greater in the deterministic analysis than the mean probabilistic analysis.

The cost-effectiveness acceptability curve (Figure 33) indicates that at a willingness to pay of £170,000, the probability of burosumab being cost-effective is [redacted]%.

Table 59. Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard of care	[redacted]	25.872			
Burosumab	[redacted]	34.382	[redacted]	8.510	[redacted]

Figure 32. Cost-effectiveness plane

Figure 33. Cost-effectiveness acceptability curve

12.5.14 What were the main findings of each of the sensitivity analyses?

The one-way sensitivity analysis shows the cost-utility results are most sensitive to the utilities. The results are also sensitive to the gender distribution of the cohort (up to 12% change in ICER). The model is insensitive to all other parameters (<1% change in ICER).

The scenario analysis shows the results are most sensitive to discount rates. Results are also sensitive to the age of stopping treatment, with ICERs ranging between £[redacted] and £[redacted]. Results are sensitive to all scenarios that relate to the cost of burosumab: weight, dosage and dose rounding. In these scenarios, the ICER ranges between £[redacted] and £[redacted]. Applying an alternative method of handling missing data in the UK chart review data used for SoC transition probabilities results in an 11% improvement in incremental QALYs and an ICER of £[redacted]. Using Study CL002 data for SoC transition probabilities results in a significant increase to the ICER, resulting in a cost per QALY of £[redacted], which is driven by a 14% reduction in incremental QALYs. Results are insensitive to changes in the baseline age and severity distribution and the burosumab transition probabilities. Results are also insensitive to structural assumptions around the continued use of conventional drug therapy in adults with healed rickets and the surveillance needed in XLH patients who enter adulthood with healed rickets.

12.5.15 What are the key drivers of the cost results?

Any parameters relating to treatment costs are the key driver of the cost results, which includes age of stopping treatment, dosage, dose rounding and patient weight.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

In line with the scope, no subgroups were considered.

12.6.2 Define the characteristics of patients in the subgroup(s).

In line with the scope, no subgroups were considered.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

In line with the scope, no subgroups were considered.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to

that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

In line with the scope, no subgroups were considered.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

In line with the scope, no subgroups were considered.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Due to the rarity of XLH, it is difficult to validate many aspects of the model. Clinical expert opinion was sought to validate all costs considered. Validation of the utilities was conducted against the limited published literature (see Section 10.1.9).

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Not applicable; there are no published cost-effectiveness analyses published in XLH.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A strength of the analysis is that it includes a breadth of evidence, considering the rarity of the disease, including UK chart reviews and UK derived utilities by XLH patient severity. Although each are associated with uncertainties, these additional evidence sources are a significant contribution to the knowledge surrounding XLH - a condition which is not well documented in the literature. A potential weakness of the analysis is that some assumptions that are pivotal to results are scientifically appropriate but long-term data to support the assumption is not yet available. For example, the assumption that patients remain in their health state upon transitioning from adolescence to adulthood.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Generation of utilities measured by patients or caregivers would enhance to robustness of the analysis; this is part of ongoing data collection by Kyowa Kirin. The results will become available during the NICE appraisal.

The availability of data from the ongoing Phase 3 study comparing burosumab to conventional therapy will also enhance the robustness of the results.

Collection of clinical effectiveness data in patients aged 13-17 would add certainty to the results. The current model assumed the treatment effect in this age group is the same as in 5-12-year olds.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

There are some published studies estimating the prevalence of XLH in Europe. Due to the variability of these estimates, Kyowa Kirin have collected UK-specific data to estimate the number of patients.

[redacted].

This prevalence has been applied to the general population for England in children aged between 1 and 17 years (Office for National Statistics, 2016) to estimate that there are [redacted] children with XLH eligible for treatment with burosumab (Table 60). [redacted].

Given that XLH is associated with skeletal deformations, pain and functional impairment, it is unlikely that there are undiagnosed children that would benefit from treatment with burosumab. Thus, the estimated prevalence based on primary care data is unlikely to be a significant underestimate.

A Danish study estimates the incidence of XLH to be 3.9 per 100,000 (Beck-Nielsen et al., 2009), which would equate to 26 new patients annually in England. Given the size of the prevalent population, this is considered implausible. Furthermore, the size of the patient population is not expected to change with time as patients are only treated if they have growing skeletons i.e. each year there may be new patients but there will also be a likely similar number of patients ceasing treatment. Furthermore, XLH is not associated with an increased risk of death, compared to the standard population (Nielsen et al., 2014). Therefore, the overall population size is not expected to change. This results in a potential (theoretical) eligible population that is assumed to remain constant year on year.

Table 60. Derivation of number of XLH children on treatment in their first year

Parameter	Value	Reference
Population of females aged 1-16 years in England (2016)	5,695,613	(Office for National Statistics, 2016)
Population of males aged 1-17 years in England (2016)	5,110,255	(Office for National Statistics, 2016)
Prevalence of XLH	[redacted]%	Draft abstract (Delmestri et al., 2018)
Number of patients eligible for burosumab per year	[redacted]	

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

Using the prevalence estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] prevalent children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab. These expected uptake rates are based on interaction with clinical experts during discussions over potential early access schemes for burosumab.

Table 61. Market update of burosumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected uptake of burosumab	40%	65%	90%	90%	90%
Patients treated with burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

After initiation of treatment with burosumab, fasting serum phosphate should be measured every two weeks for the first three months of treatment, so up to five additional nurse visits and blood tests per patient are expected in the first year of treatment only. This equates to a cost of £126.55 per child treated with burosumab

(Table 50). Following this, burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by Kyowa Kirin and will therefore not have any additional financial or resource impact on the NHS.

13.4 Describe any estimates of resource savings associated with the use of the technology.

Oral phosphate and vitamin D analogues should be discontinued one week prior to initiation of treatment with burosumab (Summary of Product Characteristics (Crysvita), 2017). Therefore, if a patient is treated with burosumab, there will be savings in the costs of oral phosphate and vitamin D analogues. The costs of these treatments in children are £492.57 per year (Table 51).

As captured in the cost-effectiveness model, there are also savings to be made with regards to fewer surgical interventions, as well as reduced and/or deferred need for physiotherapy to manage the long-term consequences attributed to XLH. For simplicity, these have not been factored in the budget impact analysis given its short time horizon. Therefore, no resource savings beyond drug costs have been factored into the budget impact model.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

See response to 13.4.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Although it has not yet been possible to quantify because burosumab is a new treatment, it is highly likely that there will be significant long-term savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab, since patients may lead normal lives and be less impacted by their symptoms. For example, patients may be able to work more, or obtain further career progression through improved education not inhibited by XLH. In the short term, parents might not have to take time off from work to care for their child suffering with XLH.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The weight, gender distribution and dosage of burosumab used to calculate treatment costs per age in the budget impact analysis is in line with the cost-effectiveness model (Table 49). The distribution of patients age was obtained from Study CL201 and CL205 (Table 36), to estimate mean number of 10mg, 20mg, 30mg vials required per patient, across the treated cohort.

At the list price of £2,992, £5,984 and £8,976 for 10 mg, 20 mg and 30 mg vials, respectively, the average annual treatment cost is £142,419 per patient in the first year of treatment (which accounts for initial titration) and £151,994 per patient in their subsequent years of treatment.

Factoring in costs of monitoring and cost savings through displaced conventional therapy results in a net budget impact of £[redacted] in Year 1, £[redacted] in Year 2 and £[redacted] per year thereafter (Table 62).

Table 62: Net budget impact of burosumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients treated with burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of continuing patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of burosumab (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offsets in drug costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

[redacted]:

- [redacted].
- [redacted].
  - [redacted].
  - [redacted].
  - [redacted].
  - [redacted].

[redacted].

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

Although it is not possible to quantify at this stage in development, it is highly likely that there will be significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab, since patients may lead normal lives and be less impacted by their symptoms. For example, patients may be able to work more, or obtain further career progression through improved education not inhibited by XLH. In the short term, parents might not have to take time off from work to care for their child suffering with XLH.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It has not been possible to identify and quantify at this stage costs to other government bodies. In the long-term, avoiding life-long disability in people with XLH via treatment with burosumab will reduce serious complications and the resultant incapacitation. The more independent and capable the patient is, the less dependent they – or their caregivers – will be on respite care, or on disability and other welfare payments.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Most children experience interruptions to their schooling to attend hospital and GP appointments. Consequently, family member or caregivers may have to take time off work to attend these appointments, in addition to bearing the costs of travel. Due the limited number of specialist centres, patients may have to travel a considerable distance to attend consultant appointments. In the online survey, carried out in January 2018 (Acaster Lloyd Consulting, 2018), [redacted].

Berndt et al assessed the clinical and psychosocial aspects of the disease in 23 adults in Germany using a standardised questionnaire on pain and psychosocial rehabilitation (schooling, vocational training, employment and marital status). Responders indicated that they struggled due to a lack of schooling and vocational training resulting from a lifetime of managing disease-related complications (Berndt et al., 1996):

- Thirteen out of 20 patients were able to attend school regularly and to finish school adequately. Seven patients reported to have missed school repeatedly because of multiple hospitalisations leading to class repetition and to an inappropriate school qualification in four of them.
- Twelve out of 20 patients finished vocational training, five did not start and three attended but did not complete vocational training.
- Eight patients were employed, four were unemployed, four women were housewives, two patients received a social insurance payment because of inability to work (two patients did not answer questions on vocational training and profession).

Many adults with XLH require surgery to correct skeletal deformities: In burden of illness study, CL001, [redacted] (Ultragenix, 2016). In a case-note review of 59 adults with XLH, attending a single inherited metabolic disease service in the UK from 1998, 42% had had an osteotomy (Chesher et al., 2018). Having surgery requires time off work for the surgery and recovery. For an osteotomy, patients are not able to return to work for between two weeks and four months, depending on the nature of the work they do.

Most adult patents require [redacted] (Ultragenix, 2016).

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

It has not been possible to quantify this.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The clinical trial programme for burosumab, that included studies CL201, CL002 and CL205, represents the first studies designed for registration in XLH and is pioneering in this field. The study programme contributes a wealth of knowledge on the progression of disease in the context of conventional therapy with phosphates and active vitamin D, as well establishing outcome measures for clinical trials of XLH.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Burosumab represents a step-change in the management of XLH because it addresses the underlying pathophysiology. The award of a Promising Innovative Medicine (PIM) designation by the MHRA for burosumab encourages other companies to see that the UK is willing to encourage accelerated access to therapies that offer a major advantage over methods currently used in the UK for seriously debilitating conditions with a high unmet need. This all supports the strands of the UK Life Sciences Strategy. A positive, timely recommendation for burosumab by NICE would signal that innovation can be rewarded and help meet the strategic goal of the UK Life Sciences Strategy that the UK should be in the top quartile of comparator

countries, both for the speed of adoption and the overall uptake of innovative, cost-effective products, to the benefit of all UK patients by the end of 2023 (Office for Life Sciences, 2017).

Companies with innovative technologies such as burosumab will ultimately be most attracted to willing to invest in those countries that are ready and able to adopt and reimburse these technologies for the benefit of patients.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

Kyowa Kirin has initiated an international, multicentre, prospective, non-interventional, observational registry of patients with X-linked hypophosphatemia (XLH). The primary objective of the registry is to collect natural history data to characterise the treatment, progression and long-term outcomes of XLH in both adult and paediatric patients, whilst the secondary objective is to describe the efficacy and safety of treatments used to manage the symptoms and signs of XLH.

Eligible patients of any age will have a diagnosis of XLH in the opinion of the treating physician (clinical presentation, radiological, biochemical or genetic investigation results that support diagnosis of XLH).

Once informed consent has been obtained by the patient or their legally designated representative, patients will be enrolled into the XLH Registry, whereby anonymised clinical data will be captured in a secure electronic database. Only clinical data captured as part of the patient's routine clinical practice will be recorded, including the following data sets 1) medical history including drug history and PHEX mutation 2) physical examinations and growth assessments 3) laboratory assessments 4) cardiological investigations 5) radiological examinations alongside patient outcome measures/quality of life information.

Access to anonymised data sets for investigation into the natural history of XLH will be controlled by the XLH Registry Steering Committee, comprising of international clinical and scientific experts in XLH. A key function of the committee includes the review of applications to ensure analysis methods are scientifically sound and relevant to the XLH patient community. Upon application, researchers wishing to access anonymised data must agree to abide by conditions of access set out by the XLH Registry Steering Committee.

The registry is registered on clinicaltrials.gov (Identifier NCT03193476).

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

The clinical trial programme for burosumab is ongoing. Additional analyses are expected from the phase 2 studies as follows and [redacted]:

- Long-term extension of Study CL201 is expected to complete in [redacted].
- The final 64-week analysis of Study CL205 is expected in [redacted].

UX023-CL301 is a Phase III study evaluating the safety and efficacy of burosumab compared to conventional therapy in 60 paediatric patients aged 1 to ≤12 years with XLH who have confirmed evidence of rickets. In addition, this study will evaluate whether every two-week dosing of burosumab improves mobility and health-related quality of life in children with XLH. The primary efficacy and safety analysis from study UX023-CL301 is expected to be available [redacted]. [redacted].

Two additional studies are planned:

- UX023-CL207, open-Label, Phase 3 study, assessing safety, pharmacodynamics and efficacy of burosumab in paediatric patients under one year with XLH.
- UX023-CL401, XLH Disease Monitoring Program, observing disease progression and associated side effects for up to 250 children and adults with XLH.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The draft Summary of Product Characteristics for burosumab states that treatment should be initiated by a physician experienced in the management of patients with metabolic bone diseases. Discussions with NHS England have suggested that treatment with burosumab would only be initiated and prescribed by specialist centres that are members of ERN-BOND: European Reference Network on Rare Bone Disorders. It is planned that burosumab will be supplied via a homecare provider once patients have been established on a maintenance dose. During the initial dose titration period burosumab will be supplied directly to designated hospitals where this option is required. The blood tests required for burosumab monitoring can be carried out in line with local arrangements, without the requirement for a visit to the specialist centre.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Following initiation of treatment at the specialist centre, burosumab is expected to be provided to patients via a homecare service (to be provided and funded by the manufacturer). Therefore, no other additional facilities, technologies or infrastructure will be required to implement the use of burosumab.

Section F - Managed Access Arrangements

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

[redacted]

15.2 Describe the specifics of the MAA proposal

[redacted]

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

[redacted]

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Surender, K., Kochar, I.P.S., Ahmad, A., et al. (2014) Hereditary vitamin D rickets: A case series in a family. Journal of Pediatric Endocrinology and Metabolism, 27 (11–12): 1217–1222

Thacher, T.D., Fischer, P.R., Pettifor, J.M., et al. (2000) Radiographic scoring method for the assessment of the severity of nutritional rickets. Journal of tropical pediatrics [online], 46 (3): 132–139. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10893912

The Human Gene Mutation Database (at the Institute of Medical Genetics in Cardiff

(n.d.). [online]. Available from: http://www.hgmd.cf.ac.uk/ac/gene.php?gene=PHEX [Accessed 5 January 2018]

The XLH Network Inc. (2017) Weak Bones, Strong Wills: The Stories of XLH. 1st ed. CreateSpace Independent Publishing Platform

Ultragenix (2016) UX023-CL001 Online Questionnaire to Characterize the Burden of Illness in Adults and Children with X-linked Hypophosphatemia (XLH)

Ultragenyx (2016) UX023-CL002 Clinical Study Interim Report: A Retrospective Longitudinal Study of Skeletal Outcomes in Children with X-linked Hypophosphatemia (XLH)

Ultragenyx (2017) UX023-CL201 Clinical Study Report

Veilleux, L.N., Cheung, M.S., Glorieux, F.H., et al. (2013) The muscle-bone relationship in X-linked hypophosphatemic rickets. Journal of Clinical Endocrinology and Metabolism, 98 (5)

Vera, C.L., Cure, J.K., Naso, W.B., et al. (1997) Paraplegia due to ossification of ligamenta flava in X-linked hypophosphatemia: A case report. Spine, 22 (6): 710–715

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Xie, F., Cen, Z., Chen, L., et al. (2014) Cervical spinal cord compression caused by X-linked hypophosphatemic rickets with a novel PHEX mutation. Neurology India. 62 (4) pp. 457–459

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XLH Link (2018b) Your Emotional Wellbeing [online]. Available from: http://xlhlink.com/en/health-wellness/your-emotional-wellbeing.html [Accessed 26 January 2018]

Yamazaki, Y., Okazaki, R., Shibata, M., et al. (2002) Increased Circulatory Level of Biologically Active Full-Length FGF-23 in Patients with Hypophosphatemic Rickets/Osteomalacia. The Journal of Clinical Endocrinology & Metabolism [online], 87 (11): 4957–4960. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12414858 [Accessed 5 February 2018]

Yue, H., Yu, J., He, J., et al. (2014) Identification of Two Novel Mutations in the PHEX Gene in Chinese Patients with Hypophosphatemic Rickets/Osteomalacia. PLOS ONE [online], 9 (5): e97830. Available from: https://doi.org/10.1371/journal.pone.0097830

Zhang, L., Watts, L., Turner, A., et al. (2016) Using the RUDY study platform to capture quality of life of adults with rare diseases of the bone. Osteoporosis International Conference: World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2016): Poster Abstracts [online], 27 (1): 79–548. Available from: https://doi.org/10.1007/s00198-016-3530-x

Živičnjak, M., Schnabel, D., Staude, H., et al. (2011) Three-year growth hormone treatment in short children with X-linked hypophosphatemic rickets: effects on linear growth and body disproportion. The Journal of clinical endocrinology and metabolism [online], 96 (12): E2097-105. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21994957

17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases searched were Medline, Embase and the Cochrane Library (Central Register of Controlled Trials).

17.1.2 The date on which the search was conducted.

Initial searches of Embase and Medline were carried out in April 2016. Searches were updated in April 2017 and November 2017.

The Cochrane Library was searched on the 23rd January 2018. It should be noted that this search was carried out independently from the main review and is not considered in the PRISMA diagram shown in Figure 5. There were nine results from this search, of which two were considered relevant to the scope of this submission:

- Carpenter TO, Olear EA , Zhang JH , et al. Effect of paricalcitol on circulating parathyroid hormone in X-linked hypophosphatemia: a randomized, double-blind, placebo-controlled study. Journal of clinical endocrinology and metabolism, 2014, 99(9), 3103
- Carpenter TO , Keller M , Schwartz D , et al. 24,25 Dihydroxyvitamin D supplementation corrects hyperparathyroidism and improves skeletal abnormalities in X-linked hypophosphatemic rickets -a clinical research center study. Journal of clinical endocrinology and metabolism, 1996, 81(6), 2381

Both are duplicates of studies identified in the main review.

17.1.3 The date span of the search.

MEDLINE and EMBASE were searched from the earliest date available for each database up to the end of October 2017.

The Cochrane Library was searched from inception to December 2017.

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A search of the MEDLINE was performed using medical subject heading (MeSH) term “familial hypophosphatemic rickets” or (X-linked hypophospha$) AND exploded MeSH terms: “Case-Control Studies”, “Cohort Studies”, “Longitudinal Studies”, “Follow-Up Studies”, “Cohort Effect”, “Retrospective Studies”, “Prospective Studies”, “Cross-Sectional Studies”, “clinical trial”, “random allocation”, (observational stud$), (case control), (cohort$), (longitudinal), (follow-up), (retrospective), (prospective) OR (cross sectional)

A search of EMBASE was performed using the MeSH term “familial hypophosphatemic rickets” or (X-linked hypophospha$) AND exploded MeSH terms: “Case-Control Study”, “Cohort Analysis”, “Longitudinal Study”, “Follow-Up”, “Retrospective Study”, “Prospective Study”, “Cross-Sectional Study”, “”clinical trial (topic)””, “Controlled clinical trial”, “randomization”, (observational stud$), (case control), (cohort$), (longitudinal), (follow-up), (retrospective), (prospective) OR (cross sectional)

The Cochrane Library was searched using the MeSH term: “Familial Hypophosphatemic Rickets”.

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

The EU Clinical Trials Register was searched to identify ongoing studies. The U.S. National Institutes of Health clinical trials *registry and results* database (clinicaltrails.gov) was searched to identify ongoing studies or results that may not have been published (i.e. reducing the risk of publication bias in the review).

A public web search engine was used to search for centres offering counselling for patients with the disorder, rare diseases in general and networks that establish collaboration between XLH patients, XLH researchers and government bodies that administer national medical resources for the condition. Online case reports and clinical studies published by these organisations and networks were manually searched. Three main journals in Endocrinology and bone research were also hand searched for additional relevant references (Endocrine Reviews, Journal of Bone and Mineral Research, Bone). Reference lists in any relevant systematic reviews, in

relevant publications from centres of XLH applied research or from authors who frequently publish XLH related articles were manually hand-searched to identify studies that may have been missed in the computer-assisted search strategy. Experts and clinical specialists of XLH were consulted for information (e.g. protocols or results) about unpublished or ongoing studies and missing references from the computer-assisted search strategy including articles or reports that may not have been available in the databases.

17.1.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Children or adults with XLH.
Interventions	Any
Outcomes	Reported statistical findings on clinical outcomes (either benefits or adverse effects).
Study design	Studies with a quantitative analytical approach and a study design of case comparison or interventional design (experimental or observational), including: Randomised Control Trials (RCTs), cluster RCTs, non-randomised controlled studies (including controlled before and after studies) and interrupted time series studies (with time points before and after the intervention to establish an underlying trend in the outcome).
Language restrictions	English
Search dates	Database inception to October 31st 2017 (Embase and Medline) and to December 2017 (Cochrane Register of Controlled Trials)
Exclusion criteria	
Population	None
Interventions	None
Outcomes	None
Study design	Animal studies or biochemical or cellular level investigations. Studies with a qualitative design, review articles or articles that investigate the genetic characteristics of XLH.
Language restrictions	Languages other than English.
Search dates	None

17.1.7 The data abstraction strategy.

The review author independently assessed the titles and abstracts of all citations identified by the literature search strategy for clinical outcomes of treatment strategies of XLH. In this process all irrelevant titles were excluded and full-text papers obtained where titles were deemed to be relevant. Where there was uncertainty as to the eligibility based on title and abstract alone the full text was reviewed. If more information was required to determine the articles eligibility the

reviewer read the full text to find if a process article associated with the study which outlines further information was available. If no such article was available, the authors were contacted for additional information. Where there was uncertainty as to the relevance of the information presented in the articles, a second independent researcher reviewed it in a duplicate, independent and unblinded manner to achieve a consensus.

When an included study referred to a process evaluation or other methodological detail published elsewhere in a separate paper these additional articles were obtained (when referred to in the primary paper) and considered as part of the included study. This is because they will likely contain important information needed to understand the implementation of the intervention and adequately assess the risk of bias of the study. Multiple reports of the same study were collated, so that each study (rather than each article) is the unit of interest in the review. To avoid duplication of clinical evidence, articles with identical clinical treatment that did not report any new outcomes were excluded.

17.2 Appendix 2: Search strategy for adverse events

Adverse events were included in the searches described in 17.1.

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The databases searched included all those above: Medline, Embase, EconLIT and the NHS Economic Evaluation Database.

Three main journals in Endocrinology and bone research were also hand searched for additional relevant references (Endocrine Reviews, Journal of Bone and Mineral Research, Bone). Reference lists in any relevant systematic reviews, in relevant

publications from centres of XLH applied research or from authors who frequently publish XLH related articles were also manually hand-searched to identify studies that may have been missed in the computer-assisted search strategy. Experts and clinical specialists of XLH were consulted for information (e.g. protocols or results) about unpublished or ongoing studies and missing references from the computer-assisted search strategy including articles or reports that may not currently be available in the databases.

17.3.2 The date on which the search was conducted.

November 2017.

17.3.3 The date span of the search.

All databases were searched starting at the earliest date available for each database and ending in October 2017.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A search of MEDLINE was performed using medical subject heading (MeSH) term “familial hypophosphatemic rickets” or (X-linked hypophospha$) AND exploded MeSH terms “Economics”, “”Cost and Cost Anlysis””, “cost-benefit analysis”, “cost-benefit”, (cost AND benefit), (cost AND analysis), (benefit AND analysis), (cost effectiveness), (cost-minimization), (simulation model), (economic$ analys$), (economic$ evaluation$),(cost-utility), (cost-minimi$), (cost minimi$), (cost-consequence$),(cost consequence$), (value-of-information),(value of information), (decision-tree), (decision tree), (markov), (state-transition) or (state transition), (individual-patient simulation), (health-economi$), (economi$), (decision-analytic$), (quality-adjusted) , (quality adjusted), (QALY), (QALYs), (disability-adjusted), (DALY), (DALYs), (utility).

A search of EMBASE was performed using medical subject heading (MeSH) term “familial hypophosphatemic rickets” or (X-linked hypophospha$) AND exploded MeSH terms “Economics”, “Health Economics”, “”cost benefit analysis””, “”cost minimization analysis””, “”cost effectiveness analysis””, “”cost utility analysis””, “”program cost effectiveness””, “”cost of illness””, (cost AND benefit), (cost AND analysis), (benefit AND analysis), (cost effectiveness), (cost-minimization),

(simulation model), (economic$ analys$), (economic$ evaluation$),(cost-utility), (cost-minimi$), (cost minimi$), (cost-consequence$),(cost consequence$), (value-of-information),(value of information), (decision-tree), (decision tree), (markov), (state-transition) or (state transition), (individual-patient simulation), (health-economi$), (economi$), (decision-analytic$), (quality-adjusted), (quality adjusted), (QALY), (QALYs), (QALITY), (disability-adjusted), (DALY), (DALYs), (utility).

A search of ECONLIT was performed using medical search terms (hypophosphat£) OR (genetic rickets), (X-lin$), (X lin$).

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The systematic literature review reported for the cost-effectiveness covered resource identification, measurement and valuation. See section 17.3.1.

17.4.2 The date on which the search was conducted.

See section 17.3.2.

17.4.3 The date span of the search.

See section 17.3.3.

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 17.3.4.

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See section 17.3.5.

17.4.6 The inclusion and exclusion criteria.

See section 11.1.2.

17.4.7 The data abstraction strategy.

All studies that met the inclusion criteria were considered. The quality of any studies included is discussed in section 12.3.2.

17.5 Appendix 5: Burosumab publication list and conventional therapy studies identified in the clinical literature review

Table 63. Burosumab publication list

Study	Citation
CL201	Carpenter, T. O., et al. (2016). "Randomized, open-label, dose-finding, phase 2 study of KRN23, a human monoclonal anti-FGF23 antibody, in children with x-linked hypophosphatemia (XLH)." Endocrine Reviews **Conference**: 98th Annual Meeting and Expo of the Endocrine Society, ENDO 2016. United States. Conference Start: 20160401. Conference End: 20160404. 20160437 (20160402 Supplement 20160401)
CL201	Carpenter T, Högler W, Imel WE, et al (2016). Effect of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Rickets Children with X-linked Hypophosphatemia (XLH):40- Week Interim Results from a Randomized, Open-label Phase 2 Study. Latin American Society for Pediatric Endocrinology (SLEP), November 8-11, 2016, Buenos Aires, Argentina.
CL201	Carpenter T, Imel E, Boot A, et al (2016). A Randomized, Open-label Phase 2 Study of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, in 52 Children with X-linked Hypophosphatemia (XLH): 40-Week Results. Presented at: American Society for Bone and Mineral Research (ASBMR), September 16-19, 2016, Atlanta, GA, USA.
CL201	Carpenter T, Imel E, Boot A, et al. (2017) A Randomized, Open-label Phase 2 Study of KRN23, an Investigational Fully Human Anti-FGF23 Monoclonal Antibody, in Children with Xlinked Hypophosphatemia (XLH): 64-Week Results. Presented at: World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO). March 23-26, 2017, Florence, Italy/ Osteoporosis International **28 (1 Supplement 1)**: S63.
CL201	Hogler, W., et al. (2017). "A randomized, open-label phase 2 study of KRN23, an investigational fully human anti-FGF23 monoclonal antibody, in children with X-linked hypophosphatemia (XLH): 64-week results." Calcified Tissue International **100 (1 Supplement 1)**: S129-S130.
CL201	Padidela R, Hogler, W, Portale, A et al (2017). A Randomized, Open-label Phase 2 Study of KRN23, an Investigational Fully Human Anti-FGF23 Monoclonal Antibody, in Children with X-linked Hypophosphatemia (XLH). International Conference on Children's Bone Health, 10-13 June 2017 , Würzburg Germany.
CL201	Padidela R, van't Hoff W, Högler W, et al (2016). Effect of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Rickets in Children with X-linked Hypophosphatemia (XLH): 40-Week Interim Results from a Randomized, Open-label Phase 2 Study. Presented at: British Society for Paediatric Endocrinology and Diabetes (BSPED), November 23-25, 2016, Nottingham, UK
CL201	Imel E, Carpenter T, Boot A, et al (2016). Effect of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Rickets in Children with X-linked Hypophosphatemia (XLH): 40-week Interim Results from a Randomized, Open-label Phase 2 Study. Presented at: European Calcified Tissue Society (ECTS) Annual Meeting, May 14-17, 2016, Rome, Italy

CL201	Imel E, Carpenter T, Linglart A, et al (2016). Evaluating the Effects of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Functional Outcomes in Children with X-linked Hypophosphatemia (XLH): 40-week Interim Results from a Randomized, Open-label Phase 2 Study. Presented at: American Society for Bone and Mineral Research (ASBMR), September 16-19, 2016, Atlanta, GA, USA
CL201	Carpenter T, Imel E, Linglart A et al (2017). Effects of Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody, on Functional Outcomes in Children with X-linked Hypophosphatemia (XLH): Final Results from a Randomized, 64-week, Open-label Phase 2 Study. Presented at: the American Society for Bone and Mineral Research (ASBMR), September 8-11, 2017, Denver, Colorado.
CL201	Whyte M, Portale, A, Imel, E et al (2017). Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody for X-linked Hypophosphatemia (XLH): Final 64-Week Results of a Randomized, Open-label, Phase 2 Study of 52 Children. PPresented at: the American Society for Bone and Mineral Research (ASBMR), September 8-11, 2017, Denver, Colorado.
CL201	Boot AM, Linglart, A van't Hoff W, et al (2017). A Randomized, Open-label Phase 2 Study of KRN23, an Investigational Fully Human Anti-FGF23 Monoclonal Antibody, in Children with X-linked Hypophosphatemia (XLH): 64-Week Results. Presented at: Dutch Endocrine Meeting (DEM), February 11, 2017, Noordwijkerhout, Netherlands.
CL201	Linglart A, Carpenter T, Imel E, et al. (2016) Effect of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Rickets in Children with X-linked Hypophosphatemia (XLH): 40-week Interim Results from a Randomized, Open-label Phase 2 Study. Presented at: European Society for Paediatric Endocrinology (ESPE), September 10-12, 2016, Paris, France
CL201	Linglart A, Dvorak-Ewell M, Marshall A et al (2015). Impaired Mobility and Pain Significantly Impact the Quality of Life of Children with X-Linked Hypophosphatemia (XLH). Presented at: International Conference on Children's Bone Health (ICCBH), June 27-30, 2015, Salzburg, Austria
CL201	Linglart A, Imel E, Boot A, et al. (2016) A Randomized, Open-label Phase 2 Study of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, in 52 Children with X-linked Hypophosphatemia (XLH): 40-Week Results. Presented at: Congrès de la Société Française d'Endocrinologie (SFE), October 5-8, 2016, Bordeaux, France.
CL201	Portale A, Imel E, Boot A. (2016) Effect of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Rickets in Children with X-linked Hypophosphatemia (XLH): 40-week Interim Results from a Randomized, Open-label Phase 2 Study. Presented at: American Academy of Pediatrics (AAP), October 22-25, 2016, San Francisco, CA
CL201	Portale A, Imel E, Linglart A, et al. (2016) KRN23, a Fully Human Monoclonal Antibody to FGF23, Reverses Renal Phosphate Wasting and Improves Rickets in Children with Xlinked Hypophosphatemia (XLH). Presented at: American Society of Nephrology (ASN), November 17-20, Chicago, IL
CL205	Imel E , Carpenter T, Gottesman GS, et al (2017). KRN23 Effects on Phosphate and Vitamin D Dysregulation in Children <5 Years Old With X-linked hypophosphatemia (XLH). Presented at: International Conference on Children's Bone Health (ICCBH), June 10-13, 2017, Würzburg, Germany.
CL205	Imel E , Carpenter T, Gottesman GS, et al (2017). The Effects of Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody, on Phosphate Metabolism and Rickets in 1 to 4 Year-Old Children with X-linked Hypophosphatemia (XLH). Presented at: American Society for Bone and Mineral Research (ASBMR), September 8-11, 2017, Denver, Colorado.

CL205	Carpenter T , Imel E, Gottesman GS, et al. (2017) KRN23 Effects on Phosphate and Vitamin D Metabolism in Children <5 Years Old With X-linked Hypophosphatemia (XLH). Presented at: 10th International Meeting of Pediatric Endocrinology, September 14-17, 2017, Washington, DC.

Table 64. List of conventional studies in paediatric patients (n=29)

Reference	Study design	Study population	Treatment	Outcome summary	Citation
Adamsbaum, Lempicki et al. 2015	Cross-section, Prospective study.	27 XLH children (Age of children not stated).	Phosphate, active vitamin D3.	Bone structure: The median maximum width of physis was 5.6 mm (4.8 - 7.8) and medium transverse extent of the widening was 55% (42.9 - 66.2). Treatment failed to prevent: Zone of provisional calcification appearance on 21 MRIs (78%). Harris lines on 24 MRIs (89%). Bone marrow signal abnormalities on 16 MRIs (59%). (7%) with Osteochondritis.	C. Adamsbaum, M. Lempicki, A. Rothenbuhler, V. et al 2015. MRI features as surrogate markers of X-linked hypophosphatemic rickets activity Pediatric Radiology 1: S350
Al-Jundi, Al-Naimy et al. 2010	Retrospective, cross section, case comparison (to healthy patients)	21 children with hypophosphataemic rickets (mean age:10.07±3.2)	Review of medical records, dental inspection. Treatment regimen of XLH patients not stated.	Treatment failed to prevent: Smaller dental arches in patients with XLH.	S. H. Al-Jundi, Y. F. Al-Naimy and S. Alsweedan. 2010 Dental arch dimensions in children with hypophosphataemic Vitamin D resistant rickets European archives of paediatric dentistry: official journal of the European Academy of Paediatric Dentistry 11 (2): 83-87
Alon 2013	Prospective study, Long term follow up (21.2± 5.3 months)	8 children (median age: 13.9y, range: 7.8-20.9y)	Phosphate, Calcitriol, Cinacalcet.	The addition of the calcimimetic: (1) resulted in significant (information on critical levels not available) decreases in PTH and FGF23 and increase in TP/GFR enabling significant decreases in calcitriol. Height SDS improved in 2 patients, were unchanged in 2 and decreased in 1 (information on mean changes not available). Nephrocalcinosis present in one child at baseline did not change. It developed in another child during study.	U. Alon. 2013. Cinacalcet as adjunct therapy in familial hypophosphatemic rickets: 18 months experience Journal of Bone and Mineral Research. Conference 28 (no pagination)
Alon, Levy-Olomucki et al. 2008	Prospective study, case comparison, short term follow up (between 2 and 6 weeks).	N=8 with XLH (median age at enrollment: 13y; range: 6-19y)	Phosphate, calcitriol, cinacalcet.	XHL group: Serum Ca (mmol/L, Baseline: 1.28±0.03; final follow up: 1.24±0.07); Serum Pi (mmol/L, Baseline: 2.1±0.4; final follow up: 2.9±0.6); PTH(pg/ml, Baseline: 53±13; final follow up: 33±15); FGF23 (ng/mL, Baseline: 149±67; final follow: 247±195); serum values of 1,25(OH)2D(Baseline: 75±44;final follow: 14±6); TMP/GFR(mg/dl , Baseline: 1.81±0.42;final follow: 1.86±0.7);UCa/Cr (Baseline: 0.06±0.04);final follow: 0.14±0.05)	U. S. Alon, R. Levy-Olomucki, W. V. Moore, et al. 2008. Calcimimetics as an adjuvant treatment for familial hypophosphatemic rickets Clinical journal of the American Society of Nephrology : CJASN 3 (3): 658-664
Ariceta and Langman 2007	Retrospective, long term follow up (up to 10 years).	27 children with XLH (medium age: 10.12 y, range: 1.58-18.56)	Phosphate, calcitriol, growth hormone (n=4)	Z-height: at baseline = −1 (−4.58; 0.54); at final follow up −0.91 (−4.56; 0.17) P=0.465. At final follow up n=8 (29.2%) had a Z-height more negative then −2SD. Treatment did not lead to: “catch up” in patients’ growth, despite optimal medical treatment and rickets judged to be healed.	G. Ariceta and C. B. Langman 2007 Growth in X-linked hypophosphatemic rickets European Journal of Pediatrics 166 (4): 303-309

Reference	Study design	Study population	Treatment	Outcome summary	Citation
Brasseur and Linglart 2011	Retrospective, cross section	46 XLH patients (range: 10-16 y)	Phosphorus, alfacalcidol, calcitriol,	A decrease in calciuria, widely variating phosphaturia, increased incidence of hyperparathyroidism (statistics not available). Treatment failed to prevent: hyperparathyroidism.	B. Brasseur and A. Linglart. 2011. Retrospective review of a cohort of X-linked hypophosphatemic rickets adolescent patients: How could we do better? Hormone Research in Paediatrics 76: 62
Capelli, Donghi et al. 2015	Cross-section, Prospective study.	26 XLH children (mean age at beginning of treatment: 3y7m, range: 1y2m - 9y10m)	Phosphate, Calcitriol	Treatment failed to prevent: n=24 (92%) bowing of legs, n=2 (8.3%) poor growth, n=2 (8.3%) swelling of wrist and/or ankle, n=1 (4.1%) delayed dentition	S. Capelli, V. Donghi, K. Maruca, et al. Weber 2015 Clinical and molecular heterogeneity in a large series of patients with hypophosphatemic rickets. Bone 79: 143-149
Colares Neto, Correa et al. 2012	Prospective study, cross section	7 XHL child (age information not available)	Genetic analysis, renal ultrasound, CT scan, treatment regimen not known.	No patients had nephrolithiasis, hypocitraturia or impaired renal function	G. Colares Neto, P. H. Correa and R. Matsunaga. 2012. Nephrolithiasis and nephrocalcinosis screening by CT scan in children with X-linked hypophosphatemic rickets confirmed by the presence of PHEX mutations. Hormone Research in Paediatrics 78: 36
Colares Neto, De Souza et al. 2012	Prospective study, cross section	9 XHL child (age information not available)	Dental inspection, genetic analysis, Treatment regimen not known.	None had dental abscesses or periapical lesions. N=1 (11%) with dental caries; n=3 (33.3%) with teeth restoration; N=4 (44%) with permanent dentition; n=4 (44%) with mixed dentition; n=1 (11%) with deciduous teeth. Treatment failed to prevent: N=6 (66.7%) with areas of hypomineralization; N=7 (77.8%) with taurodontism.	G. Colares Neto, S. De Souza, R. Antequera, et al. 2012 Dental abnormalities in children with X-linked hypophosphatemic rickets confirmed by the presence of PHEX mutations. Hormone Research in Paediatrics 78: 37
De Paula Colares Neto, Silveira Corre et al. 2013	Retrospective, cross section	11 children with XLH (No information available on ages)	Vitamin D analogues, phosphate	All had leg deformities, hyperphosphaturia and most had short stature (statistics not available). N= 4 (36.4%) signs of bilateral nephrocalcinosis. Treatment failed to prevent: leg deformities, hyperphosphaturia, short stature, nephrocalcinosis.	G. De Paula Colares Neto, P. H. Silveira Corre and R. M. Martin. 2013. Evaluation of nephrocalcinosis and nephrolithiasis in eleven children with X-linked hypophosphataemic rickets confirmed with mutations in PHEX gene Hormone Research in Paediatrics 80: 219
Endo, Fukumoto et al. 2015	Cross-section, survey design	84 FGF23- related hypophosphatemic diseases: 41 children (0-9 y) with genetic hypophosphatemic disease, 36 XLH children (0-7y).	Phosphate, active vitamin D3.	Prevalence XHL: 1 in 20,000. Serum Pi and TmP/GFR was not normalized with treatment	I. Endo, S. Fukumoto, K. Ozono, N. Namba, et al. 2015. Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: Prevalence, biochemical data and treatment Endocrine Journal 62 (9): 811-816
Glorieux, Marie et al. 1980	Prospective study, long term follow up (2850 patient days), control (healthy children)	11 XHL children (age at enrollment mean: 7.84y, range: 1.75y to 11.5y); 43 healthy child controls (1-14 y)	Phosphate, calcitriol, ergocalciferol	Treatments failed to prevent: Renal phosphate leak or mineralization of endosteal bone surface	Glorieux FH, Marie PJ, Pettifor JM, et al. 1980. Bone response to phosphate salts etigocalciferol and calcitriol in hypophosphatemic vitamin-D resistant rickets. N Engl J Med 303:1023-31

Reference	Study design	Study population	Treatment	Outcome summary	Citation
Glorieux, Scriver et al. 1972	Prospective follow up, long term follow up (11297 patient days), control (healthy children)	Eight children with XLH (age not stated)	Phosphate, vitamin D2	During treatment: Serum Pi 4.0±0.8 mg per 100ml (range, 2.8±0.4 to 4.9 +- 0.9). Serum Pi with treatment different from absence of treatment ($p<0.05$) and not different ($p<0.05$) from control. Average linear-growth velocity for the patient group: 63±24 (before treatment) and 126±22 (after treatment) per cent of the normal rate on the 50th percentile. A difference ($p<0.05$) in whole-blood oxygen pressure at 50 per cent oxygen saturation between: those with and without treatment; with treatment and the control group. No differences ($P>0.05$) between treated and control in haemoglobin concentration, haematocrit or blood pH. N=8 (100%) had rickets resolved (not statistics of rickets severity presented). N=5 (62.5%) had Dwarfism corrected. Treatment resulted in: N=5 (62.5%) with hypercalcemia; N=1 (12.5%) with severe hyperparathyroidism. Generalized hyperaminocidura was apparent when secondary hyperarathyroidism developed.	F. H. Glorieux, C. R. Scriver, T. M. Reade, H. Goldman et al. 1972. Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia. The New England journal of medicine 287 (10): 481-487
Kruse, Hinkel et al. 1998	Prospective, control (healthy patients), long term follow up (12 to 68 months, median 27 months).	8 infants with XLH	Phosphate, calcitriol	Treatment failed to prevent: Height SDS: n=2 (25%) below x-2 SD; n=4 (50% slightly decreased within the normal range. N=3 (37.5%) and n=1 (12.5%) radiological signs of rickets and biochemical signs of rickets;n=4 (50%) moderate leg deformities; n=5 (62.5%) transient metaphyseal widening, fraying and slight cupping of the distal femur and proximal tibia; n=3 (37.5%) medial tibial condyles being 3±4 cm; n=1 (12.5%) genu valgum with a space of 4 cm between the internal malleoli. Treatment associated with: N=2 (12.5%) grade 1 nephrocalcinosis; n=1 (25%) grade 2 nephrocalcinosis.	K. Kruse, G. K. Hinkel and B. Griefahn. 1998. Calcium metabolism and growth during early treatment of children with X- linked hypophosphataemic rickets. European Journal of Pediatrics 157 (11): 894-900
Lempicki, M., et al. 2017	Prospective single-centre observational study	27 XLH patients (median age 9.2 years)	Phosphate supplements and alfacalcidol	The study describes correlations with MRI and disease activity and concluded that MRI of the knee provides precise rickets patterns that are correlated with ALP.	Lempicki, M., et al. 2017. "Magnetic Resonance Imaging Features as Surrogate Markers of X-Linked Hypophosphatemic Rickets Activity." Hormone Research in Paediatrics 87(4): 244-253.
Makitie, Doria et al. 2003	Retrospective review, long term follow up (up to 17 years)	19 XLH patients (n=8 early treatment “group 1”, median age 0.35 y, range: 0.15–0.58 y; n=11 with treatment onset at a median age of 2.1 y, range: 1.3–8.0 y “group 2”).	Phosphate, calcitriol	Mean change in height z score by age 9.0 yr was - 0.3 SDS in group 1 and - 0.5 SDS for group 2. In the first year of treatment: High Pi dose associated with less grow (mean change, - 0.5 SDS) than lower doses (mean change, - 0.2 SDS; P>0.05); Serum Pi and Alk phos normalised in: n=6 (75%) [median, -1.5 SDS] and n=5 (26.5%) [median, -0.8 SDS ; P=0.07] in group 1; n=1 (9%) [median, -3.0 SDS; P>0.05] and n=3 (27.2%) [median, +2.6 SDS; P=0.07] in group 2 . Treatment associated with: Secondary hyperparathyroidism in N=18 (95.7%); tertiary hyperparathyroidism in N=1 (5.2%); nephrocalcinosis in n=11 (57.8%); varus deformity and craniosynostosis in n=2 (10.5%); significant skeletal rickets.	O. Makitie, A. Doria, S. W. Kooh, W. G. et al. 2003 Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets Journal of Clinical Endocrinology and Metabolism 88 (8): 3591-3597

Reference	Study design	Study population	Treatment	Outcome summary	Citation
Miyamoto, Koto et al. 2000	Retrospective study, long term follow up (at least 5 years)	22 XLH patients: 10 XHL treated with vitamin D2 (Mean age: 54.7 ± 50.3months); 12 XHL treated with 1 a-hydroxyvitamin D3(Mean age: 47.0±42.7m)	Phosphate, vitamin D2. 1 alpha(OH)D 3	All patients (z scores): Initial Height (2.38±0.88);Final Height (-1.69±1.11);Change in height (-1.31±1.10, P<0.01). Treated with vitamin D2 (z scores): Initial Height (-2.73±0.78);Final Height (-2.07±0.84);Change in height (-1.41±1.21; P <0.01). Treated with 1 alpha(OH)D3(z scores): Initial Height(-2.07±0.88);Final Height(-1.38±1.24);Change in height(-1.19±1.14 P <0.01) Treatment failed to prevent: Stunting	J. Miyamoto, S. Koto and Y. Hasegawa 2000. Final height of Japanese patients with X-linked hypophosphatemic rickets: Effect of vitamin D and phosphate therapy Endocrine Journal 47 (2): 163-167
Nielsen, Rahbek et al. 2014	Retrospective, cross section	15 HR children (mean age during study: 7.7 months). 12 (80%) of which were XHL (mean age during study: 8.3 months)	Phosphate, active vitamin D3	Mean change height SD from baseline was –0.8 ± 1.4. At the last follow-up, 40% (n = 6) had a height below –2.0 SD. 40% (n = 6) went through one or more bone deformity corrective surgeries of the lower limbs, with an average of two surgeries per patient. Treatment failed to prevent: Short stature: At the last follow-up, 40% (n = 6) had a height below –2.0 SD. 40% (n = 6) required deformity corrective surgeries (average of two surgeries per patient). 6.7% (n=1) developed nephrocalcinosis from overdosing of phosphate. 87% (n = 13) had Secondary Hyperparathyroidism (average PTH max of 11.6 pmol/l)	L. H. Nielsen, E. T. Rahbek, S. S. Beck-Nielsen and H. T. Christesen. 2014. Treatment of hypophosphataemic rickets in children remains a challenge Danish medical journal 61 (7): A4874
Oliveira, Glorieux et al. 2013	Prospective study. Case comparison (between osteogenesis imperfecta (OI) patients, XLH and healthy patients)	152 individuals: 31 with XLH (14.7 ± 7.6 yr), 12 with OI type 6 (26.8 ± 23.3 y), 79 patients with other OI types (12.6 ± 4.8 y) and 30 healthy subjects (20.8 ± 16.1 y).	Vitamin D analogues, phosphate.	Circulating sclerostin levels were higher in the XLH group (31.4 +/- 17.8 pmol/l) than in: healthy controls (22.6 ± 9.6 pmol/l , p = 0.03); OI subjects (21.84 ± 11.8 pmol/l, p = 0.002)	T. Oliveira, F. Glorieux and F. Rauch. 2013. Elevated levels of circulating sclerostin in hypophosphatemic rickets Journal of Bone and Mineral Research. Conference 28 (no pagination)
Ozono, Hasegawa et al. 2014	Prospective study, short-term follow up (1 year 3 months).	16 child XLH patients (Mean: 8.1y ±3y, Range: 3-14y)	Phosphate, active vitamin D3, growth hormone formulation (for 44% of patients)	Delta z-score height: 120.07 ± 17.78; 25OHD vitamin D (ng/ml): 25.0 ± 5.5; 1,25(OH)2D: 71.01 ± 32.05; FGF23 (ng/mL): 319.5 ± 614.6; Treatment associated with: N=16 (100%) experienced adverse conditions. Gastrointestinal adverse drug reactions; 6.3% abdominal pain; 6.3% diarrhea; 44% kidney Calcification. Some patients had PTH levels of more than 130 pg/mL	K. Ozono, Y. Hasegawa, M. Minagawa, et al. 2014. Therapeutic use of oral sodium phosphate (Phosribbon combination granules) in hereditary hypophosphatemic rickets Clinical Pediatric Endocrinology 23 (1) 9-15

Reference	Study design	Study population	Treatment	Outcome summary	Citation
Petersen, Boniface et al. 1992	Retrospective, long term follow up (3 years of treatment), literature review	20 child XLH patients (ages not specified)	Phosphate, calcitriol	Genu vamm: n=2 (10%) at baseline; N=16 (95%) after treatment. Lower extremity deformities: N=15 (90%) at baseline; n=7 (35%) after treatment. n=12 (60%) had Growth velocity Z scores greater than or equal to 0 “G1” and n=8 (40%) below 0 “G2”. Means in G1 and G2 (baseline; after treatment) in: height Z score (G1: -1.92±0.24; - 1.08±0.18)(G2: -2.20±0.26;-2.48±0.27); Urinary Ca excretion (G1:65±9;36±20)(G2:66±16; 153±24 mg Ca per g Cr); Serum Cr (G1:0.51±0.06;0.40±0.06)(G2:0.49±0.05;0.40±0.05); Crclearance (G1:125±26;168±27)(G2:108±32;144±12); Serum Ca(G1:9.75±0.10;9.86±0.07mmol/L)(G2:9.49±0.09;9.69±0.06); Alk phos (G1:388±25;318±16)(G2:359±25,276±32) Treatment associated with: subradiographic nephrocalcinosis present in N=2 (10%) and developed during treatment in n=1 patient (5%).	D. J. Petersen, A. M. Boniface, F. W. Schranck, et al. 1992. X-linked hypophosphatemic rickets: A study (with literature review) of linear growth response to calcitriol and phosphate therapy. Journal of Bone and Mineral Research 7 (6): 583-597
Phatarakijnirund, V., et al. 2016	Long term follow up (15.1 + 4.9 years (6.6-24.1 yrs))	28 former pediatric XLH patients who returned for an outcome study	Phophate, bio-active vitamin D	No efficacy outcomes reported. GFR at Rx cessation was significantly lower in +NC (Nephrocalcinosis) than -NC group (137.4 + 14.8 vs 153.6 + 17.2 mL/min/1.73m2 , p = 0.01). However, no significant difference existed at follow-up: +NC mean GFR 120.8 + 18.9 mL/min/1.73m2 vs. - N C mean GFR 121.8 + 24.5 mL/min/1.73m2 (p = 0.9).	Phatarakijnirund, V., et al. (2016). "Longitudinal study of renal function in adults with x-linked hypophosphatemia and nephrocalcinosis acquired in childhood during treatment with calcitriol and inorganic phosphate." Endocrine Reviews Conference: 98th Annual Meeting and Expo of the Endocrine Society, ENDO 2016. United States. Conference Start: 20160401. Conference End: 20160404. 20160437 (20160402 Supplement 20160401) (no pagination).
Quinlan, Guegan et al. 2012	Retrospective cohort, long term follow up (16 years), case comparison: group 1 (G1) were those who started treatment before 1 year of age, and group 2 (G2) were those who started treatment after 1 year of age	23 children with XHL. N=10 in G1 (medium 8.5y, range: 4.0–15.2y) N=13 in G2 (medium 1.9y, range: 6.2–14.3y)	Phosphate, vitamin D	Median height standard deviation score (HSDS) at treatment onset was normal in G1: 0.1 (interquartile range (IR): -1.3 to 0.4) and significantly (p=0.004) lower in G2 (2.1 IR: -2.8 to -1.4). Final HSDS was significantly (p=0.009) better in G1 [-0.7 IR: -1.5 to 0.3) vs G2 [-2.0 IR: -2.3 to -1.0). Median estimated GFR at final follow-up was [82.3 ml/min/1.73 m2 (IR 72.7–95.9)] for those with nephrocalcinosis and [92.5 (IR 84.4–101.1); p=0.29] for those without it. Treatment failed to prevent: 15 (65.2%) had nephrocalcinosis (68%): 12 (52%) were classified as mild, 3 (12%) as moderate, and none as severe.	C. Quinlan, K. Guegan, A. Offiah, R. O. Neill, et al. 2012. Growth in PHEX-associated X-linked hypophosphatemic rickets: The importance of early treatment. Pediatric Nephrology 27 (4): 581-588
Rabbani, Rahmani et al. 2012	Prospective study, cross section with healthy adult control	19 patients with XLH (mean age was 10 ± 4.23y, range 3-17y).	Dental inspection. Treatment regimen not known.	N=9 (47.3%) with dental caries; N=9 (47.3%) with eruption of the dentition; N=8 (42.1%) had enamel hypoplasia; N=3 (15.8%) had taurodontism; N=2 (10.9%). Dental caries significantly more frequent by 10.5% (P=0.04) than in healthy control matched group. Treatment regimen failed to prevent: Dental defects.	A. Rabbani, P. Rahmani, V. Ziaee and S. Ghodoosi. 2012. Dental problems in hypophosphatemic rickets, a cross sectional study. Iranian Journal of Pediatrics 22 (4) 531-534

Reference	Study design	Study population	Treatment	Outcome summary	Citation
Rafaelsen, Johansson et al. 2016	Retrospective, follow up study.	21 children XLH patients. Mean age at end of study: 12.1y, range: 1.3 to 18.3y.	Phosphate, active form of vitamin D	Prevalence: 1 in 60 000. At final follow up, height z score: -1.4; Delta z-score height: -0.1. Treatment associated with: N=9 (43%) with Nephrocalcinosis (43%). Treatment failed to prevent: n=13 (62%) limb bowing.	S. Rafaelsen, S. Johansson, H. Raeder and R. Bjerknes. 2016. Hereditary hypophosphatemia in Norway: A retrospective population-based study of genotypes, phenotypes, and treatment complications. European Journal of Endocrinology 174 (2): 125-136
Verge, Lam et al. 1991	Prospective study, long term follow up, control (untreated patients)	N=24 XHL patients (age at treatment start, medium: 1.8, range: 0.2 to 11.1)	Phosphate, calcitriol	Height SD score after treatment: -1.08(treated), -2.05(untreated); group SD difference 0.97 (p=0.01). Change in height SD score (only in the period of calcitriol and phosphate therapy) was 0.33 (p=0.05) from baseline of -1.58 to -1.25. Treated: Serum calcium 2.15 to 2.53 mmol per litre; N=3 with serum calcium concentrations >2.75 mmol per litre (range of occasions per patient: 1 to 4); n=15 >2.50mmol (range of occasions per patient: 1 to 11); Urinary Ca excretion was 0.0007 to 0.12 mmol per kilogram per day and Urinary Ca/Cr was 0.015 to 0.89; Serum Cr normal (values not stated); GFR: 1.9±0.4 ml per second per 1.73 m squared of body surface area (range, 1.2 to 2.4). Treatment associated with: n=19 with nephrocalcinosis (79%): of which 37% had grade 1, 26% grade 2, 37% grade 3 and none had grade 4. 42% of patients whom measurements were available had 31 episodes of hypercalciuria	Verge C, Lam A, Simpson J et al. 1991. Effects of Therapy in X-Linked Hypophosphatemic Rickets. N Engl J Med 325:1843-1848
Zivicnjak, Schnabel et al. 2011	Propspective study, case comparison to healthy patients, long term follow up (mean follow-up time 2.6 y)	76 XLH patients (Median age at time of enrolment, 7.3y, range: 2.0–17.4y	Phosphate, calcitriol, active vitamin D.	Stature at study entry (SDS) (−2.5±1.2). During the study: TmP/GFR (0.64±0.22); Serum Pi (mmol/L) (0.90±0.25); PTH (pg/ml) (65.9±39.3); Alk phos (IU/L) (508±196); UCa/Cr(0.30±0.32); Genetic target height (SDS) (−0.17±0.14); XLH patients had significantly reduced stature and shorter body segments than healthy children (i.e. mean stature −2.48 SDS, sitting height −0.99 SDS, arm length −1.81 SDS, leg length −2.90 SDS, each p<0.001) and markedly elevated sitting height index (mean 2.8 SDS, 95% CI 2.58–3.01, p<0.001 vs. healthy children) Treatment failed to prevent: Stunting; disproportionate growth of body segments (trunk and leg length)	M. Zivicnjak, D. Schnabel, H. Billing, et al. 2011. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. Pediatric Nephrology 26 (2): 223-231
Ben Ameur, S., et al. 2017	Retrospective study	8 children with hereditary vitamin D-resistant rickets (HVDRR)	Intermittent intravenous calcium	Six patients were treated with intermittent intravenous calcium treatment via the peripheral route with a clear improvement in 5 cases.	Ben Ameur, S., et al. 2017. "Clinical and Genetic Characterization of Tunisian Children with Hereditary 1,25-Dihydroxyvitamin D-Resistant Rickets." Hormone research in pediatrics 87(1): 23-29.
Ghazi, A. A., et al. 2017	Case study	2 siblings with Hereditary vitamin D resistant rickets (HVDRR)		The 2 siblings were followed up for 27 years. They had rickets, growth retardation, muscle weakness, hypocalcemia and alopecia totalis since early childhood	Ghazi, A. A., et al. 2017. "Hereditary vitamin D resistant rickets: Clinical, laboratory, and genetic characteristics of 2 Iranian Siblings." International Journal of Endocrinology and Metabolism 15(3).

17.6 Appendix 6: Results of deterministic one way sensitivity analysis

Table 65. Deterministic one-way sensitivity analysis results

Parameter	Incremental QALYs		% difference in QALYs		Incremental costs (£)		% difference in costs	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Base case	10.414				[redacted]			
Proportion Female (%)	10.561	10.284	1.4%	-1.3%	[redacted]	[redacted]	-10.3%	4.7%
Specialist Consult cost – children (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Specialist Consult cost – adults (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Laboratory Monitoring cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Radiography cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Renal Ultrasonography cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Dental Check Up cost - children (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Dental Check Up cost - adults (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Specialist Consult resource use – children (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Laboratory Monitoring resource use – children (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Radiography resource use – children (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Renal Ultrasonography resource use – children (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Dental Check Up resource use – children (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Specialist Consult resource use – adults (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Laboratory Monitoring resource use – adults (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Radiography resource use – adults (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Renal Ultrasonography resource use – adults (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Dental Check Up resource use – adults (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%

Parameter	Incremental QALYs		% difference in QALYs		Incremental costs (£)		% difference in costs	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Oral Phosphate cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.1%	-0.1%
Alfacalcidol cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.1%	-0.1%
Oral Phosphate dose – children (tablet/day)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Alfacalcidol dose – children (nanogram/kg/day)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Oral Phosphate dose – adults (tablet/day)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.1%	-0.1%
Alfacalcidol dose – adults (nanogram/kg/day)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.1%	-0.1%
Nurse visit cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Blood test cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Nurse visit frequency (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Blood test frequency (visit/year)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Physiotherapy cost child (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Physiotherapy cost adult (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.1%	-0.1%
Physiotherapy resource child (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Physiotherapy resource adult (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.1%	-0.1%
Dental Abnormalities cost - child (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Osteotomy cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Stapling of Growth Plates cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Dental Abnormalities cost - adult (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Hip Arthroplasty cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Knee Arthroplasty cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Dental Abnormalities resource use – child (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Osteotomy resource use (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Stapling of Growth Plates resource use (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%

Parameter	Incremental QALYs		% difference in QALYs		Incremental costs (£)		% difference in costs	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Dental Abnormalities resource use - adult (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Hip Arthroplasty resource use (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Knee Arthroplasty resource use (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Injection site reaction cost (£)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Injection site reaction resource use (%)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Severe utility (age 1-4)	10.424	10.403	0.1%	-0.1%	[redacted]	[redacted]	0.0%	0.0%
Moderate utility (age 1-4)	10.414	10.407	0.0%	-0.1%	[redacted]	[redacted]	0.0%	0.0%
Mild utility (age 1-4)	10.396	10.432	-0.2%	0.2%	[redacted]	[redacted]	0.0%	0.0%
Healed utility (age 1-4)	10.401	10.427	-0.1%	0.1%	[redacted]	[redacted]	0.0%	0.0%
Severe utility (age 5-12)	10.552	10.276	1.3%	-1.3%	[redacted]	[redacted]	0.0%	0.0%
Moderate utility (age 5-12)	10.414	10.060	0.0%	-3.4%	[redacted]	[redacted]	0.0%	0.0%
Mild utility (age 5-12)	10.121	10.483	-2.8%	0.7%	[redacted]	[redacted]	0.0%	0.0%
Healed utility (age 5-12)	10.230	10.493	-1.8%	0.8%	[redacted]	[redacted]	0.0%	0.0%
Severe utility (age 13+)	12.405	9.011	19.1%	-13.5%	[redacted]	[redacted]	0.0%	0.0%
Moderate utility (age 13+)	10.414	10.414	0.0%	0.0%	[redacted]	[redacted]	0.0%	0.0%
Mild utility (age 13+)	8.334	12.793	-20.0%	22.9%	[redacted]	[redacted]	0.0%	0.0%
Healed utility (age 13+)	7.191	13.637	-30.9%	30.9%	[redacted]	[redacted]	0.0%	0.0%

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Highly Specialised Technologies (HST)

Burosumab for treating X-linked hypophosphataemia [ID1151]

Dear Paul,

The Evidence Review Group, Kleijnen Systematic Reviews Ltd (KSR), and the technical team at NICE have looked at the submission received on 12 February 2018 from Kyowa Kirin Limited. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **12noon** on **Wednesday 21 March**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/46663

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Paling, Technical Lead (Thomas.Paling@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.Ekeledo@nice.org.uk).

Yours sincerely,

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Section A: Clarification on effectiveness data

Literature searching

A1. **Priority Question**: Please provide the following information for each individual database searched (MEDLINE, Embase, CENTRAL, EU Clinical Trials Register, ClinicalTrials.gov) in sufficient detail that they can be reproduced:

- Database host/interface (e.g. Ovid, ProQuest etc.).
- Database field(s) searched for each search term.
- Number of results retrieved by each search line, and the overall number retrieved from each database.

A2. **Priority Question**: The searches run for clinical effectiveness data would appear insufficient to also identify adverse events data (section 9.7.1) – for example no search terms are included for the intervention in the strategy. Please supply and run additional searches suitable for identifying studies on adverse events.

Clinical evidence

A3. **Priority Question**: Please provide full Clinical Study Reports (CSRs) for studies CL201, CL205 and CL002, including all tables and appendices.

A4. **Priority Question**: Please provide full details, results and the full CSR for the study mentioned on page 13 of the company submission (CS) "Kyowa Kirin also commissioned a longitudinal review of patient records from three expert UK centres to provide additional data (n=43)".

A5. **Priority Question:** Please provide the full data set provided to Kyowa Kirin by the British Paediatric and Adolescent Bone Group (BPABG) in May 2017, used to estimate the number of patients in key treatment centres in England, and mentioned on Page 17.

A6. **Priority Question**: Please provide any data, including interim data, that are available from the head to head study CL301, and please provide an exact date (or set of dates) when results from this trial will be available. Is it possible to present results to NICE before the second appraisal committee meeting on 25 July 2018?

A7. **Priority Question:** As the historical retrospective study (CL002) is also ongoing, when is the final data anticipated from this study and can this be included in the submission? Page 75 states that 53 children had been enrolled at the time of the latest data cut (August 2016): are more recent data available than the August data cut?

A8. In Table 12 the study CL002 sample size is stated as [redacted] (providing [redacted] paired wrist and knee images), but it seems logical that [redacted] corresponds to [redacted] paired images. Please explain this apparent discrepancy?

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City Tower
Manchester
M1 4BT
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A9. As stated in the CS, the two studies, CL002 and CL201, were identical in terms of endpoints and similar in terms of patient population and timeframes (page 75).

i. Therefore, how did you judge that any differences between them in baseline characteristics were large enough to require the use of propensity score matching?

ii. Which baseline characteristics were affected by imbalances (page 125) and were they only those listed in Table 30?

iii. Why was propensity score matching used for the analysis of rickets only, or also for other outcomes listed in the scope?

iv. How was the outcome of rickets improvement defined?

v. Please provide the data and statistical programs used for the propensity score matching.

A10. On page 60 of the CS, it says “A total of 58 published studies report on conventional therapy were identified”. However, the numbers below add up to 56. Please explain.

A11. In Table 13 (CS, page 82), demographic and baseline characteristics for studies CL201, CL002 and CL205 are presented. For study CL002 only data for the Radiographic analysis set ([redacted]) are presented; please provide the same data for the Full Analysis Set ([redacted]).

A12. On page 75 of the CS it is stated that study CL002 was performed in the USA. On page 89 it is stated that patients were from the USA, Canada and France. Please clarify. Are any data from Canada and France available? If so, please include these in the analyses. If no data are available from Canada and France, please clarify whether the Table on page 89 is completed based on the protocol or based on actual performance in the study.

A13. Table 17 (page 94 of the CS) provides results for the Radiographic analysis set ([redacted]) from study CL002; please provide the same results for the Full Analysis Set ([redacted]).

A14. **Priority Question**: Please explain how the Effect Size reported in Table 17 (CS, page 94) was calculated in study CL002. What was ‘before’ and what was ‘after’ and how long was this period for each of the [redacted] patients included in the full analysis set? Please indicate which of these patients were also included in the Radiographic analysis set ([redacted]).

i. Is there a correlation between effect size and length of follow-up?

ii. Please provide separate results for patients with no more than 40 weeks between baseline and post-baseline assessment and for patients with no more than 64 weeks between baseline and post-baseline assessment.

iii. Please also indicate how many of the [redacted] patients included in the full analysis set of CL002 fulfil all in- and exclusion criteria for study CL201 as specified in Table 10 of the CS (CS, pages 67-68) and how many of these patients were also included in the Radiographic analysis set (N=[redacted]). Please provide separate results for patients in CL002 that fulfil all in- and exclusion criteria for study CL201.

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City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

A15. **Priority Question**: Please provide the full results of the online survey study CL001, and clarify what proportion of both the paediatric and adult populations were from the UK. Please provide online survey study results specifically for the UK (or Europe alone), if available.

A16. In section 6.2 of the CS (page 42), [redacted] is deemed to be more likely than a prevalence of 442 patients (based on the incidence of 3.9 per 100,000 live births). Please explain why this is more likely. The information from the British Paediatric and Adolescent Bone Group (BPABG) in May 2017 was based on the number of patients in key treatment centres in England. With 20% new mutations and quite variable disease severity, could there be a pool of undiagnosed new patients or even families; or could there be patients outside these key treatment centres?

A17. In the description of the prevalence of dental disease and dental abscesses in adult patients with XLH (described on Page 40), could the company provide comparative data (including references) for the healthy adult population? Do the frequencies reported for people with XLH represent a significant increase over the average population rates?

A18. **Priority Question**: [redacted]

i. Could the company clarify if the estimated prevalence value was based on the highly likely cases alone or a combination of the cases (highly likely, probable, possible and unlikely).
ii. Could the company clarify the method used to define these probability populations? Please provide a full breakdown of the results in terms of the XLH read codes, lab values for alkaline phosphate along with the threshold cut-offs for each probability state, lab values for serum phosphate along with the threshold cut-offs for each probability state, patient status with regards to the question, 'has at least one year of prescriptions with 1-alfacalcidol or phosphate supplements?', and the ultimate designation for each of the 522 potential cases (highly likely, probable, possible and unlikely).
iii. Please provide the weight given to each parameter (i.e. read codes, lab values ect.) when defining
iv. Could the company also comment on the reason that the prevalence of XLH appears to be fluctuating quite considerably over time, particularly in the 1-4 year age category?

A19. **Priority Question**: In the [redacted], the estimated overall prevalence of XLH was reported to be 0.75 cases per 100,000. However, in the section describing this data (Page 42), [redacted]. Could the

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City Tower
Manchester
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United Kingdom

+44 (0)845 003 7780

company describe how the latter prevalence figure was arrived at? Removing the age ≥18 data does not appear to be sufficient to explain the change.

A20. On Page 44, it states that the general population norm for the mean SF-10 physical health and SF-36 PCS are given (50); the values provided are for the US general population. Please provide the corresponding figures for the UK population.

A21. On page 54, it states human growth hormone therapy is often required. Please clarify what proportion of patients with XLH currently require additional supplementation with growth hormone in the UK. If UK data is not available please provide data from other countries and common on its generalisability to the UK.

A22. Could the company expand on their statement that, “Kyowa Kirin will provide a homecare service in the UK for the administration of maintenance doses of burosumab”, and outline how they anticipate this integrating into current NHS care pathways? E.g. who will be responsible for referrals, monitoring (during both initial (short-term) and maintenance (long-term) dosing), bloodwork etc.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Section B: Clarification on cost-effectiveness data

Literature searching

B1. **Priority Question**: Please provide the following information for each individual database searched (MEDLINE, Embase, EconLit, NHS EED) in sufficient detail that they can be reproduced:

- Database host/interface (e.g. Ovid, ProQuest etc.)
- Database field(s) searched for each search term.
- Number of results retrieved by each search line, and the overall number retrieved from each database.

B2. **Priority Question**: The searches run for cost effectiveness data would appear insufficient to also identify resource identification, measurement and valuation studies (section 12.3.2). Please supply and run additional searches suitable for identifying studies on resource identification, measurement and valuation studies.

Cost-effectiveness review

B3. The PRISMA diagram shown in Figure 23 indicates that eight studies were included in the evaluation of evidence. However, on page 152, it is stated that only one economic study was identified in the review.

i. Please clarify whether one or eight studies were identified.

ii. Please also provide justification why these studies were not deemed relevant for the economic evaluation.

iii. If there is more than one relevant study, then please indicate whether those studies (if any) would be considered as relevant source(s) for the model.

B4. Forestier-Zhang et al. 2016 was deemed not relevant because it uses hypothetical costs. However, this paper might be used to populate other parts of the model (for example, this paper reports EQ5D). Please provide justification why Forestier-Zhang et al. 2016 was not deemed relevant to inform some inputs (other than costs) of the model.

Data source

B5. **Priority question**. Please clarify, with the help of the points below, why for some parameters the UK averages were considered to be more appropriate but for other parameters the trial data have been used. Further to this, in some instances combined studies CL201 and CL205 data are used, but for other parameters only data from one study are used. Please provide a detailed explanation for the inconsistency in the choice of the data sources used to inform the following parameters:

i. Weight of patients (p. 160): The average weight of UK children is used. However, no data on weight in children with XLH (who have growth impairments) have been reported. The weight of the patients enrolled in the clinical trials could have been used instead.

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M1 4BT
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ii. Starting state distribution (pp. 161-162); For the starting age distribution combined trial data were used, but UK averages were used for weight.
iii. The distribution over the health states is based on rickets severity score (RSS) where the data from the trial population was used to inform these parameters.
iv. Transition probabilities for burosumab patients older than 5 years are estimated from CL201 based on the 26 patients on Q2W regimen. This is inconsistent with the approach used to estimate the initial distribution of patients per age and health states (CL201 and CL205 combined).

Adverse events

B6. Adverse events (AEs) are not included in the base case analysis on the basis that the AEs observed in the trials are "typical for paediatric population" or frequent manifestations of the disease.
i. Please specify which AEs are judged to be typical for a paediatric population, and which are likely to be a manifestation of disease.
ii. The latter AEs should be included in the model or a justification for their exclusion should be provided. Please provide an estimation of the frequencies of the AEs in the comparator arm to justify that choice.
iii. In case the frequencies of AEs in the comparator arm are different to the burosumab arm, please adapt the model to include (the most influential) AEs.
iv. Please clarify whether AEs might be related to the severity of the disease.
v. On pages 166 and 167, it is mentioned that "injection site reactions" were included as an AE in sensitivity analysis. We observed that this is included in the cost section only, but not in the utility calculations. Please confirm whether this is the case or not. And if it is not included in the utility section, then please adapt the model by including the disutility estimate for this AE.

Utilities

B7. **Priority question**. Please provide full details of the vignettes study (including the vignettes for the various health states) other than those reported by Lloyd et al.

B8. **Priority question**. On page 146, it is mentioned that there is an ongoing study (a survey of parents of children with the disease) whose results will be "reported during the NICE appraisal of burosumab". Please indicate when these results are expected to be available. If they are available, please adapt the model to include these utilities in the economic analysis (e.g. as scenario analysis).

B9. **Priority question**. On page 184, it is mentioned that the utilities in PSA are bounded so that the utilities of the "better" health states are always higher than those in the "worse" health states. Please adapt the model so that it is possible to run the analyses without this constraint, and provide the accompanying results.

B10. Please indicate whether the papers identified in Section 10.1.6 have been used for validation of the utilities used in the model. If so, please provide details about this validation exercise.

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B11. Given the limited HRQoL data to inform the economic model, please indicate whether the company has attempted to use data from Forestier-Zhang et al., 2016. In that paper, it is indicated that the authors are willing to share raw data from the RUDY study, which might be appropriate for the economic model.

Mortality

B12. **Priority question**. On page 155, it is mentioned that the disease (or medication) is not associated with additional mortality (the model includes only background mortality). Please justify this assumption. In particular, please comment on whether patients with more severe clinical manifestations would have a more sedentary life style and higher inflammation parameters, with the associated risks in old age, and whether specific XLH risks (operation risk, fractures etc.) would impact on mortality risk. If more severe patients are likely to have a significant reduction in life expectancy compared to an "average" UK patient, please include this additional mortality risk in the model.

Model structure

B13. **Priority question**. Please clarify the clinical rationale behind the definition of RSS severity states in the cost-effectiveness model (healed rickets (RSS 0), mild rickets (RSS 0.5 and 1.0), moderate rickets (RSS 1.5 and 2.0) and severe rickets (RSS 2.5 or greater)). Since the RSS scale typically extends to 6.5 in a real-world XLH setting (as described on page 41 of the company submission), please describe how the decision was made to allocate a RSS change of 0.5 between the first three states (healed, mild and moderate rickets) while allocating a RSS change of 4.5 (2.0 to 6.5) to the final state (severe rickets). Furthermore, please indicate how an RSS equal to 1.4 or 1.92 (see Table 13) should be interpreted in terms of the health states of the model.

B14. **Priority question**. Please clarify the rationale for the transition probabilities for patients treated with each of burosumab and Standard of Care (SoC) (Section 12.2.1 Transition probabilities).

i. No worsening (or stagnation) of rickets is observed in patients treated with burosumab in the two trials. Please provide a rationale for why worsening will not occur at any time during treatment (i.e. until 16 or 17 years of age).

ii. In the patients treated with SoC, both improvements as well as worsening of rickets is observed (tables 44 and 46 on page 165). The two most obvious explanations of the observed transitions in the SoC group are as follows: 1) with SoC, rickets fluctuates i.e. can improve one year but deteriorate again the next year (implicitly assumed in the Markov model), or 2) the population is heterogeneous i.e. some patients improve on SoC, whilst others do not. Please explain the chosen approach for incorporating fluctuations in rickets in the model.

iii. If there are patients in the UK chart review for which there are more than 2 observations per person, which might reveal such fluctuation, then these could be used to substantiate this explanation. If there is evidence from multiple observations per person then please re-estimate the transition probabilities to incorporate some memory of prevision transitions.

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B15. Please clarify what “tunnel states” mean in the model. The term “tunnel states” is most often used to indicate a state in which patients can only reside for the duration of one cycle. In that case, please provide a schematic diagram of the model with these tunnel states drawn explicitly (by showing how exactly they are implemented in the model). By looking at the model implementation, it seems that a 5-state model is running 12 times for each starting age. Then the weighted average of the distributions of the cohort over the states in all models for each cycle is taken. That is a valid approach, but not what it is usually referred to as tunnel states.

Transition probabilities

B16. **Priority question**. The approach to derive one-year transition probabilities from the trial observations seems to be invalid. This method would be valid for a single transition from health state A to health state B, but since the model has more than two health states, a “multivariate version” of this method should have been applied. In addition, it is unclear what is described in point 4 of this method on p. 163. Please clarify why probabilities do not add up to 1 if they are correctly derived from the trial observations. The following references could be useful in answering this question:

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5045797/
- https://cran.r-project.org/web/packages/mstate/mstate.pdf
- https://cran.r-project.org/web/packages/TPmsm/TPmsm.pdf

B17. **Priority question**. It is unclear whether the transition probabilities are treatment, time or age dependent.

i. On page 155, it is mentioned that 12 tunnel states were used to track patients by age. If tunnel states were used to make transition probabilities only up until age 12, it implies that transition probabilities beyond age 12 are not age dependent. In that case, please clarify how age specific mortality is incorporated in the model.

ii. If transition probabilities are not age dependent, please justify the use of two different sets of transition probabilities for burosumab (1-4 years and 5+ years).

iii. For the SoC arm only one set of transition probabilities was used for all ages. Although these transition probabilities when based on CL002 are obtained from patients aged 5-14, data are 1-2 years apart (median 102 weeks in Table 12) while in the burosumab arm is 40 or 64 weeks. Please clarify why in the SoC arm, it is assumed that the transition probabilities used for patients 1-4 years old, are the same as those 5+ years, when a different approach was used for the burosumab group.

B18. **Priority question**. Page 16 states: “Probabilities of moving between these health states with standard of care (SoC) were derived from the UK chart review providing 34 patient transitions over a median follow-up of approximately 5 years.” Please provide details on the three leading XLH centres from the UK chart review that was used to calculate transition probabilities for the control group in the base case analysis.

B19. **Priority question**. In the treatment arm, transition probabilities are based on trial data, and the probability of being in the severe health state is 0. In the comparator arm, when

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City Tower
Manchester
M1 4BT
United Kingdom

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the transition probabilities are based on the UK chart review the probability staying in the severe health state is about 70%, but when they are based on CL002, the probability of staying in the severe health state is also 0 for the comparator arm. Please discuss the validity of these figures (and all transition probabilities in general) and indicate the rationale for not using CL002 data for the base case analysis.

B20. In the model "Transition probabilities" sheet, when CL002 option is chosen, it seems to be based on 31 observations. However, on page 16 this is suggested to be [redacted] while in Table 13, [redacted] are mentioned. Please explain this discrepancy.

B21. CL205 data at 40 weeks are used in the model to inform transition probabilities for patients aged 1-4 years. Please indicate when the data at 64 weeks will become available. Furthermore, please clarify whether these data are based on n=13 (text) or n=14 (model) patients.

B22. Please explain why the linear extrapolation and the last observation carried forward (LOCF) methods were chosen to extrapolate transition probabilities in the SoC arm. On page 163, it is mentioned that of the two methods described on page 162, LOCF for treatment arm transition probabilities is more conservative. Please justify this statement when the results indicate that the linear interpolation seems to be the most conservative approach (i.e. resulting in a higher ICER).

B23. **Priority question**. When calculating the "Cumulative Gamma functions" (see e.g. "Transition probabilities" sheet, cell Q9) a factor 0.05 has been added to the random draw of the Gamma distributions. It seems that this factor has been added to "correct" for non-observed transitions in the PSA (e.g. from Severe to Severe), which seems an appropriate approach. However, the choice of 0.05 seems arbitrary and the model is sensitive to changes in that value. Please provide a rationale for choosing 0.05 in the base case and perform sensitivity/scenario analyses on this factor. Furthermore, if the purpose of this factor is indeed to correct for 0 events observed, then when UK chart data is chosen for the comparator arm, this adjustment is not needed because all possible transitions are observed. Please correct this in the model.

B24. For the transition probabilities in the burosumab arm for 1-4 years old patients, there is an option called "Match age 5+" in the model. Please explain what this option exactly means.

Costs

B25. **Priority question**. On pages 170 and 171, it is unclear whether vial sharing is applied or not (see Table 49). Please explain how vials are supposed to be used (e.g. If 7.5mg are used for one dose from a 10mg vial, what happens with the remaining 2.5mg) and how is that implemented in the model.

B26. **Priority question**. It seems that in the model transition probabilities do not depend on the on the dosage of burosumab taken. For example, when patients are 5 years old, the recommended dose is 14.8mg but the rounded dose is 10mg. This implies that

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Manchester
M1 4BT
United Kingdom

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these patients are receiving only 2/3 of the recommended dose but it seems that in the model, the assumption was that these patients get the full benefit of burosumab since the transition probabilities are not adjusted for any dose. Please indicate whether this is the case and clarify the rationale for this assumption.

B27. Orthopaedic interventions are only considered occurring in patients with a rickets score of 1.5 or higher (p. 156), but no evidence is referred that this is a relevant cut-off for this. In section 12.1.5, it is also mentioned that there is no data for this. Please justify this assumption, and clarify whether the RSS is determined in XLH patients undergoing orthopaedic surgery.

B28. Monitoring costs are applied only in the first year of treatment for the purpose of dose adjustments. Please clarify whether it is realistic that at no other point in all the subsequent years (which can be as much as 17 years) more monitoring is performed.

B29. Treatment costs of the comparator are not age specific, but rather an average treatment cost for all patients age 1 to 17 is used. It is mentioned that this is done because of the computational complexity of modelling treatment costs by age. However, the model accommodates age specific treatment costs for burosumab via the use of tunnel states. Please clarify what is meant by this computational complexity and justify why this approach has been considered.

B30. In Section 12.3.7 it is mentioned that 'Only patients that have rickets in childhood are assumed to receive the cost of vitamin D analogues and phosphate supplements in adulthood.' It is not clear what "have rickets in childhood means". Please clarify whether this means at any given time during childhood, or persisting until the end of childhood (i.e. not in the healed rickets state by age 17). In case of the former, please indicate how this can be determined in a (memoryless) Markov model.

B31. Some of the cost items are based on 2015-16 costs/tariffs while others are from 2016-17. Please clarify whether the same year has been used to inform all costs and otherwise please adjust (inflate) all needed costs to reflect the same year (2016-17).

Results

B32. Please include transition probabilities in the DSA.

B33. Please justify why a 25% variation around the mean has been implemented in the deterministic and probabilistic sensitivity analyses to calculate the confidence intervals of several parameters.

B34. The description of the scenario sensitivity analysis (p. 182) mentions that a scenario will be assessed that considered a cohort of XLH patients with an even age distribution between 1-12 years, rather than the age distribution in the clinical trials. However, the

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Manchester
M1 4BT
United Kingdom

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results of this sensitivity analysis (table 58, p. 196) indicate that instead of this, the age and severity distribution of the Q2W dosing group in the trial was used. Please clarify this.

B35. Figures 29 and 30 show how QALYs are accrued over time under standard treatment and burosumab, respectively. Y-axis interval goes from 0 to 1, but the base case cohort size of the simulation is 1000. Please correct this. Furthermore, a 'sawtooth' like shape is seen in both figures where the number of QALYs accrued declines sharply between two consecutive cycles. Please indicate which assumptions/parameters in the model are possibly causing this characteristic in the results.

Validation

B36. **Priority question**. Please provide details of the validation efforts conducted on the model. These should include all aspects of validation (i.e. internal validation, cross-validation, etc…) as explained for example in the AdvisHE (https://advishe.wordpress.com/) tool, and not only face validity (which has been briefly reported in the CS). Please include also the results of the ongoing external validation indicated on page 167.

Section C: Textual clarifications and additional points

C1. Please provide a complete version of Table 47 (a large number of parameters included in the model are missing).

C2. Please include a full list of assumptions in Section 12.1.5. A number of implicitly made assumptions are missing from the overview, such as RSS is a relevant proxy for overall XLH health states.

Manufacturer response to ERG clarification questions relating the HST appraisal of burosumab for XLH, received 8th March 2018

Section A: Clarification on effectiveness data

Literature searching

A1. Priority Question: Please provide the following information for each individual database searched (MEDLINE, Embase, CENTRAL, EU Clinical Trials Register, ClinicalTrials.gov) in sufficient detail that they can be reproduced:

- **Database host/interface (e.g. Ovid, ProQuest etc.).**
- **Database field(s) searched for each search term.**
- **Number of results retrieved by each search line, and the overall number retrieved from each database.**

MEDLINE, MEDLINE(R) In-Process and Embase were searched using Ovid. The database field(s) searched for each search term and the number of results retrieved by each search line are reported in Table 1 and Table 2.

Table 1. MEDLINE search terms for clinical SLR

1	exp Familial Hypophosphatemic Rickets/	449
2	X-linked hypophospha$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	723
3	exp Case-Control Studies/	901318
4	exp Cohort Studies/	1718747
5	exp Longitudinal Studies/	113253
6	exp Follow-Up Studies/	586067
7	exp Retrospective Studies/	675095
8	exp Cohort Effect/	650
9	exp Prospective Studies/	465874
10	exp Cross-Sectional Studies/	259245
11	exp Clinical Trial/	789896
12	exp Random Allocation/	93479
13	case control.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	282309
14	observational stud$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	110368

15	cohort$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	535510
16	longitudinal.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	251110
17	follow-up.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1152057
18	retrospective.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	805810
19	prospective.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	684618
20	cross sectional.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	374824
21	1 or 2	1015
22	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	3663057
23	21 and 22	153
24	limit 23 to yr="1945 - 2017"	149

Table 2. **Embase search terms for clinical SLR**

1	exp familial hypophosphatemic rickets/	740
2	X-linked hypophospha$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1103
3	exp case control study/	140201
4	exp cohort analysis/	348713
5	exp longitudinal study/	109286
6	exp follow up/	1254549
7	exp retrospective study/	617897
8	exp prospective study/	428034
9	exp cross-sectional study/	243031
10	exp "clinical trial (topic)"/	259610
11	exp controlled clinical trial/	665120
12	exp randomization/	77344
13	observational stud$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	174090

14	case control.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	191715
15	cohort$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	798643
16	longitudinal.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	287246
17	follow-up.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1614665
18	retrospective.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	918184
19	prospective.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	834380
20	cross sectional.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	406965
21	1 or 2	1329
22	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	4544810
23	21 and 22	208
24	limit 23 to yr="1945 - 2017"	20

CENTRAL:

- Database host: Cochrane Library
- Database fields: The term ‘Familial Hypophosphatemic Rickets’ was used to search ‘All Text’ (limited to Trials)
- Number of results: 9

A2. Priority Question: The searches run for clinical effectiveness data would appear insufficient to also identify adverse events data (section 9.7.1) – for example no search terms are included for the intervention in the strategy. Please supply and run additional searches suitable for identifying studies on adverse events.

The search carried out was broad, to identify clinical evidence for any intervention used in the treatment of XLH, and therefore did not restrict to any particular intervention.

Burosumab is being developed by Kyowa Hakko Kirin Co., Ltd (Kyowa Kirin) and Ultragenyx Pharmaceutical Inc (Ultragenyx), who are jointly responsible for the clinical trials for burosumab. There are no studies of burosumab that have been carried out by independent centres, and therefore all the available safety data are derived from the Kyowa Kirin and Ultragenyx sponsored studies. As such Kyowa Kirin is aware of all the available safety data and can confirm that all adverse event data has been identified.

As agreed in the clarification call between Kyowa Kirin, NICE and the ERG (13th March 2018), there is therefore no need to carry out additional searches.

Clinical evidence

A3. Priority Question: Please provide full Clinical Study Reports (CSRs) for studies CL201, CL205 and CL002, including all tables and appendices.

The CSRs have been provided.

A4. Priority Question: Please provide full details, results and the full CSR for the study mentioned on page 13 of the company submission (CS) "Kyowa Kirin also commissioned a longitudinal review of patient records from three expert UK centres to provide additional data (n=43)".

Kyowa Kirin commissioned this case review specifically for NICE, and the data were only made available just prior to submission. For this reason, no CSR was constructed as the data has not been submitted to regulatory agencies. The synopsis below provides details on the rationale, methodology and results.

Rationale and objectives: The historical control study CL002 provides reference group data in a similar paediatric XLH population to those enrolled in Study CL201. CL002 provides data on the demographic characteristics and rate of disease progression in a population of XLH patients aged 5 to 14 years who had received long-term conventional therapy with oral phosphate and active vitamin D. The data available for CL002 are from a population of patients who were managed in the US. In order to address potential concerns regarding generalisability of the US data to the UK, a retrospective case series that collected demographic and rickets severity data from a UK paediatric XLH population was carried out. The study was carried out in paediatric centres, however no restrictions were placed on age, in order to generate data from a broad age range of patients and more in line with anticipated marketing authorisation.

Patient population: The study included paediatric patients (up to age 18) with a confirmed diagnosis of XLH, as defined by radiological and clinical evidence of rickets, with documentation of a confirmed PHEX mutation. To be included in the analysis patients must have had at least two sequential radiographs.

Location: Data were collected from two participating expert centres (Birmingham Children's Hospital NHS Foundation Trust and Central Manchester University Hospitals NHS Foundation Trust).

Data collection: Data were collected using a pre-defined data collection form, as follows:

- Visit A (diagnosis):
    - Patient demographics: age, date of diagnosis, ethnicity and sex
    - Medical history,
    - Family history of XLH

    - Basic parameters: weight, blood pressure, height and biochemical parameters (calcium [corrected], parathyroid hormone, phosphate and alkaline phosphatase)
    - Current medications
    - Rickets severity
- Visit B (most recent):
    - Significant events (for example, new comorbidities, fractures, hospitalisations, ectopic calcifications, orthopaedic surgery)
    - Basic parameters (as above)
    - Current medications
    - Rickets severity
- Other available X-rays: rickets severity

Rickets severity was graded using the Rickets Severity Score (RSS; Thacher scores), as used in the burosumab clinical trial program. The same consultant radiologist based in Manchester provided RSS scores for all radiographs in the review.

Planned analyses and outcomes:

- Assessment of RSS at different timepoints, based on availability of radiographic data
- Assessment of patient weight by age and sex

Results:

Data were collected from 43 patients. The three expert centres that provided data were:

[redacted]

[redacted]

[redacted][Note: Nottingham is not an expert centre itself however patients are managed at, and were identified by, Birmingham Children's Hospital NHS Foundation Trust]

Patients were diagnosed between June 1992 and August 2016, and as such represents a population currently or recently being managed in expert centres.

The data was provided in a raw format, with RSS scores for patients at all available intervals. Of the 43 patient histories, data from 38 patients was included as it provided two radiographic scores.

Demographic characteristics at diagnosis are shown in Table 3. The mean age of patients at first RSS was lower in the chart review than CL002 (4 vs 8 years), which is unsurprising given the chart review contains full patient chart histories. However, the mean age at each RSS observation across the patients was 7.5 years, which is therefore similar to CL201 and CL002.

Table 3. Baseline characteristics across cohorts

	CL201	Study CL002	UK data
	Q2W (n=26)	Radiographic analysis set (n=[redacted])	Radiographic analysis (n=38)
Age (years), mean (SD)	8.7 (1.72)	[redacted]	[redacted]
Sex, male n (%)	12 (46.2%)	[redacted]	[redacted]
Race			
White	23 (88.5%)	[redacted]	[redacted]
Black/ African-American	2 (7.7%)	[redacted]	[redacted]
Other	1 (3.8%)	[redacted]	[redacted]
Weight (kg), mean (SD)	31.87 (7.92)	NR	[redacted]
Height (percentile for age and gender), mean (SD)	[redacted]	NR	NR

Due to the nature of a retrospective chart review, which provides RSS scores with varying time between visits, annualised estimates of changes in RSS score have not been analysed in detail. However, the transition matrices used in the cost-effectiveness model provide clear indication of the RSS progression amongst patients (Table 4). Nearly half of the x-rays conducted indicated that patients had severe rickets, as 50 of the 107 (47%) observations were from severe rickets. This is comparable to the baseline characteristics of the CL205 and CL201 studies, in which 43% of patients were severe. Half of the patients with mild rickets (RSS 0.5 or 1) did not have a significant change in RSS between visits, but in those that did, more deteriorated than improved (9 vs 3 patients). Few patients had healed rickets at any one time (9 of 107 x-rays) but the healed status appeared to be temporary as only one remained healed at the next x-ray

Table 4. Rickets status at x-rays from UK chart review, based on RSS

Year n+1 / Year n	Mild	Moderate	Severe	Healed	Total
Mild	12	5	4	3	24
Moderate	7	14	5	2	28
Severe	4	10	33	3	50
Healed	1	1	2	1	5
Total	24	30	44	9	107

A5. Priority Question: Please provide the full data set provided to Kyowa Kirin by the British Paediatric and Adolescent Bone Group (BPABG) in May 2017, used to estimate the number of patients in key treatment centres in England, and mentioned on Page 17.

[redacted]

Table 5. Patient numbers by centre

Hospital	Department	Consultants	Confirmed XLH patients (1-17yrs)
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Endocrinology		[redacted]
[redacted]	Paediatric Endocrinology		[redacted]
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Nephrology	[redacted]	[redacted]

[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatric Endocrinology	[redacted]	[redacted]
[redacted]	Paediatrics	[redacted]	[redacted]
Other centres	Various	Various	[redacted]
TOTAL (ERN BOND*):			[redacted]
TOTAL (ALL CENTRES)			[redacted]

A6. Priority Question: Please provide any data, including interim data, that are available from the head to head study CL301, and please provide an exact date (or set of dates) when results from this trial will be available. Is it possible to present results to NICE before the second appraisal committee meeting on 25 July 2018?

[redacted]

A7. Priority Question: As the historical retrospective study (CL002) is also ongoing, when is the final data anticipated from this study and can this be included in the submission? Page 75 states that 53 children had been enrolled at the time of the latest data cut (August 2016): are more recent data available than the August data cut?

Study CL002 is complete. The final CSR will not include any new radiographic analyses as only subjects from Shriners Hospital in St. Louis (n=[redacted]) met the x-ray criteria to serve as a comparator group for the 201 study.

A8. In Table 12 the study CL002 sample size is stated as [redacted] (providing [redacted] paired wrist and knee images), but it seems logical that [redacted] corresponds to [redacted] paired images. Please explain this apparent discrepancy?

The [redacted] patients contributed a total of [redacted] paired radiographic images (wrists and knees). [redacted] of the [redacted] evaluable paired radiographs had evidence of fused growth plates and were

not included in RSS evaluation since open epiphyses are required for RSS scoring. Therefore, [redacted] were evaluable for RSS and [redacted] were evaluable for RGI-C (Ultragenyx, 2016).

Excerpt from the CSR: "Overall, [redacted] subjects contributed [redacted] paired radiographs of the wrists and knees for rickets evaluation, with [redacted] subjects contributing more than 1 pair." The remaining [redacted] subjects contributed only 1 pair of x-rays that met the criteria of having bilateral wrist AND knee x-rays taken 1-2 years apart (+/- 3 months). For example if Subject A had bilateral wrist and knee x-rays taken at ages 5, 6 and 7 then this subject would contribute 3 pairs. The x-rays taken at ages 5 and 6 would make the first pair, the x-rays taken at ages 5 and 7 would make a second pair and the x-rays taken at ages 6 and 7 would make a third pair. We did allow a pair to be used more than once as long as the criteria of being taken 1-2 years apart was met.

A9. As stated in the CS, the two studies, CL002 and CL201, were identical in terms of endpoints and similar in terms of patient population and timeframes (page 75).

i. Therefore, how did you judge that any differences between them in baseline characteristics were large enough to require the use of propensity score matching?

As mentioned on page 125 of the submission, Study CL002 was a retrospective radiograph and chart review study rather than a prospective natural history cohort, [redacted] In addition, Study CL002 has a [redacted] compared with that of Study CL201. A Propensity Score (PS) approach was used to generate a more comparable sample that would diminish the impact of selection bias on the comparison of the changes in rickets observed with burosumab and conventional therapy in Study CL201 and Study CL002 (Statistical Analysis Plan to Evaluate the Long-term Efficacy of Burosumab [UX023-CL201] Compared to Conventional Therapy [UX023-CL002] using Propensity Score Methodology).

ii. Which baseline characteristics were affected by imbalances (page 125) and were they only those listed in Table 30?

[redacted]

iii. Why was propensity score matching used for the analysis of rickets only, or also for other outcomes listed in the scope?

The propensity score matching was only used for the analysis of rickets. The planned primary endpoints for this analysis were: Change from baseline in RSS total score and RGI-C global

score. Other endpoints included change from baseline in RSS wrist score and RSS knee score, RGI-C wrist score and RGI-C knee score.

iv. How was the outcome of rickets improvement defined?

Improvements in rickets was assessed by comparing the change from baseline in RSS total and RGI-C global scores.

v. Please provide the data and statistical programs used for the propensity score matching.

The statistical programs have been provided as requested.

A10. On page 60 of the CS, it says "A total of 58 published studies report on conventional therapy were identified". However, the numbers below add up to 56. Please explain.

The figures have been corrected below.

- A total of 58 published studies report on conventional therapy were identified:
    - 11 studies were in adults
    - 14 studies included both children and adults
    - 29 studies included children (up to 18 years of age)
    - 4 studies did not report the age of participants

A11. In Table 13 (CS, page 82), demographic and baseline characteristics for studies CL201, CL002 and CL205 are presented. For study CL002 only data for the Radiographic analysis set (N=[redacted]) are presented; please provide the same data for the Full Analysis Set (N=[redacted]).

Table 1 provides the available demographic characteristics for the Full Analysis Set (FAS). Data collected from the FAS were demographics, XLH family history, XLH treatment history growth and biochemical parameters. Since there was no analysis of changes in rickets in this population, there was no baseline timepoint, therefore baseline characteristics are not reported.

Table 6. Demographic and baseline characteristics in studies CL201, CL002 and CL205

	CL201	Study CL002	Study CL002	CL205
	Q2W (n=26)	**Radiographic analysis set ([redacted])**	**Full analysis set ([redacted]**	**(n=13)**
Age (years), mean (SD)	8.7 (1.72)	[redacted]	N/A[b]	2.9 (1.15)
Sex, male n (%)	12 (46.2%)	[redacted]	[redacted]	9 (69.2%)
Race White Black/ African-American Other	 23 (88.5%) 2 (7.7%) 1 (3.8%)	 [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted]	 12 (92.3%) 1 (7.7%) 0
Weight (kg), mean (SD)	31.87 (7.92)	NR	NR	12.92 (1.81)
Height (percentile for age and gender), mean (SD)	[redacted]	NR	NR	[redacted]
Standing Height (z-score), mean (SD)	-1.72, 1.03	[redacted]	N/A[b]	-1.38 (1.19)
Renal ultrasound score, (0 – 5 scale) – n (%) 0 1 2	 [redacted] [redacted] [redacted]	NR	NR	NR
Number (%) of Subjects Who Received Prior Conventional Therapy	24 (92.3%)	[redacted]	[redacted]	13 (100%)
Duration of Prior Conventional Therapy, mean (SD)	7.02 (2.14) years	[redacted]	N/A[b]	16.7 (14.39) months
Age When Conventional Therapy Was Initiated (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacodynamic parameters, mean (SD) Serum Phosphorus, mg/dL TmP/GFR (mg/dL) Serum 1,25(OH)$_2$ D (pg/mL) ALP (U/L	 [redacted] [redacted] [redacted] [redacted]	 NR NR NR NR	 NR NR NR NR	 [redacted] [redacted] [redacted] [redacted]
Rickets Severity RSS Total Score, mean (SD)	 1.92 (1.17)	 [redacted]	 N/A[b]	 2.92 (1.37)

a At baseline paired radiograph (the earlier radiograph pair)
b For the Full Analysis Set there was no baseline timepoint, therefore these are not reported

A12. On page 75 of the CS it is stated that study CL002 was performed in the USA. On page 89 it is stated that patients were from the USA, Canada and France. Please clarify. Are any data from Canada and France available? If so, please include these in the analyses. If no data are available from Canada and France, please

clarify whether the Table on page 89 is completed based on the protocol or based on actual performance in the study.

[redacted]. Further detail is provided on page 135 of the submission.

A13. Table 17 (page 94 of the CS) provides results for the Radiographic analysis set (N=[redacted]) from study CL002; please provide the same results for the Full Analysis Set (N=[redacted]).

It is not possible to provide this, since assessment of rickets was only carried out in the Radiographic Analysis Set. The patients in the FAS that were excluded from the Radiographic Analysis Set did not have an evaluable set of radiographs, hence assessment of rickets in these patients was not possible.

A14. Priority Question: Please explain how the Effect Size reported in Table 17 (CS, page 94) was calculated in study CL002. What was 'before' and what was 'after' and how long was this period for each of the [redacted] patients included in the full analysis set? Please indicate which of these patients were also included in the Radiographic analysis set (N=[redacted]).

Effect size

RGI-C data were analyzed in a similar manner to those in Study UX023-CL201, based on the categories of healing with a global score of +1.0 indicating minimal healing and a +2.0 score indicating substantial healing. More than [redacted] of subjects in the overall group ([redacted]%), higher RSS subgroup ([redacted]%), and lower RSS subgroup ([redacted]%) had at least minimal healing. Substantial healing of rickets was seen in [redacted]% of radiographs in the overall group, [redacted] % in the higher RSS subgroup, and [redacted]% in the lower RSS subgroup (Table 2-6).

Before and After

Including a mean (SD) duration between baseline and post-baseline radiographs of [redacted] years (median [redacted] years), subjects had received a total of approximately [redacted] of conventional therapy, from the initiation of therapy until the end of the observed period.

Patients in the radiographic analysis set

The [redacted] subjects from Shriners Hospital for Children, St. Louis, Missouri, contributed a total of [redacted] paired radiographic images (wrists and knees), [redacted] evaluable for RSS and [redacted] evaluable for RGI-C. Radiographic images were taken 1 to 2 years (mean [redacted] weeks]) apart from the initial baseline radiographs when the subjects were between the ages of 5 and 14 years.

i. Is there a correlation between effect size and length of follow-up?

We did not evaluate the correlation between effect size and length of time between x-ray pairs. Although many images were received, the only x-rays that were scored were the pairs of bilateral wrist and knee images that came from the [redacted] natural history study subjects. These subjects had x-rays taken as part of their study visit and met the criteria of 1-2 years between x-rays. The remaining subjects had x-rays pairs that were taken more than 2 years apart.

ii. Please provide separate results for patients with no more than 40 weeks between baseline and post-baseline assessment and for patients with no more than 64 weeks between baseline and post-baseline assessment.

Unfortunately, we did not run the data this way due to the small number of x-ray pairs that met the criteria for 40 and 64 weeks, respectively. The mean duration between x-ray pairs was actually [redacted] weeks so we would not have had adequate images for comparison if we were to adhere to the 40 and 64 week criteria. It is important to note that bilateral wrist and knee x-rays do not appear to be taken annually as part of standard clinical practice. This is why we were not able to get x-rays from any other site except Shriners who was collecting these images as part of a natural history study and not standard clinical practice.

Excerpt from CSR "For the Radiographic Analysis Set (N=[redacted]), the mean (SD) age when conventional therapy was initiated was [redacted] years. The mean (SD) age corresponding to baseline radiographs of the [redacted] paired wrist and knee images was [redacted] years, indicating that subjects had received [redacted] year of conventional therapy prior to the time of the baseline radiographs. Including a mean (SD) duration between baseline and post-baseline radiographs of [redacted] years (median [redacted] years [redacted] weeks]), subjects had received a total of approximately [redacted] of conventional therapy, from the initiation of therapy until the end of the observed period."

iii. Please also indicate how many of the [redacted] patients included in the full analysis set of CL002 fulfil all in- and exclusion criteria for study CL201 as specified in Table 10 of the CS (CS, pages 67-68) and how many of these patients were also included in the Radiographic analysis set (N=[redacted]). Please provide separate results for patients in CL002 that fulfil all in- and exclusion criteria for study CL201.

The CL002 study was a non-interventional, retrospective study evaluating the medical records of paediatric subjects with XLH. The inclusion and exclusion criteria are detailed below.

Individuals eligible to participate in this study met all of the following criteria:

1. Male or female, with radiographic images from at least two time points taken between the ages of 5 and 14 years, inclusive
2. Diagnosis of XLH based on confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance, or a clinical diagnosis of XLH based on biochemical profile and clinical symptoms

3. Willing to provide access to prior medical records for the collection of demographics; diagnostic and treatment history; historical radiographs; and growth and biochemical data (where available)
4. Willing and able to provide written, signed informed consent, or where appropriate for subjects currently under the age of 18 years, provide written assent (where required) and written informed consent by a legally authorized representative after the nature of the study has been explained. To obtain and review medical records of deceased individuals, informed consent was sought and obtained from next of kin or appropriate legal entity

Individuals who met any of the following exclusion criteria were not eligible to participate in the study:

1. Unwilling to sign informed consent to release radiographs or medical records
2. Currently or previously treated with burosumab in Ultragenyx Pharmaceutical Inc. (Ultragenyx) protocol UX023-CL201

A15. Priority Question: Please provide the full results of the online survey study CL001, and clarify what proportion of both the paediatric and adult populations were from the UK. Please provide online survey study results specifically for the UK (or Europe alone), if available.

Full results of the survey are included in the Interim Report that has been provided alongside the CSRs. Of the adult population surveyed, 22 (9.5%) of patients were from the UK. In the paediatric survey, 4 (4.4%) of the patients surveyed were from the UK. Online survey study results were not analysed by country or region.

A16. In section 6.2 of the CS (page 42), [redacted] is deemed to be more likely than a prevalence of 442 patients (based on the incidence of 3.9 per 100,000 live births). Please explain why this is more likely. The information from the British Paediatric and Adolescent Bone Group (BPABG) in May 2017 was based on the number of patients in key treatment centres in England. With 20% new mutations and quite variable disease severity, could there be a pool of undiagnosed new patients or even families; or could there be patients outside these key treatment centres?

The method used to derive the incidence of 3.9 per 100,000 live births (Beck-Nielsen et al., 2009) started with an evaluation of patients with a recorded episode of hypophosphatemia then the authors conducted an analysis to calculate the incidence. The approach used to calculate [redacted] patients was to determine the number of patients with a diagnosis of XLH currently being managed in a specialist centre. A prevalence of 442 based on this Dutch study is inconsistent with the estimates of UK patient numbers.

Eligibility for treatment with burosumab requires radiographic evidence of bone disease in children and adolescents. It is highly unlikely that patients with radiographic bone disease would be undiagnosed as this degree of disease is likely to be symptomatic. As noted in page

17 of the submission, XLH is associated with skeletal deformations, pain and functional impairment, therefore it is unlikely that there are undiagnosed eligible children outside of these centres.

A17. In the description of the prevalence of dental disease and dental abscesses in adult patients with XLH (described on Page 40), could the company provide comparative data (including references) for the healthy adult population? Do the frequencies reported for people with XLH represent a significant increase over the average population rates?

To date, we have been unable to identify comparative data for the healthy adult population. However, severe dental disease with recurrent abscesses is nearly always present in adults with XLH and is a key feature of XLH, and therefore represents a significant increase over the average population.

A18. Priority Question: [redacted].

i. Could the company clarify if the estimated prevalence value was based on the highly likely cases alone or a combination of the cases (highly likely, probable, possible and unlikely).

The prevalence was based cases coded as highly likely and probable.

ii. Could the company clarify the method used to define these probability populations? Please provide a full breakdown of the results in terms of the XLH read codes, lab values for alkaline phosphate along with the threshold cut-offs for each probability state, lab values for serum phosphate along with the threshold cut-offs for each probability state, patient status with regards to the question, 'has at least one year of prescriptions with 1-alfacalcidol or phosphate supplements?', and the ultimate designation for each of the 522 potential cases (highly likely, probable, possible and unlikely).

The probability populations were defined by two expert clinicians reviewing the available read codes, laboratory and prescriptions. The breakdown is provided in Appendix 1.

iii. Please provide the weight given to each parameter (i.e. read codes, lab values ect.) when defining

The weighting was based on clinical expertise taking into account age of presentation and read codes. Following this initial classification of the cases as highly likely or probable, verification of the cases is ongoing by directly contacting the GPs of the patients to validate whether or not the patient has XLH. Results of this verification are expected in Q2 2018.

iv. Could the company also comment on the reason that the prevalence of XLH appears to be fluctuating quite considerably over time, particularly in the 1-4 year age category?

The variability reflects the small number of cases in the 1-4 year group.

A19. Priority Question: In the [redacted], the estimated overall prevalence of XLH was reported to be [redacted] cases per 100,000. However, in the section describing this data (Page 42), [redacted]. Could the company describe how the latter prevalence figure was arrived at? Removing the age ≥18 data does not appear to be sufficient to explain the change.

[redacted]

A20. On Page 44, it states that the general population norm for the mean SF-10 physical health and SF-36 PCS are given (50); the values provided are for the US general population. Please provide the corresponding figures for the UK population.

A UK normative dataset for SF-10 is not available. The UK general population norm for the SF-36 PCS is 50 with a standard deviation of 10 (95% CI 49.8 – 50.2) (Jenkinson, 1999). This indicates the UK norm values are the same as the US values thus the conclusion from CL001 still applies, whether comparing to UK or US norms.

A21. On page 54, it states human growth hormone therapy is often required. Please clarify what proportion of patients with XLH currently require additional supplementation with growth hormone in the UK. If UK data is not available please provide data from other countries and common on its generalisability to the UK.

In order to clarify this point we consulted two clinical experts in the UK:

- Dr Jeremy Allgrove, Consultant Paediatric Endocrinologist, Great Ormond Street Hospital
- Dr Christine Burren, Consultant in Paediatric Diabetes, Endocrinology and Bone at Bristol Royal Hospital for Children, University Hospitals Bristol NHS Foundation Trust

They both stated that, although it has been tried in the past, growth hormone is not licensed in the UK for this purpose and isn't used to treat XLH patients in the UK.

A22. Could the company expand on their statement that, "Kyowa Kirin will provide a homecare service in the UK for the administration of maintenance doses of burosumab", and outline how they anticipate this integrating into current NHS care pathways? E.g. who will be responsible for referrals, monitoring (during both initial (short-term) and maintenance (long-term) dosing), bloodwork etc.

Patients will be initiated on burosumab and have their dose titrated at the specialist centre. After initiation of treatment with burosumab, fasting serum phosphate should be measured every two weeks for the first month of treatment, every four weeks for the following two months and thereafter as appropriate. This monitoring required for titration is more frequent, but not different, from the monitoring requirements following initiation of conventional therapy, where serum calcium, phosphorus, potassium, and creatinine levels are measured monthly until stable and thereafter every three months. This monitoring is therefore expected to continue according to local arrangements used in current clinical practice.

Once titration is completed, patients will receive burosumab via a homecare service. The long-term monitoring required with burosumab, including monitoring for signs and symptoms of nephrocalcinosis, monitoring fasting serum phosphate levels, and periodic measurement of serum parathyroid hormone, is already carried out for conventional therapy and therefore this is also expected to continue as per current clinical practice.

Monitoring of fasting serum phosphate levels and serum parathyroid hormone require blood tests that can be carried out in either in a general hospital or other local arrangement, with the results assessed by the consultant in the specialist centre and any dose adjustments made without the need to see the patient. A renal ultrasound is required to monitor nephrocalcinosis. This would be carried out in the specialist centre at the time of regular follow-up, as is currently done for patients on conventional therapy.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. Priority Question: Please provide the following information for each individual database searched (MEDLINE, Embase, EconLit, NHS EED) in sufficient detail that they can be reproduced:

- **Database host/interface (e.g. Ovid, ProQuest etc.)**
- **Database field(s) searched for each search term.**
- **Number of results retrieved by each search line, and the overall number retrieved from each database.**

MEDLINE, MEDLINE(R) In-Process and Embase were searched using Ovid. The database field(s) searched for each search term and the number of results retrieved by each search line are reported in Table 7 and Table 8.

Table 7. MEDLINE search terms for economic SLR

Label	Search term	Studies found
1	exp familial hypophosphatemic rickets/	448
2	exp epidemiology/	24597
3	exp incidence/	226667
4	exp prevalence/	248031
5	exp prognosis/	1397522
6	exp history/	373159
7	exp "sensitivity and specificity"/	518405
8	exp diagnosis/	7790235
9	exp therapy/	4111320
10	X-linked hypophospha$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	660
11	1 or 10	951
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	10920024
13	11 and 12	314
14	exp Familial Hypophosphatemic Rickets/	448
15	exp Epidemiology/	24597
16	exp Incidence/	226667
17	exp Prevalence/	248031
18	exp Prognosis/	1397522
19	exp Natural History/	751
20	exp "Sensitivity and Specificity"/	518405
21	exp Diagnosis/	7790235
22	exp Therapeutics/	4111320
23	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	10606967
24	X-linked hypophospha$.mp.	660
25	14 or 24	951
26	23 and 25	313
27	limit 26 to yr="1946 - 2017"	313
28	exp Familial Hypophosphatemic Rickets/	448

29	X-linked hypophospha$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	660
30	exp Economics/	555286
31	exp "Costs and Cost Analysis"/	212684
32	exp Cost-Benefit Analysis/	71851
33	cost.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	374109
34	benefit.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	342091
35	analysis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3728059
36	effectiveness.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	321977
37	cost effectiveness.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	42306
38	cost-minimization.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	749
39	simulation model.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5023
40	economic$ analy$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4939
41	economic$ evaluation$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8520
42	cost-utility.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3231
43	utility.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	139593

44	cost-minimi$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1033
45	cost minimi$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1033
46	cost-consequence$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	386
47	cost consequence$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	386
48	value-of-information.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	834
49	value of information.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	834
50	decision-tree.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4446
51	decision tree.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4446
52	markov.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	18089
53	state-transition.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1625
54	state transition.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1625
55	individual-patient simulation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	14
56	individual patient simulation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	14

57	health-economi$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5828
58	economi$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	250268
59	decision-analytic$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2176
60	decision analytic$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2176
61	QALY.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5739
62	QALYs.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4207
63	quality-adjusted.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13505
64	quality adjusted.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13505
65	disability-adjusted.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2080
66	disability adjusted.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2080
67	DALY.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1128
68	DALYs.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1214
69	utility.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	139593
70	33 and 34	91378
71	33 and 35	176044

72	34 and 35	142879
73	28 or 29	951
74	30 or 31 or 32 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	964758
75	73 and 74	10
76	limit 75 to yr="1945 - 2017"	10

Table 8. Embase search terms for economic SLR

Label	Search term	Studies found
1	exp Familial Hypophosphatemic Rickets/	742
2	X-linked hypophospha$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1122
3	exp Economics/	241217
4	exp "Costs and Cost Analysis"/	316730
5	exp Cost-Benefit Analysis/	77037
6	cost.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	746356
7	benefit.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	575212
8	analysis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	7654560
9	effectiveness.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	667792
10	cost effectiveness.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	151863
11	cost-minimization.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3566
12	simulation model.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	7874
13	economic$ analy$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	8432
14	economic$ evaluation$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	21393

15	cost-utility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	9955
16	utility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	229787
17	cost-minimi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3919
18	cost minimi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3919
19	cost-consequence$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	727
20	cost consequence$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	727
21	value-of-information.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1303
22	value of information.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1303
23	decision-tree.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	12780
24	decision tree.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	12780
25	markov.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	25437
26	state-transition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	2477
27	state transition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	2477
28	individual-patient simulation.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	32
29	individual patient simulation.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	32
30	health-economi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug	43373

	manufacturer, device trade name, keyword, floating subheading word]	
31	economi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	600904
32	decision-analytic$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3959
33	decision analytic$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3959
34	QALY.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	12899
35	QALYs.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	9578
36	quality-adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	24272
37	quality adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	24272
38	disability-adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3235
39	disability adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3235
40	DALY.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1796
41	DALYs.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1980
42	utility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	229787
43	6 and 7	118595
44	6 and 8	348335
45	7 and 8	280303
46	3 or 4 or 5 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45	1443456
47	exp economics/	241217
48	exp health economics/	762730

49	"cost benefit analysis"/ or "cost minimization analysis"/ or "cost effectiveness analysis"/ or "cost utility analysis"/ or "program cost effectiveness"/ or "cost of illness"/	217970
50	1 or 2	1349
51	46 or 47 or 48 or 49	1678112
52	50 and 51	24
53	limit 52 to yr="1945 - 2017"	23
54	exp Familial Hypophosphatemic Rickets/	742
55	X-linked hypophospha$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1122
56	exp Economics/	241217
57	exp "Costs and Cost Analysis"/	316730
58	exp Cost-Benefit Analysis/	77037
59	cost.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	746356
60	benefit.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	575212
61	analysis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	7654560
62	effectiveness.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	667792
63	cost effectiveness.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	151863
64	cost-minimization.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3566
65	simulation model.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	7874
66	economic$ analy$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	8432
67	economic$ evaluation$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	21393
68	cost-utility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	9955
69	utility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	229787

70	cost-minimi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3919
71	cost minimi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3919
72	cost-consequence$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	727
73	cost consequence$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	727
74	value-of-information.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1303
75	value of information.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1303
76	decision-tree.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	12780
77	decision tree.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	12780
78	markov.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	25437
79	state-transition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	2477
80	state transition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	2477
81	individual-patient simulation.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	32
82	individual patient simulation.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	32
83	health-economi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	43373
84	economi$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	600904
85	decision-analytic$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug	3959

	manufacturer, device trade name, keyword, floating subheading word]	
86	decision analytic$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3959
87	QALY.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	12899
88	QALYs.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	9578
89	quality-adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	24272
90	quality adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	24272
91	disability-adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3235
92	disability adjusted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3235
93	DALY.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1796
94	DALYs.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	1980
95	utility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	229787
96	59 and 60	118595
97	59 and 61	348335
98	60 and 61	280303
99	56 or 57 or 58 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98	1443456
100	exp economics/	241217
101	exp health economics/	762730
102	"cost benefit analysis"/ or "cost minimization analysis"/ or "cost effectiveness analysis"/ or "cost utility analysis"/ or "program cost effectiveness"/ or "cost of illness"/	217970
103	54 or 55	1349
104	99 or 100 or 101 or 102	1678112
105	103 and 104	24
106	limit 105 to yr="1945 - 2017"	23

B2. Priority Question: The searches run for cost effectiveness data would appear insufficient to also identify resource identification, measurement and valuation studies (section 12.3.2). Please supply and run additional searches suitable for identifying studies on resource identification, measurement and valuation studies.

Given the rarity of XLH, it is highly unlikely that relevant articles detailing the costs associated with XLH have been omitted from the search results. The search of ECONLIT was not limited to outcome terms so will have been sufficient to identify relevant resource studies. Search terms that were used for MEDLINE that are likely to have identified resource studies in the SLR include:

- exploded MeSH terms “Economics” and “Cost and Cost Analysis”
- (cost AND analysis), (economic$ analys$), (health-economi$), (economi$)

Similarly, search terms that were used for EMBASE that are likely to have identified resource studies in the SLR include:

- exploded MeSH terms “Economics”, “Health Economics”
- (cost AND analysis), (economic$ analys$), (economic$ evaluation$),
- (health-economi$), (economi$)

Furthermore, no relevant studies were identified through grey literature searching.

Cost-effectiveness review

B3. The PRISMA diagram shown in Figure 23 indicates that eight studies were included in the evaluation of evidence. However, on page 152, it is stated that only one economic study was identified in the review.

i. Please clarify whether one or eight studies were identified.

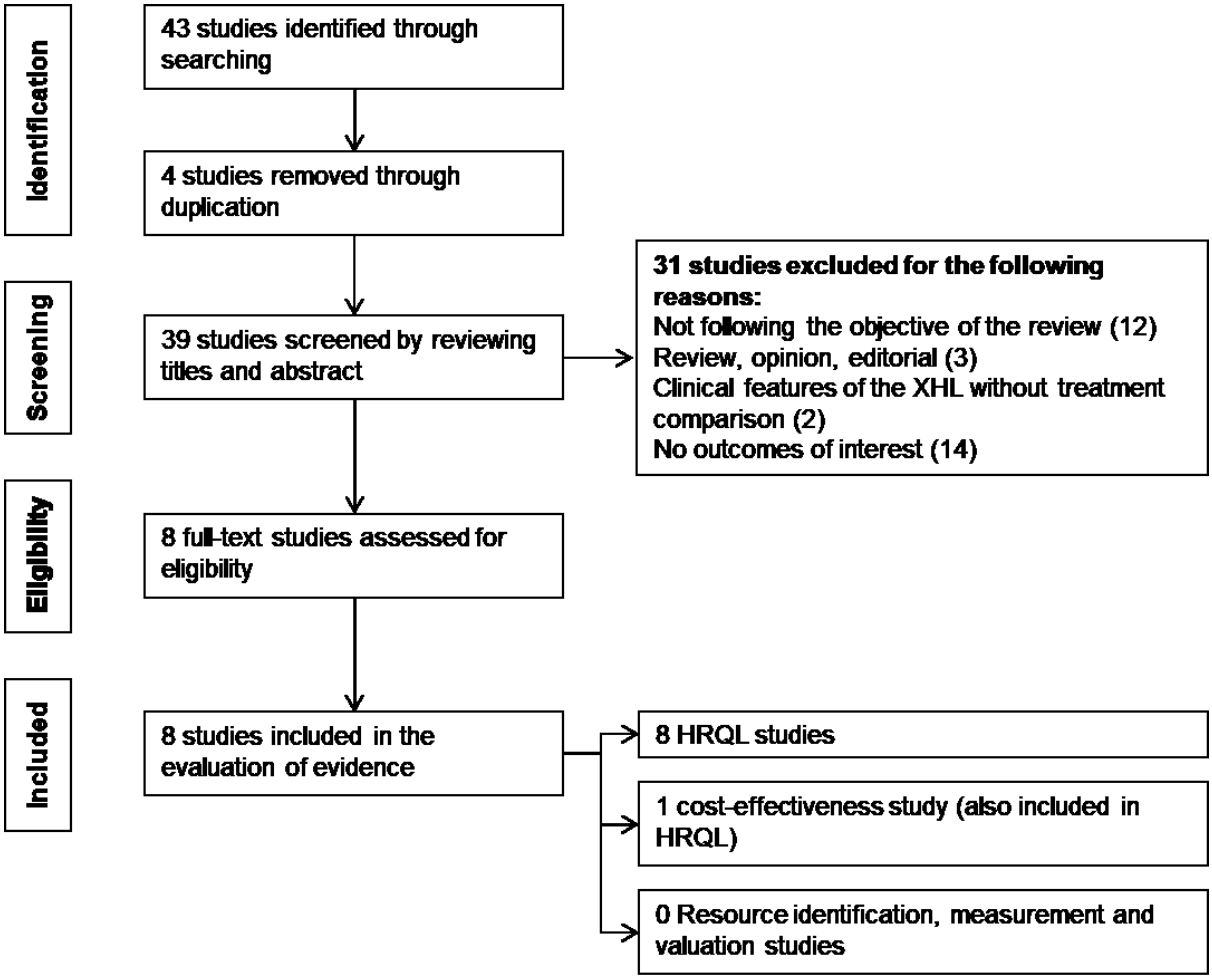
ii. Please also provide justification why these studies were not deemed relevant for the economic evaluation.

iii. If there is more than one relevant study, then please indicate whether those studies (if any) would be considered as relevant source(s) for the model.

As stated in section 10.1.15, one systematic literature review covered both cost-effectiveness, cost/resource and HRQL. Eight publications consisting of six studies were included in the review. An overview of the six studies is given in Section 10.1.16.

All six studies were considered in terms of HRQL but only one study related to an economic evaluation. For this reason, Figure 23 reports eight studies, which are listed in section 10.1.16, but page 152 is written in the context of cost-effectiveness, of which only one study was found. For clarity, an updated PRISMA diagram is presented in Figure 1.

Figure 1: Updated PRISMA diagram for economic SLR



B4. Forestier-Zhang et al. 2016 was deemed not relevant because it uses hypothetical costs. However, this paper might be used to populate other parts of the model (for example, this paper reports EQ5D). Please provide justification why Forestier-Zhang et al. 2016 was not deemed relevant to inform some inputs (other than costs) of the model.

As detailed in Section 10.1.6 of the submission, the study reported only a mean EQ-5D utility (0.648) with standard deviation (0.290) (Forestier-Zhang et al., 2016) therefore the study could not be used to estimate utilities by health state. In terms of other inputs, the study did not consider resources other than hypothetical treatment costs (as detailed in Section 11.2.1).

Data source

B5. Priority question. Please clarify, with the help of the points below, why for some parameters the UK averages were considered to be more appropriate but for other parameters the trial data have been used. Further to this, in some instances combined studies CL201 and CL205 data are used, but for other parameters only data from one study are used. Please provide a detailed

explanation for the inconsistency in the choice of the data sources used to inform the following parameters:

i. **Weight of patients (p. 160): The average weight of UK children is used. However, no data on weight in children with XLH (who have growth impairments) have been reported. The weight of the patients enrolled in the clinical trials could have been used instead.**

The weights of patients included in the UK chart review have been compared to the weights of the general population used in the base case analysis in Figure 2 (girls) and Figure 3 (boys). As illustrated in these figures, the weight of XLH patients is comparable to the weight of the general population. It is most appropriate for us to consider weight of UK patients in the analysis, since the modelled cohort should represent the cohort expected to be treated in clinical practice.

In addition, age and weight of 28 XLH patients in Germany that have enrolled in a compassionate use programme (CUP) for burosumab have also become available. This data is included in the figures comparing the UK data to the weights of the general population. The German CUP data indicates that XLH patients are a comparable weight to the general population.

Figure 2. Weight of girls with XLH compared to the general population

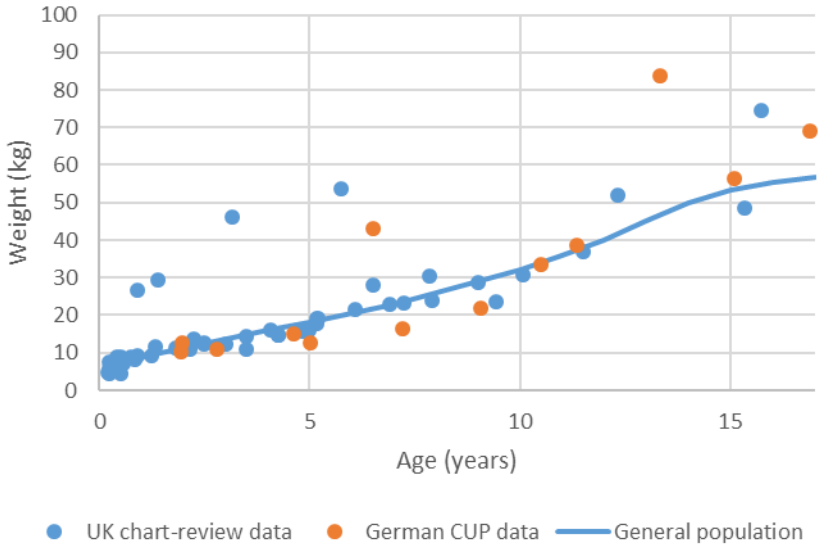
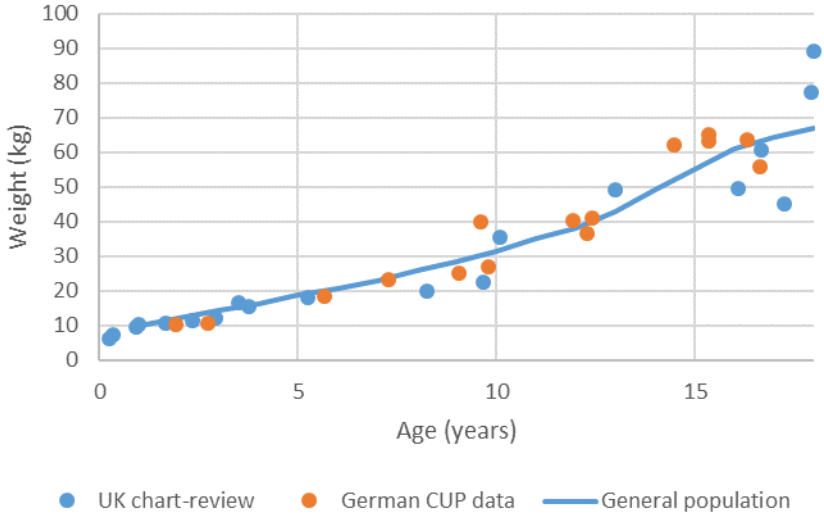
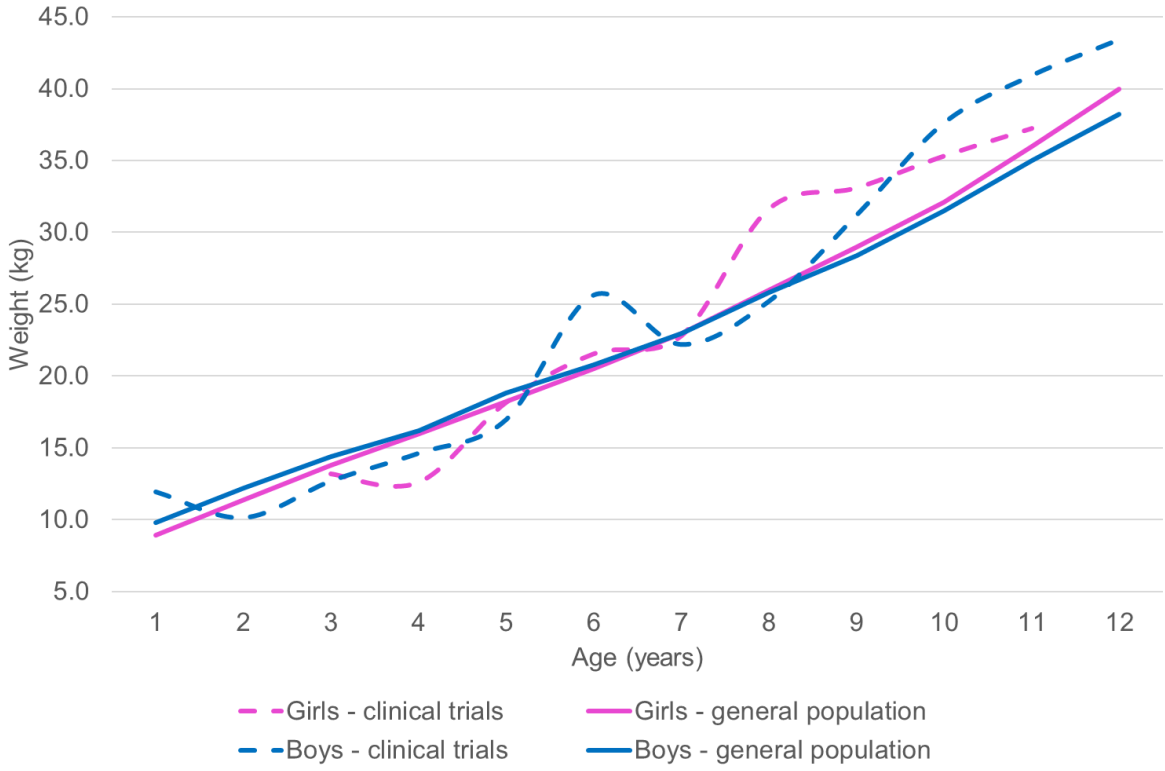


Figure 3. Weight of boys with XLH compared to the general population



Since treatment with burosumab is received up to the age of 17, weights of patients up to the age of 17 are required. Since patients enrolled in the clinical trials were only aged 1-12 years, using weights from the clinical trial would not provide sufficient data for the model. In addition, due to the varying number of patients at each age, the average weight fluctuates up and down (Figure 4) which is not representative of expected weight gain in a growing child. Furthermore, the clinical trials were conducted across many countries, where the weight of patients may not be representative of the UK. Therefore, weights of patients from the clinical trial were not considered.

Figure 4. Weight of girls and boys in the clinical trials compared to the general population



ii. Starting state distribution (pp. 161-162); For the starting age distribution combined trial data were used, but UK averages were used for weight.

The UK data is a retrospective chart-review which includes patient histories following diagnosis and therefore is not indicative of the age distribution of patients likely to start treatment. We believe this will be best represented by the trial population. An alternative scenario exploring the starting age distribution assumes an equal distribution of patients across age groups (Table 58 of submission).

iii. The distribution over the health states is based on rickets severity score (RSS) where the data from the trial population was used to inform these parameters.

As per the starting age distribution, the UK data is a retrospective chart-review which includes patient histories following diagnosis and therefore is not indicative of the starting RSS distribution of patients likely to start treatment. We believe this will be best represented by the trial population.

iv. Transition probabilities for burosumab patients older than 5 years are estimated from CL201 based on the 26 patients on Q2W regimen. This is inconsistent with the approach used to estimate the initial distribution of patients per age and health states (CL201 and CL205 combined).

The transition probabilities are based on data for the licensed dose as they capture the treatment effect of the dose expected to be used in practice. The use of effectiveness data for the unlicensed dose would not be appropriate. The baseline distribution of patients was based on all patients, rather than limiting to those with the Q2W dose as it is preferable to use all available data and since it was baseline, it was not impacted by which treatment dose. A scenario was conducted using health state severity baseline distribution of only patients from Study CL201 that received the expected licensed dose of burosumab (i.e. consistent with the data used for transition probabilities).

Adverse events

B6. Adverse events (AEs) are not included in the base case analysis on the basis that the AEs observed in the trials are "typical for paediatric population" or frequent manifestations of the disease.

i. Please specify which AEs are judged to be typical for a paediatric population, and which are likely to be a manifestation of disease.

Table 1 shows the treatment-emergent adverse events (TEAEs) occurring in Study 201 and whether they are considered typical for a paediatric population or a frequent manifestation of XLH. Some of the adverse events are related to treatment administration.

Table 9. Treatment-emergent adverse events occurring in ≥ 3 of subjects – Study 201

System Organ Class **Preferred Term**	**Q2W** **(N = 26)**	**Classification (i.e. whether a manifestation of XLH or typical for paediatric population)**
Subjects with any treatment-emergent adverse events	26 (100.0%)	
Infections and infestations	[redacted]	
Nasopharyngitis	[redacted]	Typical for a paediatric population
Upper respiratory tract infection	[redacted]	Typical for a paediatric population
Pharyngitis streptococcal	[redacted]	Typical for a paediatric population
Tooth abscess	[redacted]	Typical for a paediatric population
Viral upper respiratory tract infection	[redacted]	Typical for a paediatric population
Influenza	[redacted]	Typical for a paediatric population
Viral infection	[redacted]	Typical for a paediatric population
Gastrointestinal disorders	[redacted]	
Vomiting	[redacted]	Typical for a paediatric population
Diarrhoea	[redacted]	Typical for a paediatric population
Abdominal pain upper	[redacted]	Typical for a paediatric population
Toothache	[redacted]	Typical for a paediatric population
Nausea	[redacted]	Typical for a paediatric population
Abdominal discomfort	[redacted]	Typical for a paediatric population
Mouth ulceration	[redacted]	Typical for a paediatric population
General disorders and administration site conditions	[redacted]	
Injection site reaction	[redacted]	Treatment administration
Injection site erythema	[redacted]	Treatment administration
Pyrexia	[redacted]	Typical for a paediatric population
Injection site swelling	[redacted]	Treatment administration
Pain	[redacted]	Frequent manifestation
Respiratory thoracic and mediastinal disorders	[redacted]	
Cough	[redacted]	Typical for a paediatric population
Oropharyngeal pain	[redacted]	Typical for a paediatric population
Nasal congestion	[redacted]	Typical for a paediatric population
Rhinorrhoea	[redacted]	Typical for a paediatric population
Epistaxis	[redacted]	Typical for a paediatric population
Nervous system disorders	[redacted]	
Headache	[redacted]	Typical for a paediatric population
Migraine	[redacted]	Typical for a paediatric population
Musculoskeletal and connective tissue disorders	[redacted]	
Pain in extremity	[redacted]	Frequent manifestation
Arthralgia	[redacted]	Frequent manifestation
Myalgia	[redacted]	Frequent manifestation

System Organ Class Preferred Term	Q2W (N = 26)	Classification (i.e. whether a manifestation of XLH or typical for paediatric population)
Back pain	[redacted]	Frequent manifestation
Injury poisoning and procedural complications	[redacted]	
Contusion	[redacted]	Typical for a paediatric population
Thermal burn	[redacted]	Typical for a paediatric population
Skin and subcutaneous tissue disorders	[redacted]	
Rash	[redacted]	Typical for a paediatric population
Investigations	[redacted]	
Vitamin D decreased	[redacted]	Frequent manifestation
Immune system disorders	[redacted]	
Seasonal allergy	[redacted]	Typical for a paediatric population
Ear and labyrinth disorders	[redacted]	
Ear pain	[redacted]	Typical for a paediatric population
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	
Skin papilloma	[redacted]	Typical for a paediatric population

The following additional AEs occurred in ≥ 2 patients in Study CL205 and would be considered typical of paediatric population: respiratory tract congestion, oral pain and hypersomnia.

ii. The latter AEs should be included in the model or a justification for their exclusion should be provided. Please provide an estimation of the frequencies of the AEs in the comparator arm to justify that choice.

Including adverse events in cost-effectiveness models should capture side effects of treatments (if appropriate). Manifestations of the disease should be captured by the model health state structure and corresponding clinical effectiveness estimates applied to the model.

The comparator arm is untreated patients, with 'effectiveness' data obtained from natural history studies: study CL002 and the UK chart-review. Neither of these studies were prospective and thus safety data is not available.

iii. In case the frequencies of AEs in the comparator arm are different to the burosumab arm, please adapt the model to include (the most influential) AEs.

See previous response - safety data for untreated patients is not available.

iv. Please clarify whether AEs might be related to the severity of the disease.

The AEs that are identified as manifestations on the condition in Table 1 are likely to be related to the severity of the disease. Patients that experienced pain are likely to have had higher RSS scores.

v. On pages 166 and 167, it is mentioned that "injection site reactions" were included as an AE in sensitivity analysis. We observed that this is included in the cost section only, but not in the utility calculations. Please confirm whether this is the case or not. And if it is not included in the utility section, then please adapt the model by including the disutility estimate for this AE.

The modelled adverse events for burosumab were only considered in terms of costs. The disutilities of comparator treatments (active vitamin D and oral phosphate) are expected to be significant given many children find them unpalatable. Since the comparator treatments are given daily, whereas burosumab is an injection bi-weekly, it is likely that disutilities associated with treatment are greater in the comparator arm than the intervention arm. However, in the absence of specific utilities for the comparator, these are not included in the model. It is likely that compared to the costs and health effects currently incorporated in the model, the inclusion of adverse events would be relatively modest.

Utilities

B7. Priority question. Please provide full details of the vignettes study (including the vignettes for the various health states) other than those reported by Lloyd et al.

The vignettes for the health states of XLH used to inform the model are outlined in Table 6.

Table 10. XLH health state vignettes

Criteria for health state	Age 1 to 4 years	Age 5 to 12 years	Adolescents & adults (13+)
HS0 (Rickets Severity Score=0). Patient is considered to have 'healed' rickets. They are receiving treatment which can give them a tummy upset /diarrhoea (In adolescents & adults (13+): They do not always take their medication)	• Patient has x-linked hypophosphatemia • Patient is able to walk nearly normally for their age. They may have a slightly non-normal gait and residual bowed legs. • Patient is able to complete usual activities such as dressing and playing. • Patient has a slightly reduced stature for their age, but it is not that noticeable. • Patient may not be as strong as an otherwise healthy person of their age • Patient does not experience pain associated with their XLH • Patient can sleep normally. They are tired sometimes. • Patient's mood, anxiety or sadness varies in the same way that an otherwise healthy person's would be expected to. • Patient can play normally and doesn't have undue problems with completing tasks. • Patient has the normal range of relationships for someone their age. • Respiratory function is normal • Patient's oral or dental health is normal. • Patient has no increased history of fractures compared to other children their age.	• Patient has x-linked hypophosphatemia • Patient is able to walk nearly normally for their age. They may have a slightly non-normal gait and residual bowed legs. • Patient is able to complete usual activities such as dressing and playing. • Patient has a slightly reduced stature for their age and a stocky appearance, but it is not that noticeable. • Patient may be slower and not as strong as an otherwise healthy person of their age. • Patient does not experience pain associated with their XLH. • Patient can sleep normally. They are tired sometimes. • Patient's mood, anxiety or sadness varies in the same way that an otherwise healthy person's would be expected to. • Patient can complete school, work and many usual activities normally and doesn't have undue problems with completing tasks. • Patient has a normal range of relationships for someone their age. • Respiratory function is normal • Patients' oral and dental health is normal	• Patient has x-linked hypophosphatemia • Patient is able to walk nearly normally. They may have a slightly non-normal gait and residual bowed legs. They may have undergone surgery to try to straighten their bowed legs which caused pain and took a long time to recover from. • Patient is able to complete usual activities such as dressing, and self care. • Patient has a slightly reduced stature for their age and is slightly stocky, but it is not that noticeable. • Patient may not be as strong as an otherwise healthy person of their age. • Patient does not experience pain associated with their XLH. • Patient can sleep normally. They are tired sometimes. • Patient's mood, anxiety or sadness varies in the same way that an otherwise healthy person's would be expected to. • Patient can complete school, work and many usual activities normally and doesn't have undue problems with completing tasks. • Patient has a normal range of relationships for someone their age. They are worried about the risk of passing on XLH to their offspring. • Respiratory function is normal

		• Patient has no increased history of fractures compared to other children their age.	• Patients' oral and dental health is normal • Patient has no increased history of fractures compared to other people their age.
HS1 (Rickets Severity Score=0.5-1.0) was defined as 'mild' rickets. They are receiving treatment which can give them a tummy upset /diarrhoea. (In adolescents & adults (13+): They do not always take their medication)	• Patient has x-linked hypophosphatemia • Patient is able to walk nearly normally for their age. They have a slight waddling gait with some muscle weakness. They have bowed legs. • Patient is able to complete usual activities such as dressing and playing. They fall over more often than other children their age. • Patient has a slightly reduced stature for their age, but it is not that noticeable • Patient may not be as strong as an otherwise healthy person of their age • Patient does not normally experience pain associated with their XLH • Patient can sleep normally. They sometimes complain of tiredness in their limbs. • Patient's mood, anxiety or sadness varies in the same way that an otherwise healthy person's would be expected to. They may be frustrated by the need for hospital visits. • Patient can play normally and doesn't have undue problems with completing tasks • Patient has the normal range of relationships for someone their age • Respiratory function is normal • Patient may have dental problems including abscesses and other	• Patient has x-linked hypophosphatemia • Patient is able to walk nearly normally for their age. They have a slight waddling gait with some muscle weakness. They have bowed legs. • Patient is able to complete usual activities such as dressing and playing. They fall over more often than other children their age. • Patient has a slightly reduced stature for their age and a stocky appearance, but it is not that noticeable • Patient may be slower and not as strong as an otherwise healthy person of their age. • Patient does experience pain associated with their XLH, particularly in their limbs. They may need pain medication at times. • Patient can sleep normally. They sometimes complain of tiredness in their limbs. • Patient may be withdrawn at times and experience feelings of sadness, frustration and they may lack confidence. They may dislike the need for hospital visits. They may suffer teasing or bullying at school. • Patient can complete school, work and many usual activities normally and doesn't have undue problems	• Patient has x-linked hypophosphatemia • Patient is able to walk nearly normally. They have a slight waddling gait with some muscle weakness. They have undergone surgery to try to straighten their bowed legs which caused pain and took a long time to recover from. • Patient is able to complete usual activities such as dressing, and self care. They sometimes fall over. • Patient has a slightly reduced stature for their age and more heavily set, but it is not that noticeable. They have a slightly long shaped head and more noticeable joints. • Patient may not be as strong as an otherwise healthy person of their age. • Patient does experience pain associated with their XLH, particularly in their limbs. They may need pain medication at times. • Patient can sleep normally. They sometimes complain of tiredness or stiffness in their limbs. • Patient may be withdrawn at times and experience feelings of sadness, frustration because of their awareness of the problems caused by XLH. They may lack confidence. They may get anxious or depressed about their stature. They may dislike

	general dental complications. They see a dentist regularly • Patient has no increased history of fractures compared to other children their age.	with completing tasks. They often experience quite severe tiredness or stiffness after taking part in sports. • Patient has a smaller range of relationships than would be expected for someone their age. • Respiratory function is normal • Patient may have dental problems including abscesses and other general dental complications. They see a dentist regularly • Patient has no increased history of fractures compared to other children their age.	the need for hospital visits. They may suffer teasing or bullying at school or find it difficult to fit in at work. • Patient can complete school, work and many usual activities normally and doesn't have undue problems with completing tasks. Their XLH has limited their career choices. They often experience quite severe tiredness or stiffness after taking part in sports. • Patient has a smaller range of relationships than would be expected for someone their age. They are worried about the risk of passing on XLH to their offspring. • Respiratory function is normal • Patient may have dental problems including abscesses and other general dental complications. They see a dentist regularly • Patient has experienced 1 or 2 fractures that have been attributed to XLH.
HS2 (Rickets Severity Score=1.5-2.0) was defined as 'moderate' rickets. They are receiving treatment which can give them a tummy upset /diarrhoea. (In adolescents & adults (13+): They do	• Patient has x-linked hypophosphatemia • Patient cannot walk normally for their age. They have a waddling gait with some muscle weakness. They have bowed legs. • Patient is able to complete usual activities such as dressing and playing. They fall over more often than other children their age. • Patient has a slightly reduced stature for their age, but it is not that noticeable	• Patient has x-linked hypophosphatemia • Patient cannot walk nearly normally for their age. They have waddling gait with muscle weakness. They have bowed legs. • Patient is able to complete usual activities such as dressing and playing. They fall over more often than other children their age. • Patient has a slightly reduced stature for their age and a stocky appearance, which is noticeable.	• Patient has x-linked hypophosphatemia • Patient cannot walk nearly normally. They have a waddling gait with muscle weakness. They have undergone surgery to try to straighten their bowed legs which caused pain and took a long time to recover from. • Patient is able to complete usual activities such as dressing, and self-care. They sometimes fall over. • Patient has a slightly reduced stature for their age and a stocky appearance, which is noticeable.

not always take their medication)	• Patient may be slower and not as strong as an otherwise healthy person of their age • Patient may experience some pain associated with their XLH • Patient can sleep normally. They sometimes complain of tiredness in their limbs. • Patient's mood, anxiety or sadness varies in the same way that an otherwise healthy person's would be expected to. They may be frustrated by the need for hospital visits. • The child's play is limited a little by their physical problems. • Patient has the normal range of relationships for someone their age • Respiratory function is normal • Patient may have dental problems including abscesses and other general dental complications. They see a dentist regularly • Patient has no increased history of fractures compared to other children their age.	• Patient may be slower and not as strong as an otherwise healthy person of their age. • Patient may experience pain associated with their XLH; particularly in their limbs. They may need pain medication at times. • Patient can sleep normally. They sometimes complain of tiredness in their limbs. • Patient may be withdrawn at times and experience feelings of sadness, frustration and they may lack confidence. They may get anxious or depressed about their stature. They may dislike the need for hospital visits. They may suffer teasing or bullying at school. • Patient can complete school, work and many usual activities normally and doesn't have undue problems with completing tasks. They often experience quite severe tiredness or stiffness after taking part in sports. • Patient has a smaller range of relationships than would be expected for someone their age. • Respiratory function is normal • Patient may have dental problems including abscesses and other general dental complications. They see a dentist regularly • Patient has no increased history of fractures compared to other children their age.	They have a slightly long shaped head and more noticeable joints. • Patient may be slower and not as strong as an otherwise healthy person of their age. • Patient experiences pain associated with their XLH quite often; particularly in their limbs. They may need pain medication at times. • Patient can sleep normally. They sometimes complain of tiredness or stiffness in their limbs. • Patient may be withdrawn at times and experience feelings of sadness, frustration because of their awareness of the problems caused by XLH. They may lack confidence. They may get anxious or depressed about their stature. They may dislike the need for hospital visits. They may suffer teasing or bullying at school or find it difficult to fit in at work. • Patient can complete school, work and many usual activities normally and doesn't have undue problems with completing tasks. Their XLH has limited their career choices. They often experience quite severe tiredness or stiffness after taking part in sports. • Patient has a smaller range of relationships than would be expected for someone their age. They are worried about the risk of passing on XLH to their offspring. • Respiratory function is normal • Patient may have dental problems including abscesses and other

			general dental complications. They see a dentist regularly • Patient has experienced 2 or more fractures that have been attributed to XLH.
HS3 (RSS>2.5) defined as 'severe' rickets. They are receiving treatment which can give them a tummy upset. (In adolescents & adults (13+): They do not always take their medication)	• Patient has x-linked hypophosphatemia • Patient cannot walk normally for their age and are not able to run or climb. They have a slight waddling gait with some muscle weakness. They have bowed legs and are not able to stand properly. • Patient is able to complete usual activities such as dressing, but playing is limited. They fall over quite frequently. • Patient has a slightly reduced stature for their age. They have some deformity. • Patient is slower and not as strong as an otherwise healthy person of their age • Patient experiences pain and swelling associated with their XLH • Patient can sleep normally but sometimes wakes up with pain. They sometimes complain of tiredness in their limbs. • Patient's mood, anxiety or sadness varies in the same way that an otherwise healthy person's would be expected to. They may be frustrated by the need for hospital visits. • The child's play is limited by their physical problems. • Patient has the normal range of relationships for someone their age	• Patient has x-linked hypophosphatemia • Patient cannot walk normally for their age and is not able to run or climb. They have a waddling gait which leaves them with difficulty walking. They have muscle weakness. They have bowed legs and are not able to stand properly. • Patient is able to complete simple activities such as dressing, but many activities are limited or not possible. They fall over quite frequently. • Patient has a reduced stature for their age and a stocky appearance. They have some deformity. • Patient is slower and not as strong as an otherwise healthy person of their age • Patient experiences pain and swelling associated with their XLH. They need pain medication at times. • Patient can sleep normally but sometimes wakes up with pain. They sometimes complain of tiredness and stiffness in their limbs. • Patient may be withdrawn at times and experience sometimes severe feelings of sadness and frustration and they may lack confidence. They may get anxious or depressed about their stature. They may dislike the	• Patient has x-linked hypophosphatemia • Patient cannot walk normally for their age and are not able to run or climb. They have a waddling gait which leaves them with difficulty walking. They have muscle weakness. They have bowed legs and have undergone surgery to try to straighten them which caused pain and took a long time to recover from. • Patient is able to complete simple activities such as dressing or self-care, but many activities are limited or not possible. They fall over quite frequently. • Patient has a reduced stature for their age and a stocky appearance. They have a slightly long shaped head and more noticeable joints. They have noticeable deformity. • Patient is slower and not as strong as an otherwise healthy person of their age • Patient experiences pain and swelling associated with their XLH. They need pain medication at times. • Patient can sleep normally but sometimes wakes up with pain. They often complain of tiredness or stiffness in their limbs. • Patient may be withdrawn at times and experience sometimes feelings of

	• Respiratory function is normal • Patient may have dental problems including abscesses and other general dental complications. They see a dentist regularly Patient has no increased history of fractures compared to other children their age.	need for hospital visits. They may suffer teasing or bullying at school. • Patient can complete school, work and some activities normally, but they are unable to take part in many activities at school. They often experience quite severe tiredness or stiffness after taking part in sports. • Patient has a smaller range of relationships than would be expected for someone their age. • Respiratory function is normal • Patient may have dental problems including abscesses and other general dental complications. They see a dentist regularly • Patient has no increased history of fractures compared to other children their age.	sadness and frustration because of their awareness of the problems caused by XLH. They may lack confidence. They may get anxious or depressed about their stature. They may dislike the need for hospital visits. They may suffer teasing or bullying at school or struggle to fit in at work. • Patient can complete school, work and some activities normally, but they are unable to take part in many physical activities. Their XLH has limited their career choices. They often experience quite severe tiredness or stiffness after physical activity and so choose not to do sports. • Patient has a smaller range of relationships than would be expected for someone their age. They are worried about the risk of passing on XLH to their offspring. • Respiratory function is normal • Patient may have dental problems including abscesses and other general dental complications. They see a dentist regularly • Patient has experienced several fractures which were attributed to their XLH.

B8. Priority question. On page 146, it is mentioned that there is an ongoing study (a survey of parents of children with the disease) whose results will be "reported during the NICE appraisal of burosumab". Please indicate when these results are expected to be available. If they are available, please adapt the model to include these utilities in the economic analysis (e.g. as scenario analysis).

Since responses to the parent survey were limited, the study has been expanded to be administered via the NHS. Collection of further data is planned pending ethics approval.

B9. Priority question. On page 184, it is mentioned that the utilities in PSA are bounded so that the utilities of the "better" health states are always higher than those in the "worse" health states. Please adapt the model so that it is possible to run the analyses without this constraint, and provide the accompanying results.

It is common to adjust sampling of ordered parameters, such as the HRQL associated with differing health states (Ren et al., 2017). Otherwise, simulations may model patients with mild rickets as lower than those with severe rickets, which is implausible given the definition of the health states. However, as requested, a function has been built into the model to enable the PSA to be run with bounded utilities or without. This can be found on the 'Utilities' sheet of the model. The PSA results (for the updated base case as per B16, B23 and B31) are given in Table 2. The scatter plot of results (Figure 5) illustrates that many more of the simulation resulted in negative QALYs compared to the PSA results with bounded utilities.

Table 11. Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard of care	[redacted]	26.02			
Burosumab	[redacted]	33.63	[redacted]	7.62	[redacted]

N.B. This analysis has been run using revised base case (addressing B16, B23, B31)

Figure 5. Cost-effectiveness plane

B10. Please indicate whether the papers identified in Section 10.1.6 have been used for validation of the utilities used in the model. If so, please provide details about this validation exercise.

Validation of the utilities id detailed on page 144 of the submission. The utility study measuring quality of life using the EQ-5D-5L in 109 UK XLH adults of mean age 46 reported a mean utility of 0.648 (Forestier-Zhang et al., 2016). The model results indicate that patients treated with conventional therapy in the UK typically have severe, moderate or mild RSS scores. Applying the age-related utility multipliers gives an estimated utility for a 46-year-old of 0.511 for moderate patients. Thus, the derived utilities or the use of age-related utility multipliers may be underestimating the utilities of adults with XLH.

B11. Given the limited HRQoL data to inform the economic model, please indicate whether the company has attempted to use data from Forestier-Zhang et al., 2016. In that paper, it is indicated that the authors are willing to share raw data from the RUDY study, which might be appropriate for the economic model.

Forestier-Zhang et al. reported only a mean utility (0.648) with standard deviation (0.290) and a kernel density estimation demonstrating the utilities were bi-modal at around 0.1 and 0.8 (Forestier-Zhang et al., 2016). We do not believe it would be possible to utilise these summary statistics to inform the model. We liaised with the authors but found that since the utilities were derived from a self-reported online survey with no physician input, there would be no way to identify the adults' radiographic severity and therefore utilities could not be stratified by health state.

Mortality

B12. Priority question. On page 155, it is mentioned that the disease (or medication) is not associated with additional mortality (the model includes only background mortality). Please justify this assumption. In particular, please comment on whether patients with more severe clinical manifestations would have a more sedentary life style and higher inflammation parameters, with the associated risks in old age, and whether specific XLH risks (operation risk, fractures etc.) would impact on mortality risk. If more severe patients are likely to have a significant reduction in life expectancy compared to an "average" UK patient, please include this additional mortality risk in the model.

Given the increased risk of fractures with XLH and the association between hip fractures and mortality in older healthy adults, a mortality risk associated with XLH would not be implausible. However, there are no published articles which have provided evidence of this, and thus in the model it was assumed that there was no excess mortality risk with XLH.

[redacted]

In light of this recent analysis, a scenario was explored in the cost-effectiveness model, in which patients with severe XLH had twice the risk of mortality from age 50 years and older. In this scenario, burosumab extends life by 2 years, providing 10.6 QALYs, with an ICER of [redacted](Table 3). Given that only one third of SOC patients were estimated to be in the severe XLH health state and utilities are age-adjusted, this increased mortality risk only reduces the ICER by 1%.

Table 12. Scenario analysis results: increased mortality risk for severe XLH patients

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard of care	[redacted]	25.729			
Burosumab	[redacted]	36.293	[redacted]	10.564	[redacted]

N.B. This analysis has been run using revised base case (addressing B16, B23, B31)

Model structure

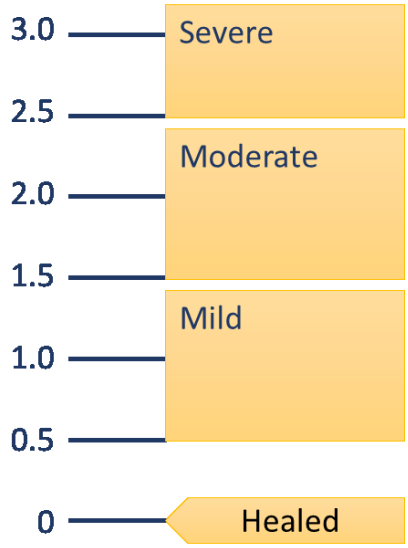
B13. Priority question. Please clarify the clinical rationale behind the definition of RSS severity states in the cost-effectiveness model (healed rickets (RSS 0), mild rickets (RSS 0.5 and 1.0), moderate rickets (RSS 1.5 and 2.0) and severe rickets (RSS 2.5 or greater)). Since the RSS scale typically extends to 6.5 in a real-world XLH setting (as described on page 41 of the company submission), please describe how the decision was made to allocate a RSS change of 0.5 between the first three states (healed, mild and moderate rickets) while allocating a RSS change of 4.5 (2.0 to 6.5) to the final state (severe rickets). Furthermore, please indicate how an RSS equal to 1.4 or 1.92 (see Table 13) should be interpreted in terms of the health states of the model.

As detailed on pages 155-156 of the submission, as radiographic severity can be related to clinical manifestations, Makitie et al assumed that the disease could be stratified by different degrees of severity (Mäkitie et al., 2003). The degree of rickets was graded by Makitie et al as normal, normal/mild, mild, mild/moderate, moderate, moderate/severe, or severe rickets. However, clinical expert opinion indicated that these seven different states did not necessarily have different economic or HRQL consequences so to better define patients with different clinical manifestations that require different healthcare utilisation, the health states were simplified to healed, mild, moderate, or severe based on RSS scores.

Makitie et al described severe rickets as acrosteolysis, periosteal resorption, severe deformity of long bones, and/or pathological fracture. XLH patients with these manifestations of X-ray characteristics are most likely to be scores as 2.5 and above. The resource utilisation and quality of life for RSS 2.5 and higher are not expected to differ significantly compared to patients in higher RSS states.

By definition, healed rickets would have an RSS of 0. According to the RSS algorithm detailed in Table 6 of the submission, RSS scores have intervals of 0.5 (Thacher et al., 2000). Therefore, the definition of mild and moderate states had to cover the interval of RR 0.5 to 2.0 (Figure 6). Therefore, assuming equal distribution over these states, mild was assumed to be an RSS of 0.5 or 1 and moderate was assumed to be an RSS of 1.5 or 2. Given this allocation, an average RSS of 1.4 would be interpreted as mild rickets, whilst an average RSS of 1.92 would be interpreted as moderate rickets.

Figure 6. Allocation of RSS scores into health states



B14. Priority question. Please clarify the rationale for the transition probabilities for patients treated with each of burosumab and Standard of Care (SoC) (Section 12.2.1 Transition probabilities).

i. No worsening (or stagnation) of rickets is observed in patients treated with burosumab in the two trials. Please provide a rationale for why worsening will not occur at any time during treatment (i.e. until 16 or 17 years of age).

The UK chart review included long-term follow up of patients up to 22 years of age. There are few differences in the transition probabilities of patients aged 5-12 years compared to older patients with XLH (Table 4). Therefore, it is reasonable to assume that the RSS progression of patients treated with SOC does not change after the age of 12. Consequently, the transition probabilities with burosumab is also not expected to change after the age of 12 i.e. worsening will not occur at any time during treatment.

Table 13. Transition observations of XLH patients in the UK chart review, split by age group

Annual transition probabilities	Age ≤ 12 years (n=175)	Age ≥ 13 years (n=29)
Same disease state	73%	79%
Improved disease state	17%	17%
Worsening in disease state	10%	3%

ii. In the patients treated with SoC, both improvements as well as worsening of rickets is observed (tables 44 and 46 on page 165). The two most obvious explanations of the observed transitions in the SoC group are as follows: 1) with SoC, rickets fluctuates i.e. can improve one year but deteriorate again the next year (implicitly assumed in the Markov model), or 2) the population is heterogeneous i.e. some patients improve on SoC, whilst others do not. Please

explain the chosen approach for incorporating fluctuations in rickets in the model.

The definitive reason for the apparent fluctuations is unknown but it is possible that both explanations proposed by the ERG could be plausible. However, in light of the number of fluctuations seen in the UK chart review, the former option is most plausible.

As detailed in page 155 of the submission, fluctuations in RSS scores could also be a result of the fact that RSS is scored independently, not compared to previous x-rays. This means that a patients' x-ray may be scored slightly differently between time points despite minimal or no change in the patients' clinical status.

Furthermore, tolerability issues with standard of care may mean adherence to SOC varies, which could be resulting in the fluctuations in RSS.

iii. **If there are patients in the UK chart review for which there are more than 2 observations per person, which might reveal such fluctuation, then these could be used to substantiate this explanation. If there is evidence from multiple observations per person then please re-estimate the transition probabilities to incorporate some memory of previous transitions.**

Please see response above.

B15. Please clarify what "tunnel states" mean in the model. The term "tunnel states" is most often used to indicate a state in which patients can only reside for the duration of one cycle. In that case, please provide a schematic diagram of the model with these tunnel states drawn explicitly (by showing how exactly they are implemented in the model). By looking at the model implementation, it seems that a 5-state model is running 12 times for each starting age. Then the weighted average of the distributions of the cohort over the states in all models for each cycle is taken. That is a valid approach, but not what it is usually referred to as tunnel states.

The interpretation is correct: a 5-state model is running 12 times for each starting age, then the weighted average of the distributions of the cohort over the states in all models for each cycle is taken.

Transition probabilities

B16. Priority question. The approach to derive one-year transition probabilities from the trial observations seems to be invalid. This method would be valid for a single transition from health state A to health state B, but since the model has more than two health states, a "multivariate version" of this method should have been applied. In addition, it is unclear what is described in point 4 of this method on p. 163. Please clarify why probabilities do not add up to 1 if they are correctly derived from the trial observations. The following references could be useful in answering this question:

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5045797/

- https://cran.r-project.org/web/packages/mstate/mstate.pdf
- https://cran.r-project.org/web/packages/TPmsm/TPmsm.pdf

The article cited by the ERG refers to a recently published (2016) study which showed that a commonly used method of converting transition probabilities to different cycle lengths can provide imprecise estimates of model outcomes. The authors presented an alternative approach based on finding the root of a transition probability matrix using eigendecomposition, or where that fails, a numerical approximation method. The proposed methods require complex computational approaches in software such as MATLAB or Mathematica, neither of which are commonly used in economic evaluations.

Importantly, despite this article being published in July 2016, no NICE appraisals have required application of this more advanced technique, rather than the commonly used method as used for the burosumab model.

O'Mahoney et al concurs that traditional conversion formulas are not necessarily exact for transition probabilities in models with multiple states and provides an example of a 3-state model in which the risk of death is greater in the 2nd state compared to the 1st over a one-year time frame. In the traditional approach, the annual risks would be converted to a shorter time horizon but this would ignore the fact that, over shorter timeframes, patients may progress first from the 1st to 2nd state and from the 2nd state, go on to have an increased risk of death. Therefore, the transition approach ignores 'competing risks' within transition probabilities. In the case of XLH and the transition probabilities for burosumab, the adjustment from 40 or 64 weeks to 52 weeks appears to be a valid approach as competing risk. To test this assumption, health state occupancy over time has been compared under a scenario in which cycle length is the same as the observations (40 week or 60 week), versus a 52-week cycle.

In conducting this comparison, one small programming error and one small methodological error has been noted. The programming error is in the calculation of transition probabilities in patients aged 5 years and over. The calculations were adjusting the observations from 40 weeks to 1 year, but data for boys aged 5 and over comes from 64-week observations. Correcting for this error increases the ICER from £[redacted] to £[redacted].

The methodological error relates to the ERG's clarification on point 4 on page 163 of the company submission, regarding adjustment to ensure probabilities add up to 1. In the model, we had converted the 40 or 64-week probabilities to annualised rates and then calculated annualised probabilities for each entry within the matrix. This resulted in many of the rows of the matrix having a probability greater or less than one (due to the time adjustment). Therefore, we divided each entry by the sum of the row to ensure that each row summed to one (see column BK to BN of the 'Transition probabilities' sheet of the model). Having considered the question received from the ERG, we have now adjusted this method such that the points 1 to 3 were performed as previously and then the probability of remaining in the same health state was calculated as: 1 minus the sum of the probabilities of transitioning to different health states. This way, the probabilities in each row of the matrix sum to one.

Under this revised method and with the programming error corrected, the ICER has changed to £[redacted]. The impact of these adjustments on the ICER is therefore an increase of 1%.

Health state occupancy over time has been compared under a scenario in which cycle length is the same as the observations (40 week or 60 week), versus a 52-week cycle, with this adjustment and correction. To simplify this comparison, a simple Markov trace has been constructed with 10 cycles (excluding mortality) of cycle lengths of 40 or 64 weeks, versus 52 weeks. Mortality was excluded because mortality is age-dependant and not within transition matrices. The comparison for the transition probabilities for 1-4 year olds is provided in Figure 7 and Table 5. The comparison for the transition probabilities for boys aged 5 years and older is provided in Figure 8 and Table 6. As evidenced by these figures, the estimated transition probabilities for one year overlap the observations at 40 or 64 weeks. Thus, the approach to derive one-year transition probabilities from the trial observations seems to be valid and a multi-variate version is not required.

Figure 7. Markov trace using no time-adjustment (square markers, no line) versus transition probabilities adjusted from 40 weeks to one year (circular markers, with line)

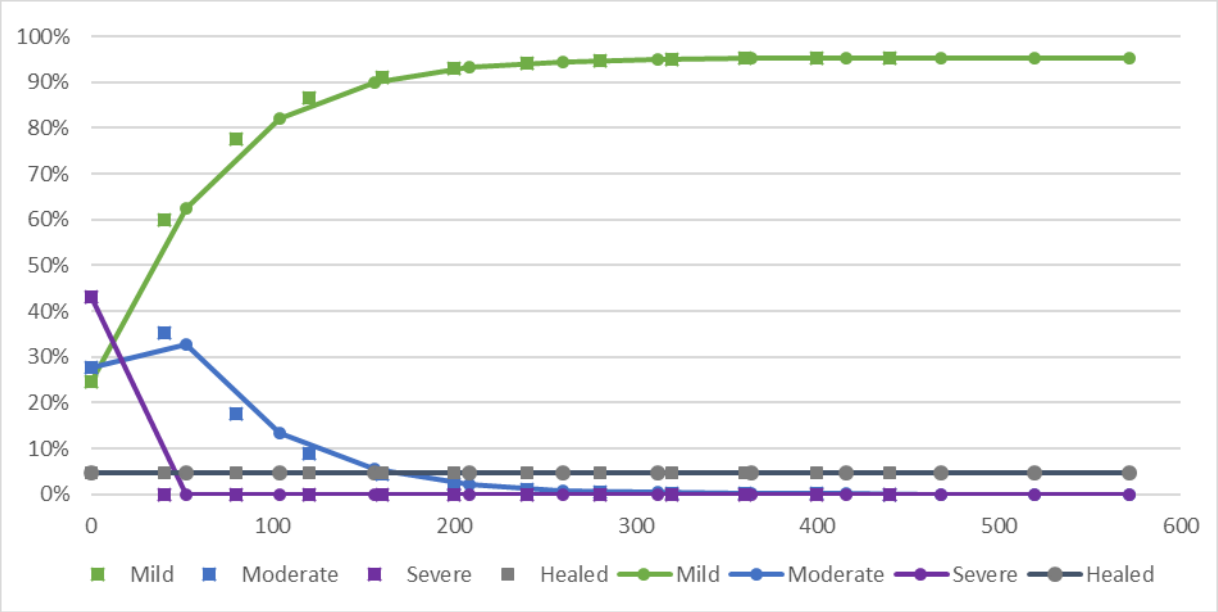


Table 14. Simplified Markov trace to compare no time-adjustment versus transition probabilities adjusted from 40 weeks to one year

Using transition probabilities from observed data					Using time-adjusted transition probabilities				
Week	Mild	Moderate	Severe	Healed	Week	Mild	Moderate	Severe	Healed
0	25%	28%	43%	5%	0	25%	28%	43%	5%
40	60%	35%	0%	5%	52	63%	33%	0%	5%
80	78%	18%	0%	5%	104	82%	13%	0%	5%
120	87%	9%	0%	5%	156	90%	5%	0%	5%
160	91%	4%	0%	5%	208	93%	2%	0%	5%
200	93%	2%	0%	5%	260	94%	1%	0%	5%
240	94%	1%	0%	5%	312	95%	0%	0%	5%
280	95%	1%	0%	5%	364	95%	0%	0%	5%
320	95%	0%	0%	5%	416	95%	0%	0%	5%

360	95%	0%	0%	5%	468	95%	0%	0%	5%
400	95%	0%	0%	5%	520	95%	0%	0%	5%

Figure 8. Markov trace using no time-adjustment (square markers, no line) versus transition probabilities adjusted from 64 weeks to one year (circular markers, with line)

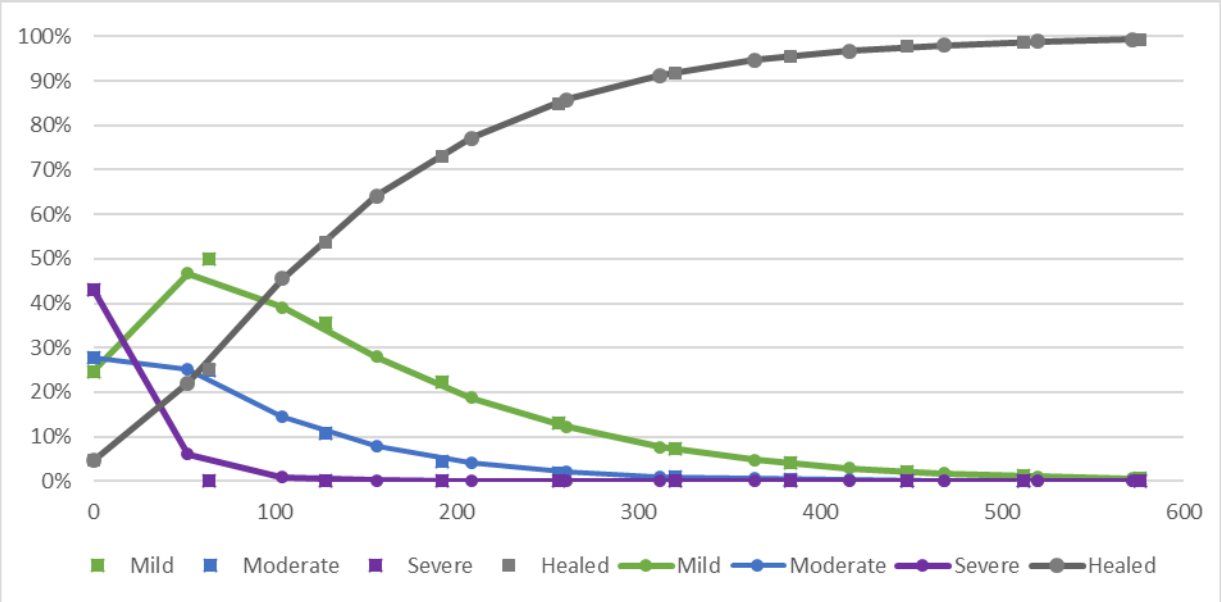


Table 15. Simplified Markov trace to compare no time-adjustment versus transition probabilities adjusted from 64 weeks to one year

Using transition probabilities from observed data					Using time-adjusted transition probabilities				
Week	Mild	Moderate	Severe	Healed	Week	Mild	Moderate	Severe	Healed
0	25%	28%	43%	5%	0	25%	28%	43%	5%
64	50%	25%	0%	25%	52	47%	25%	6%	22%
128	36%	11%	0%	54%	104	39%	15%	1%	46%
192	22%	5%	0%	73%	156	28%	8%	0%	64%
256	13%	2%	0%	85%	208	19%	4%	0%	77%
320	7%	1%	0%	92%	260	12%	2%	0%	86%
384	4%	0%	0%	96%	312	8%	1%	0%	91%
448	2%	0%	0%	98%	364	5%	1%	0%	95%
512	1%	0%	0%	99%	416	3%	0%	0%	97%
576	1%	0%	0%	99%	468	2%	0%	0%	98%
640	0%	0%	0%	100%	520	1%	0%	0%	99%

B17. Priority question. It is unclear whether the transition probabilities are treatment, time or age dependent.

The transition probabilities are treatment and age dependent:

- Transition probabilities between the healed, mild, moderate and severe states are dependent on treatment: burosumab or SOC
- For both treatments, transition probabilities are only applied up to the age of 17; from age 18 patients are not assumed to move between the health, mild, moderate and severe states
- Transition probabilities for burosumab are age dependant: one set of transition probabilities are used for patients aged 1 to 4 years, whilst another set of transitions are used for patients aged between 5 and 17 years of age.

i. On page 155, it is mentioned that 12 tunnel states were used to track patients by age. If tunnel states were used to make transition probabilities only up until age 12, it implies that transition probabilities beyond age 12 are not age dependent. In that case, please clarify how age specific mortality is incorporated in the model.

Please see response to B15 regarding the interpretation of 'tunnel states'. The 12 models of 5 health states were used to track the age of patients such that appropriate age-specific mortality rates could be applied. The 12 models of 5 health states were used over a lifetime. The transition probabilities for patients aged 5 years and older were used for patients between the age of 5 and 17. From age 18 and onwards, it was assumed that patients would not continue to transition between the severity health states and would therefore only have the probability of transitioning to the death state, otherwise they would remain in their state.

ii. If transition probabilities are not age dependent, please justify the use of two different sets of transition probabilities for burosumab (1-4 years and 5+ years).

Transition probabilities are age dependent. The two sets of transition probabilities were used since one set if from CL205 (40 week observations) whilst the other is from CL201 (64 week observations). As an alternative scenario, an option has been included within the revised model to combine the data from both age groups to estimate one set of transition probabilities applied to all patients treated with burosumab between the ages of 1 and 17. In this scenario, the ICER changes from [redacted] (the revised base case further to B16 and B31) to £[redacted]. Therefore, using two sets of transition probabilities rather than one has a minimal impact on the ICER.

Table 16. Scenario analysis results: combining two sets of transition probabilities for burosumab into one set

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard of care	[redacted]	25.989			
Burosumab	[redacted]	36.261	[redacted]	10.273	[redacted]

N.B. This analysis has been run using revised base case (addressing B16, B23, B31)

iii. **For the SoC arm only one set of transition probabilities was used for all ages. Although these transition probabilities when based on CL002 are obtained from patients aged 5-14, data are 1-2 years apart (median 102 weeks in Table 12) while in the burosumab arm is 40 or 64 weeks. Please clarify why in the SoC arm, it is assumed that the transition probabilities used for patients 1-4 years old, are the same as those 5+ years, when a different approach was used for the burosumab group.**

As stated above, the two sets of transition probabilities were used since one set was from CL205 (40 week observations) whilst the other is from CL201 (64 week observations). For the SOC arm, transition probabilities were derived from one source, either the UK chart review or Study CL002, therefore the application of two sets of transition probabilities was not required.

B18. Priority question. Page 16 states: "Probabilities of moving between these health states with standard of care (SoC) were derived from the UK chart review providing 34 patient transitions over a median follow-up of approximately 5 years." Please provide details on the three leading XLH centres from the UK chart review that was used to calculate transition probabilities for the control group in the base case analysis.

Please see the response to question A4.

B19. Priority question. In the treatment arm, transition probabilities are based on trial data, and the probability of being in the severe health state is 0. In the comparator arm, when the transition probabilities are based on the UK chart review the probability staying in the severe health state is about 70%, but when they are based on CL002, the probability of staying in the severe health state is also 0 for the comparator arm. Please discuss the validity of these figures (and all transition probabilities in general) and indicate the rationale for not using CL002 data for the base case analysis.

Given the results observed with burosumab in the clinical studies (in terms of the mode of actions and RGI-C), a 0% probability of patients with severe rickets remaining in the rickets state seems plausible. On the other hand, a 0% probability of remaining in the severe state with SOC as per CL002 does not seem plausible as it would imply that no patients remain in the severe state over time, whereas in reality, the baseline severity in CL201/205 clearly shows that patients with XLH do have severe rickets.

In CL002, there were only 2 observations for patients in the severe health state and both transitioned to the moderate health state. Conversely, transitions from the UK chart review were based on 50 patients. Given this difference in sample size, the UK chart review was chosen as it is expected to provide more robust results. Furthermore, CL002 was conducted in the US so the UK chart review is expected to be more representative of a UK cohort. However, it is acknowledged that the UK chart review is not a matched cohort for the burosumab cohort so there is uncertainty in the comparability.

B20. In the model "Transition probabilities" sheet, when CL002 option is chosen, it seems to be based on 31 observations. However, on page 16 this is suggested to be 34 while in Table 13, 35 are mentioned. Please explain this discrepancy.

Page 16 should state 31 patients. Four paired images did not have RSS total score for the baseline radiographs so could not be used to generate transition probabilities.

B21. CL205 data at 40 weeks are used in the model to inform transition probabilities for patients aged 1-4 years. Please indicate when the data at 64 weeks will become available. Furthermore, please clarify whether these data are based on n=13 (text) or n=14 (model) patients.

Data at 64-weeks is expected to be available in [redacted].

CL205 data are based on 13 patients. As stated on page 162 of the submission, there were no observations for patients healed at baseline so probabilities of transition out of the healed state could not be derived. To form a complete transition matrix, 1 observation was added from Healed to Healed, which suggests that the matrix was based on 14 observations, but in fact it is 13 observations. Since no patients aged 1-4 transitioned to the healed state, the lack of data for the healed state does not impact the model.

B22. Please explain why the linear extrapolation and the last observation carried forward (LOCF) methods were chosen to extrapolate transition probabilities in the SoC arm. On page 163, it is mentioned that of the two methods described on page 162, LOCF for treatment arm transition probabilities is more conservative. Please justify this statement when the results indicate that the linear interpolation seems to be the most conservative approach (i.e. resulting in a higher ICER).

Linear extrapolation and the last observation carried forward were two methods applied to input missing data such that transition probabilities could be calculated. Linear interpolation results in a lower ICER than LOCF (see Table 58 of the submission). For this reason, LOCF was considered the more conservative approach.

B23. Priority question. When calculating the "Cumulative Gamma functions" (see e.g. "Transition probabilities" sheet, cell Q9) a factor 0.05 has been added to the random draw of the Gamma distributions. It seems that this factor has been added to "correct" for non-observed transitions in the PSA (e.g. from Severe to Severe), which seems an appropriate approach. However, the choice of 0.05 seems arbitrary and the model is sensitive to changes in that value. Please provide a rationale for choosing 0.05 in the base case and perform sensitivity/scenario analyses on this factor. Furthermore, if the purpose of this factor is indeed to correct for 0 events observed, then when UK chart data is chosen for the comparator arm, this adjustment is not needed because all possible transitions are observed. Please correct this in the model.

The choice of 0.05 is arbitrary. The adjustment has been removed from the UK chart review analysis and the revised results are presented in Table 8, Figure 9 and Figure 10. Under the revised analysis (see response to B16), without the correction factor for the comparator transition probabilities, the cost-effectiveness acceptability curve indicates that at a willingness to pay of £170,000, the probability of burosumab being cost-effective remains at [redacted]

Table 17. Revised probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard of care	[redacted]	24.825			
Burosumab	[redacted]	36.293	[redacted]	8.120	[redacted]

N.B. This analysis has been run using revised base case (addressing B16 and B31)

Figure 9. Cost-effectiveness plane from revised probabilistic sensitivity analysis

[redacted]

Figure 10. Cost-effectiveness acceptability curve from revised probabilistic sensitivity analysis

B24. For the transition probabilities in the burosumab arm for 1-4 years old patients, there is an option called "Match age 5+" in the model. Please explain what this option exactly means.

This is to explore a scenario in which only transition probabilities from the CL201 study are used. We do not consider this to be a relevant scenario which is why the results were not included in the submission.

Costs

B25. Priority question. On pages 170 and 171, it is unclear whether vial sharing is applied or not (see Table 49). Please explain how vials are supposed to be used (e.g. If 7.5mg are used for one dose from a 10mg vial, what happens with the remaining 2.5mg) and how is that implemented in the model.

Vial sharing is not applied to burosumab. If patients received their exact dose as per their weight, which could be a proxy scenario for vial sharing, the ICER would reduce to [redacted]. The SPC indicates that all doses should be rounded to the nearest 10 mg so if a patients' weight indicates a dose of 7.5mg, then this will be rounded up to 10mg. Thus, there will not be any wastage.

Table 18. Scenario analysis results: patients receiving exact dose (i.e. no rounding of doses)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard of care	[redacted]	25.989			
Burosumab	[redacted]	36.293	[redacted]	10.304	[redacted]

N.B. This analysis has been run using revised base case (addressing B16 and B31)

B26. Priority question. It seems that in the model transition probabilities do not depend on the on the dosage of burosumab taken. For example, when patients are 5 years old, the recommended dose is 14.8mg but the rounded dose is 10mg. This implies that these patients are receiving only 2/3 of the recommended dose but it seems that in the model, the assumption was that these patients get the full benefit of burosumab since the transition probabilities are not adjusted for any dose. Please indicate whether this is the case and clarify the rationale for this assumption.

We wish to clarify that the wording of this question may be misleading as the SPC recommends that the calculated dose is rounded to the nearest 10mg. Therefore, when patients are 5 years old, the calculated dose is 14.8mg but the recommended dose to be administered is 10mg.

The recommended starting dose regimen in children is based on experience in Study CL201 and Study CL205. Rounding to the nearest 10 mg was used during dose titration in Study CL201 and is recommended in the SPC to simplify dosing. Pharmacokinetic (PK) modelled dose levels were rounded to the nearest 10 mg; a difference in dose of < 5 mg is not expected to affect response. The maximum dose of 90 mg is recommended based on PK simulations and the practical limitation of a tolerable injection volume. This information was presented to the EMA and accepted.

B27. Orthopaedic interventions are only considered occurring in patients with a rickets score of 1.5 or higher (p. 156), but no evidence is referred that this is a relevant cut-off for this. In section 12.1.5, it is also mentioned that there is no data for this. Please justify this assumption, and clarify whether the RSS is determined in XLH patients undergoing orthopaedic surgery.

Orthopaedic interventions are only required in patients that have a need for such intervention. These patients are mostly likely to have more severe rickets. If a patient has healed or mild rickets, then it is unlikely that they would require orthopaedic interventions. This assumption was seemed appropriate by UK clinical experts who validated the costs (see section 12.3.3).

B28. Monitoring costs are applied only in the first year of treatment for the purpose of dose adjustments. Please clarify whether it is realistic that at no other point in all the subsequent years (which can be as much as 17 years) more monitoring is performed.

Patients up to the age of 17 are expected to see a specialist every 3 months, regardless of whether they receive SOC or burosumab. This is incorporated into the surveillance costs which are incurred by all patients. These consultations with clinical specialists are to monitor the disease and treatment. After the first 3 months, burosumab is not expected to require any additional monitoring over that already conducted with SOC.

B29. Treatment costs of the comparator are not age specific, but rather an average treatment cost for all patients age 1 to 17 is used. It is mentioned that this is done because of the computational complexity of modelling treatment costs by age. However, the model accommodates age specific treatment costs for burosumab via the use of tunnel states. Please clarify what is meant by this computational complexity and justify why this approach has been considered.

Note that the comparator consists of two treatments, only one of which has a cost that is age-related (alfacalcidol). Since the cost of burosumab is a key driver within the model, complex calculations were included to ensure the cost per year was reflective of the exact ages within the model. See column AD of the 'Trace burosumab' sheet of the model for the calculations required to implement this within the model structure. The cost of alfacalcidol is not a driver of the model so to simplify the calculations, an average cost for children was applied.

B30. In Section 12.3.7 it is mentioned that 'Only patients that have rickets in childhood are assumed to receive the cost of vitamin D analogues and phosphate supplements in adulthood.' It is not clear what "have rickets in childhood means". Please clarify whether this means at any given time during childhood, or persisting until the end of childhood (i.e. not in the healed rickets state by age 17). In case of the former, please indicate how this can be determined in a (memoryless) Markov model.

For the proportion of patients who transition from their current state to the healed rickets health state by the time they reach 18 years, it is an assumption that upon transitioning from adolescence to adulthood patients remain in their health state (healed).

B31. Some of the cost items are based on 2015-16 costs/tariffs while others are from 2016-17. Please clarify whether the same year has been used to inform all costs and otherwise please adjust (inflate) all needed costs to reflect the same year (2016-17).

All costs within the model have been updated to reflect the same year (2016/17). Costs from the NHS Reference costs are now all from 2016/17. The cost of an osteotomy has been inflated from the published data to 2016/17 using the PSSRU (2017) HCHS index. These revisions have been included in the revised base case. The changes have only been very slight and subsequently have not impacted the results. Surveillance costs apply equally to all patients and orthopaedic interventional costs are not drivers of the results.

Results

B32. Please include transition probabilities in the DSA.

Transition probabilities have been included in the DSA, within the 90% confidence interval of the Dirichlet distribution. The results displayed in Figure 10 indicate that the model results are sensitive to the transition probabilities for patients aged 5 and older treated with burosumab. The ICER is insensitive to transition probabilities for SOC and for burosumab patients under the age of 5. The ICER increases significantly when the results are run at the upper end of the 90% confidence interval. Simulating the upper 90% confidence interval with the Dirichlet creates the transition probabilities in Table 16.

These results are driven around the uncertainty in patients remaining in the healed health state, as this was based on one observation in the trial. However, data from the RGI-C strongly support that patients had sustained improvements in rickets and therefore it is likely that a patient would remain healed once healing has occurred. This is also consistent with the restoration of phosphate that is associated with burosumab.

Table 19. Simulated upper bound of 95% confidence interval for burosumab transition matrix for patients aged 5 and over

	Mild	Moderate	Severe	Healed
Mild	53%	2%	2%	43%
Moderate	36%	46%	2%	17%
Severe	44%	26%	18%	13%
Healed	7%	7%	7%	79%

Figure 11. Tornado diagram

N.B. This analysis has been run using revised base case (addressing B16 and B31)

B33. Please justify why a 25% variation around the mean has been implemented in the deterministic and probabilistic sensitivity analyses to calculate the confidence intervals of several parameters.

The 25% variation is arbitrary.

B34. The description of the scenario sensitivity analysis (p. 182) mentions that a scenario will be assessed that considered a cohort of XLH patients with an even age distribution between 1-12 years, rather than the age distribution in the clinical trials. However, the results of this sensitivity analysis (table 58, p. 196) indicate that instead of this, the age and severity distribution of the Q2W dosing group in the trial was used. Please clarify this.

The base case scenario uses a cohort of XLH patients with a baseline age distribution from the clinical trial. To explore the sensitivity of using a baseline even age distribution between 1-12 years in the model on the ICER, this scenario has been examined in the sensitivity analysis in section 12.4.1 (p. 182). The baseline even age distribution between 1-12 years has been derived from the baseline distribution in the clinical trials such that 8% are distributed across each age group.

B35. Figures 29 and 30 show how QALYs are accrued over time under standard treatment and burosumab, respectively. Y-axis interval goes from 0 to 1, but the base case cohort size of the simulation is 1000. Please correct this. Furthermore, a 'sawtooth' like shape is seen in both figures where the number of QALYs accrued declines sharply between two consecutive cycles. Please indicate which assumptions/parameters in the model are possibly causing this characteristic in the results.

We displayed the QALY accrual by patient, rather than over the 1,000 cohort, to be in line with the reporting of other results which is done on a per-patient level. However, as requested, these are presented as Figure 11 and Figure 12.

The 'sawtooth' like shape seen in both figures where the number of QALYs accrued declines sharply between two consecutive cycles is a result of the age-related utility multipliers. In reality, utilities would decline gradually with age, but the general population utilities by age have been reported in 7 age groups, resulting in 7 'sawteeth'.

Figure 12. QALY accrual: standard of care

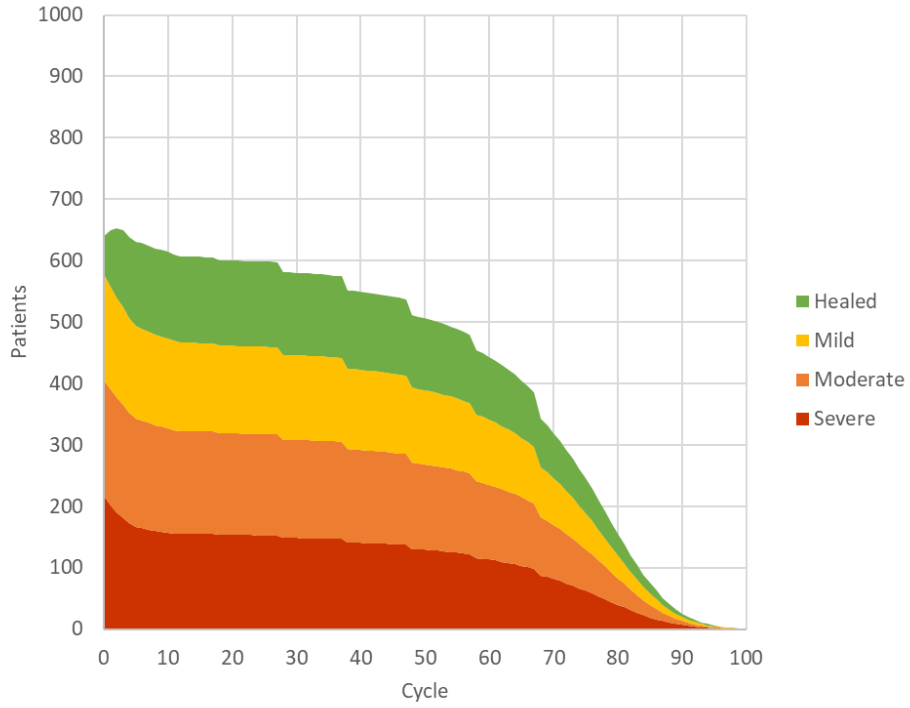
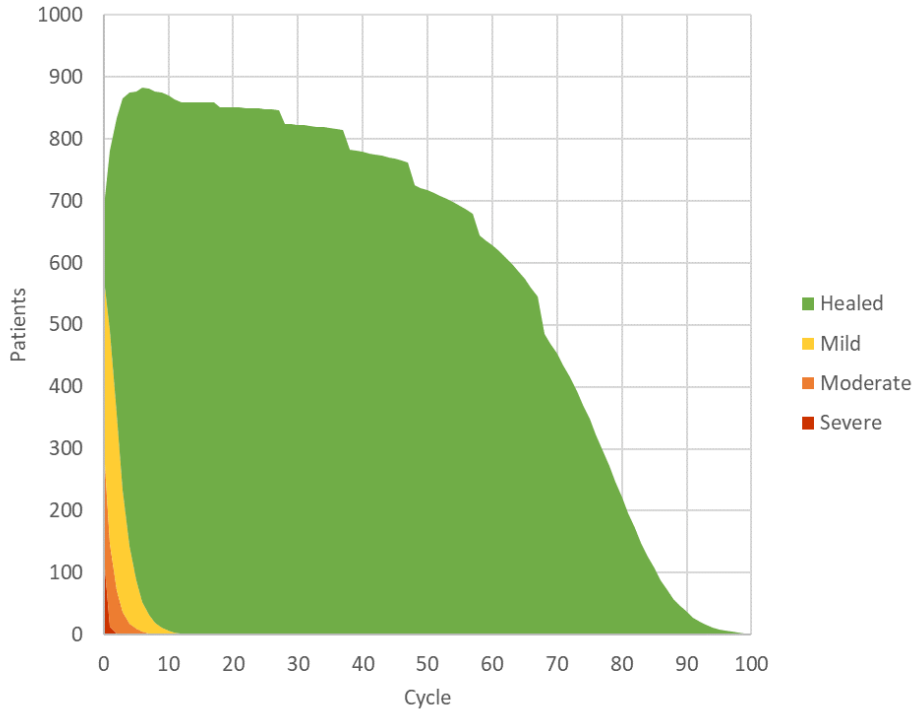


Figure 13. QALY accrual: burosumab



Validation

B36. Priority question. Please provide details of the validation efforts conducted on the model. These should include all aspects of validation (i.e. internal validation, cross-validation, etc…) as explained for example in the AdvisHE (https://advishe.wordpress.com/) tool, and not only face validity (which has been briefly reported in the CS). Please include also the results of the ongoing external validation indicated on page 167.

The conceptual model, cost and resource use variables have been validated by XLH clinical experts as detailed in section 12.3.3 of the submission.

Sources for the input parameters have used published literature where possible, supplemented by information from the clinical experts. Distributions and parameters to consider the uncertainty around the mean values have been included to establish the key drivers of the model.

Further to this, continuous internal validation has been provided in the development of the model the model by two separate health economic consultancies for the absence for apparent bugs local code structure, appropriate translation of the conceptual model.

Cross validation of the model is not possible as there are no published economic models of XLH.

Extreme value testing indicates that if the treatment effect of burosumab is zero, and the transition probabilities are therefore the same as the comparator, then the outcomes of the intervention and comparator are identical with the exception of drug and treatment monitoring costs.

Section C: Textual clarifications and additional points

C1. Please provide a complete version of Table 47 (a large number of parameters included in the model are missing).

Since Table 47 sits within the clinical inputs section, only patient demographics and clinical inputs had been included. Information from section 12.3.6 Table 50 (summary of monitoring costs), section 12.3.7 Table 52 (unit costs and resource use for health states), section 12.4.2 and 12.4.3 Table 54 (variables used in one-way deterministic sensitivity analysis) have been summarised in Table 17 to complete the table for all parameters, as requested.

Table 20. Summary of variables applied in the cost-effectiveness model

Variable	Value	Range and distribution	Source
Baseline age and severity distribution	See Table 36	Dirichlet distribution using observed values in Table 35.	Pooled baseline distribution from CL201 (all doses) and CL205
% male	50.77%	In one-way sensitivity analysis the range is 0-100%.	Pooled data from CL201 (all doses) and CL205
Weight	Median weight of the general population in Table 34	A lower weight at the 25% percentile (also Table 34) is tested in sensitivity analysis	(Royal College of Paediatrics and Child Health, 2013b, 2013a)
Transition probabilities – treated group, age 1-4 years	See Table 38	Dirichlet distribution using observed values in Table 37.	CL205 study
Transition probabilities – treated group, age 5 years and older	See Table 40	Dirichlet distribution using observed values in Table 39.	CL201 study
Transition probabilities – control group, all ages	See Table 42	Dirichlet distribution using observed values in Table 41. An alternative approach to missing data imputation is used in a scenario analysis. A further scenario analysis uses data from Study CL002.	UK chart review
Cost of burosumab	See Table 48 and 49	None	Proposed list price
Monitoring costs associated with	One-off cost of £126.55 per patient at treatment	Gamma distribution assuming standard error is 25% of the mean	Unit costs taken from PSSRU (2017) (Curtis and Burns, 2017) and

	initiation (see Table 50)		NHS Reference Costs 2016/17 (NHS Reference costs 2016 to 2017, 2017)
Surveillance costs and resource use Including (specialist consultations, laboratory monitoring, radiography, renal ultrasonography, dental check ups)	See Table 54	Gamma distribution assuming standard error is 25% of the mean	Unit costs from NHS Reference costs 2016/17 (NHS Reference costs 2016 to 2017, 2017) Resource use taken from KOL opinion Detail outlined in Table 52
Comparator costs (oral phosphate and alfacalcidol)	£492.57 per child and £394.01 per adult (see Table 51 and 53)	Gamma distribution assuming standard error is 25% of the mean	Unit costs from the BNF and resource use taken from (Carpenter et al., 2011) for children, and Che et al. (Che et al., 2016) for adults
Pain and mobility costs and resource use (physiotherapy)	See Table 52 and Table 53	Gamma distribution assuming standard error is 25% of the mean	Unit costs taken from PSSRU (2017) (Curtis and Burns, 2017) and resource use from Che et al. (Che et al., 2016) Detail outlined in Table 52
Orthopaedic intervention costs and resource use Including (dental abnormalities, stapling of growth plates, hip arthroplasty, knee arthroplasty)	See Table 52 and Table 53	Gamma distribution assuming standard error is 25% of the mean	Unit costs from NHS Reference costs 2016/17 (NHS Reference costs 2016 to 2017, 2017) Resource use and further details outlined in Table 52
Adverse event costs (injection-site reactions)	£0 - see section 12.3.8	Range £0 - £5	Assumed unit costs Resource use outlined in studies CL201 and CL205

C2. Please include a full list of assumptions in Section 12.1.5. A number of implicitly made assumptions are missing from the overview, such as RSS is a relevant proxy for overall XLH health states.

Since question 12.1.5 of the submission lies within the discussion of the model structure, the list of assumptions included related specifically to the model structure. A more comprehensive list is provided below.

- It is assumed that healing rickets will be sustained over the long term given the normalisation of serum phosphate with burosumab.
- RSS is a relevant proxy for overall XLH health states
- Based on this UK growth data, in the cost-effectiveness model, girls are assumed to remain on treatment up to 16 years of age (inclusive) and boys are assumed to remain on treatment until 17 years of age (inclusive).
- The baseline age and severity distribution used in the model is assumed to be a representative sample of the XLH population eligible to receive burosumab
- After age 17 (closure of a patient's growth plates), the patient will stay in the same health state lifelong and receive the continued support associated with that health state.
- Only patients that have rickets in childhood are assumed to receive the cost of vitamin D analogues and phosphate supplements in adulthood.
- After the age of 13, HRQL is assumed to decline at a rate proportional to the general population.
- The derived utilities for adolescents aged 13 and over have been assumed to also be applicable to adults. Since XLH is not associated with mortality, the derived utilities are used over the lifetime of the patient.
- In the first year of treatment, patients are assumed to require five additional blood tests and 15-minute consultations with nurses to take the blood tests to support dose titrations over the course of 3 months as part of the monitoring
- For oral phosphate dosage, the mean is assumed to be one tablet four times per day (derived from Carpenter et al. recommending dosing in 3-5 divided doses (Carpenter et al., 2011).
- Surveillance costs are the current costs of clinical management in the UK, to monitor and manage treatment in patients. These are assumed to be the same costs for all health states and the same in both arms (burosumab and SoC) and therefore do not impact on the base case results.
- A UK parent survey indicated that some children may receive prescription pain relief (Acaster Lloyd Consulting, 2018) but the proportion that need prescription pain relief is unknown, so it has been conservatively assumed that patients do not receive pain management costs

- It has been assumed that of the proportion of children that request physiotherapy, they would receive one session per month.
- It has been assumed that of the proportion of adults that require physiotherapy, they will receive one hour of physiotherapy per month.
- Patients that have an osteotomy procedure are assumed to require two during childhood, which is applied by assuming the cost occurs every 8 years as a child. The same assumption is made regarding stapling of growth plates.
- It has been assumed that if patients require a hip arthroplasty, they will have only one in their lifetime to calculate the average annual costs. A hip arthroplasty will usually last around 20 years, so it is possible people with XLH may require another during their lifetime; therefore this assumption may be an underestimate.
- It has been assumed that if patients require a knee arthroplasty, they will have only one in their lifetime to calculate the average annual costs. A hip arthroplasty will usually last around 20 years, so it is possible people with XLH may require another during their lifetime; therefore this assumption may be an underestimate.

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Appendix 1. Validation Rule Table

[ACADEMIC IN CONFIDENCE]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted] [redacted]

Name of your organisation: Climb

Brief de*scrip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

About the Charity
Climb has been the leading umbrella patient organisation encompassing all Inherited Metabolic Disorders (IMDs) for 36 years. The mission of the charity remains as true today as in 1981; to improve the lives of those living with IMDs and their families. Climb has recently developed a new strategy (to be launched April 2018), which will enable the charity to build on the areas in which it can make the most difference to patients and their families in an ever-changing landscape.

Providing bespoke support, advice and information to patients and their families, and connecting them with others to help reduce the isolation of living with a rare condition, has always been at the heart of the charity's activities. However, the way in which people are using Climb has changed significantly over the years. There is a vast amount of information online, supportive communities being formed on social media, and an increasing number of patient organisations focusing on one condition (or group of conditions).

There are 445 IMDs, affecting approximately 20,000 patients in the UK, and 3.5 million worldwide. The new strategy is designed to reach a higher percentage of these people, and it is vitally important that Climb provides high quality, accessible and credible information at the right time, working collaboratively and utilising the tools available to ensure that patients receive the most appropriate and effective support and information.

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Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) YES
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

How does the condition impact on patients, their families or carers?

1(i) Please explain the impact on patients of the specific symptoms, manifestations and complications of X-linked hypophosphatemia. For example, the impact of skeletal complications, neurological complications and spinal cord compression, as well as the impact of disease manifestations outside the skeleton.

Ranging from mild to severe. Symptoms include

Lower limb deformities (bow or knock-knee). Sometimes these require repeated corrective surgery which can result in infection and the patient not being able to attend school, work etc
Waddling gait
Short stature or declining growth rate
Bone pain. Children can complain of varying degrees of pain in the legs
Muscle pain and weakness
Craniosynostosis
Spontaneous tooth abscesses. These can be recurring and result in significant pain and discomfort. Problems with the formation of teeth can result in dental abscesses, not because of poor dental hygiene, but because of improper formation of dentin and other tooth structures. Like bone problems, dental problems also vary from patient to patient.
Hearing loss

The condition is life long and so the symptoms can be persistent and over time impact on a child's quality of life and ability to participate fully in activities.

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Burosumab for treating X-linked hypophosphataemia [ID1151]

(ii) Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Adult patients report that they had a delay in diagnosis until teenage years due to lack of knowledge by medical professionals of the condition.
Usually the child will present with bowing of the legs when the child starts to walk - indicative of rickets.
XLH occurs in one birth out of 20,000, so a pediatrician or GP may never see it in his or her career. Even if there is a diagnosis of the child with rickets, they might not know about XLH and presume it to be due to lack of enough vitamin D and try that first.
However, XLH resists typical Vitamin D therapy, so a patient might then be put through a complete series of tests, X-rays, and consultations with specialists and then might not be diagnosed with XLH until age 3 plus. This is a common issue for many children with XLH where there is no previous family history.

If there is family history then it is usual for testing to be carried out much earlier and a diagnosis made for children.

Upon correct diagnosis the usual treatment is typically an active form of Vitamin D and phosphorus which should be prescribed very carefully and taken in association with regular monitoring of blood and urine chemistries, including ParaThyroid Hormone (PTH) levels and urine calcium levels. However, long-term administration of phosphate and vitamin D preparations is sometimes complicated with nephrocalcinosis, secondary or tertiary hyperparathyroidism and arterial hypertension. Patients should be treated in a specialist centre to ensure careful, balanced management of the treatment to avoid such complications

Unfortunately due to delays in diagnosis and treatment, some children may require corrective surgery

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Burosumab for treating X-linked hypophosphataemia [ID1151]

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

Depending on the severity of the condition, some patients can participate in 'normal' life. However, those who are more severely affected can suffer from pain which is debilitating and can affect participation in activities, school or work.
If the condition is diagnosed early and treatment has been started, children might avoid bone defects that require surgery and so this minimises the impact on everyday life.
Those who have not been fortunate enough to receive treatment early may have had multiple surgeries and long recovery times impacting on their lives.

The treatment regime is also a difficult one requiring daily medication uses up to 6 times a day. It is extremely unpalatable and therefore difficult to ensure babies are getting correct quantities and that children are complying with the doses. It is the early years of treatment that are crucial to avoiding problems later on.

Like with any chronic condition the effects of long term pain and problems with mobility can take its toll on mood and mental well-being. This is obviously dependent on the person and other factors.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

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Burosumab for treating X-linked hypophosphataemia [ID1151]

Evidence suggests that this technology treats the underlying cause of the condition therefore early diagnosis and treatment can prevent many of the symptoms and complications developing later
Current medication is difficult to take especially for children and affects quality of life
Usually 6 doses of phosphate per day which can be difficult for parents with babies and also requires monitoring in nursery, school as the child gets a little older. The current options for this medication are not palatable and therefore treatment is difficult to maintain

1 Breakfast
2 Mid morning
3 Lunchtime
4 Mid afternoon
5 Teatime
6 Bedtime

One mum who has 2 children with the condition commented
'I used to supply them with the phosphate sandoz tablets and blackcurrant cordial and the teachers would send them to the office at the appropriate times.
The staff there were also mindful and caring of their physical limitations.' The condition and medication required regular monitoring and this involved
3 monthly blood tests, regular urine tests, x-rays and ultrasound examinations'

The new technology will improve quality of life for patients in terms treatment being an intramuscular injection, carried out fortnightly ,at a specialist centre
One parent said 'Hopefully this will become the preferred form of medication as it is much easier to have one injection than to try to have 6 doses every day'

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health

- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

The main benefits evidenced through clinical trials are

Improvements in rickets
Improvements in growth and walking ability
Improvements in Patient/Parent reported pain, fatigue and physical function/mobility

The trials have been for children age 1-12

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

The technology does not appear to reverse bone defects but if used early in life can prevent many of the issues and symptoms from occurring
Frequent visits to the metabolic bone units for the injection might prove difficult for some families in terms of time and finances

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

At a recent patient day all patients were positive and hopeful about the new technology especially for babies and children

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Children who receive the treatment on initial diagnosis will benefit more as it will prevent many of the symptoms and bone defects in later life

Adults whose bones are already fully developed may not benefit as much although the research in this area is limited and treatments to improve pain is needed

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

The current guidelines conclude that' managing XLH is complicated. Although the current standard of treatment is sub-optimal, it does improve rickets, growth and osteomalacia. Treatment requires balancing the benefits of treatment with complicated monitoring and potential risks. Multiple issues must be addressed, and choices for dose adjustment may not be straightforward. Involving clinicians with experience treating XLH is often useful. More efficacious and more convenient therapies are clearly needed'

There are 2 main types of treatment
Medication and treatment through referral to a specialist metabolic bone unit
Surgical or orthopaedic treatment.

Balanced administration of Phosphate, calcium and vitamin D - The goal with current treatment options is not to push to reach a normal serum phosphorus level, as that may result in potentially serious PTH elevations, and increasing the phosphate dosage may only result in increasing the PTH level without any increase in serum phosphorus. Instead, the goal is to improve serum phosphorus levels enough to promote bone healing while keeping calcium and PTH levels in an appropriate range

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

XLH is a rare, chronic progressive musculoskeletal disorder characterised by renal phosphate wasting caused by excess FGF23 production, and is inherited as an X-linked dominant trait affecting both males and females. XLH is first seen in infants and also affects adults.

In children, XLH causes skeletal disease, leading to lower-extremity deformity and diminished height.

The conventional treatment of XLH consists of multiple daily doses of phosphate and active vitamin D to counteract the excess effects of FGF23 but does not correct the underlying disease.

The new technology is designed to treat the underlying cause of XLH. FGF23 is a hormone that reduces serum levels of phosphorus and active vitamin D by regulating phosphate excretion and active vitamin D production by the kidney. Phosphate wasting in XLH and TIO is caused by excessive levels and activity of FGF23. The new technology is designed to bind to and thereby inhibit the biological activity of FGF23. By blocking excess FGF23 in patients with XLH it is intended to increase phosphate reabsorption from the kidney and increase the production of vitamin D, which enhances intestinal absorption of phosphate and calcium.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

The new technology will be an injection fortnightly rather than 6 doses of medication orally. This might prove an obstacle for small children or those with a needle phobia
And for those who have to travel far to a metabolic bone centre.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

N/A

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?
N/A

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

Clinical trials at Manchester children's hospital have proven effective for a child patient known to our organisation. However longer term monitoring will establish if outcomes as an adult are improved

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

If babies were diagnosed early and treatment was given then this would improve all symptoms and prevent many of the complications in adulthood and associated complications with the current treatment. Treatment of the underlying causes early in life would mean improvements in quality of life for patients. The current treatment regime is difficult and can cause complications if not monitored rigorously

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

The current treatment would still be available

(iii) Are there groups of patients that have difficulties using the technology?

(iv) Are there any situations where patients may choose not to use this technology?

Issues with injections might be a problem for some patients especially small children

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Due to better knowledge and improved testing (especially if there is a family history of the condition) most patients are known to the specialist metabolic bone units

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: XLH UK

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

XLH UK is a charitable trust formed to support the XLH community in the UK. The organisation currently has approximately 150 patient, parent and carer members across the UK, but represents 2,000 unregistered patients, parents and carers.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?

Yes

- a carer of a patient with the condition for which NICE is considering this technology?

No

- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

I am also a Trustee (voluntary role) of XLH UK in addition to a Member of the Board of Directors for The XLH Network, Inc (voluntary role)

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: *None*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

How does the condition impact on patients, their families or carers?

1(i) Please explain the impact on patients of the specific symptoms, manifestations and complications of X-linked hypophosphatemia. For example, the impact of skeletal complications, neurological complications and spinal cord compression, as well as the impact of disease manifestations outside the skeleton.

Symptom: bowed legs
Impact: If legs are bowed during childhood you'll often be referred for corrective surgery. This journey is not for the faint hearted and could begin by orthopaedic corrective surgery of the tibias and femurs using external fixation or Ilizarov/Spatial frames. This is by all means a traumatic experience for a 7 year old to wake up from 5 hour surgery with industrial-looking metal work encased around their legs after their legs having been broken and realigned. Overcoming the surgery is a fight but living with an external fixator or Ilizarov/Spatial frame on both legs for 2-6 months is also incredibly painful. You're also exposed to infection risks, with pin sites that you must clean everyday, and bolts on the frame that you must turn and tighten yourself, that, overtime change the shape of the frame to ease new bone growth into the correct position. The external fixator or Ilizarov/Spatial frame is removed through another operation where you again start to learn to walk again retrain your muscles and build your confidence. This process unfortunately repeats itself on each tibia and each femur until your legs are straight. XLH patients also often require other types of invasive surgery such as tibial osteotomies with plates or IM nails, or require staples in the knees from re-bowing or going knock-kneed. Going through all these treatments, completely kills your confidence and your ability to be strong. The psychological impact this has is often overlooked simply because you have much more pressing physical differences to address as a child.

Symptom: dental abscesses
Impact: There's nothing that quite matches the throbbing pain of a tooth abscess. These occur for most people with XLH, and appear without trauma or tooth decay unlike a regular healthy person. And so are not currently preventative. The impact of dental abscessing is significant since the financial burden of root canal and crown treatment is high, and the time-off that is needed from class or work, maybe 4-5 appointments to complete root canal treatment is more than an inconvenience.

Symptom: calcification, ossification, osteoarthritis and pain
Impact: The truth is that adult XLH patients live with a number of symptoms on a daily basis with varying degrees of pain that range from bothersome to extreme, and this appears to be true regardless of whether the patient received the current standard-of-care treatment during childhood or not. Many of our members experience, to varying degrees, a combination of the following symptoms, some daily, some less frequently, but always with significant quality-of-life consequences: bone pain in the absence of a fracture; fractures; microfactures, pseudofractures;

enthesopathy, calcification of various joints; ossification of the posterior longitudinal ligament; calcification and hypertrophy throughout the spine; muscle weakness; chronic fatigue from low phosphorus levels; and osteoarthritis from misaligned joints (at a much earlier age than is seen in the general population). Patients are strong in the face of these daily challenges. Many of them live in daily pain, accepting such pain as part of everyday life. In addition to the pain of these symptoms, there are functional consequences as well, such as reduced range of motion in the major weight-bearing joints and experiencing mobility limitations that might normally be seen in someone aged 70 or above when the XLH patient is only 40. This does not include patients who are dependent on crutches or wheelchairs in their 20s and 30s. We had been hopeful that adults who underwent the current standard-of-care (first broadly used in the 1980s) would not experience these symptoms as adults, but anecdotal evidence is that the patients who had this treatment, and are now reaching their late 20s and early 30s, can still experience significant bone pain, calcifications and fatigue. Joint replacement surgery, especially knees and hips, is also not uncommon in adults with XLH because of the high frequency of degenerative joint disease and enthesopathy.

Symptom: Hearing loss, inner ear problems and vertigo
Impact: Some patients have hearing loss that progressively gets worse over time. The severity and frequency of hearing problems vary from patient to patient. Those that have inner ear problems may also experience vertigo which can have a detrimental impact on that patients ability to work, travel or care for themselves or others. Hearing aids are almost always used in cases where the patient has significant hearing loss.

Symptom: Craniosynostosis, Chiari 1 malformation
Impact: Some patients develop craniosynostosis in relation to the poor growth of the cranial bones leaving the patient with an unusually shaped or protruding forehead. In rare instances chiari malformation is diagnosed. However, important neurological complications of Chiari malformation and spinal cord compression can occur and may require complex surgery to address the risks and complications. Those debilitating symptoms could include pain, numbness, weakness, tinnitus, hearing and balance issues. This complication has been linked to the condition and could be life threatening/ life changing if left untreated.

(ii) Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Challenges in diagnosis
Diagnosis is particularly a challenge in those where there is no family history of XLH (X-linked hypophosphatemia). Typically the condition begins to present itself where a parent has a baby who they begin to notice has not taken to crawling or walking quite as early as the other children. It's only when that child does begin to walk, that they notice the bow-leggedness seen in young toddlers has not straightened out. This realisation that their child is different from other children is often traumatic as it takes

significant back and forth with a GP to conclude that the child's reason for bowed legs is not because of nutritional neglect but a symptom of an underlying condition yet to be diagnosed. A GP's first attempt may be to treat with high doses of vitamin D which may be damaging, with little or no effect on improving the bowed legs. The next step is a referral to a paediatrician who will take the necessary steps of blood work, x-rays, and other details before ordering a genetic test. Parents at this point are increasingly concerned and this can lead to additional social pressures and anxieties on those parents lives since it is still not understood why the spontaneous mutation that causes XLH occurs.

It's also challenging to learn that delays in obtaining the diagnosis means a delay in treatment at a critical time for bone growth. The sooner treatment begins, the better the long-term outcome. In addition, there may be problems with diagnosis even when a parent has XLH. So the significant odds of the child having XLH should be known (50/50 if the mother has XLH and 100% of the daughters of an XLH father), but often are discounted. Further complicating diagnosis is that the blood levels of phosphorus vary widely in young children, and frequently the wrong lab values are used. Normal paediatric phosphorus levels are substantially higher than adult levels, so when the blood levels in a young child are compared to adult values, the results are mistakenly read as normal.

Challenges in receiving appropriate dental care

Due to the dental abnormalities and abscessing associated with XLH and the dental care system in the UK: largely local dentists offering a mix of private or NHS non-specialist services at a cost to the patient, receiving appropriate care as a patient with XLH can be a real challenge. Visiting the local dental practice is a frustrating and emotional experience as the dentists don't know about the condition and often struggle to understand that the condition and dental issues are related. It's not until root canal treatment has started, that the dentist finds that they may not have the necessary tools, and scope to complete the root canal treatment, due to the unusual shape and size of the pulp chamber and root. If attempted at the local dentist, there's a high chance of failure and the crown which has cost significant money will have to be lifted and attempted once again, or the tooth may need to be extracted. If the dentist does find that they're unable to complete the treatment you'll then be in an uphill battle to see if it's possible to find a dental hospital who will accept you as a patient. We find that dental hospitals will only take on patients if the work required is considered significant enough to warrant a student to learn from at that time. However patients do frequently find themselves being turned away, back to the family dentist to carry out subpar work at a cost to the patient. Even if patients can find a dental hospital that might accept them, the low numbers of these geographically also typically means, unless the patient lives near a major urban teaching centre such as London's Eastmans, that they may need to travel long distances.

Patients often arrive at a situation where their root canal has failed and the root has to be extracted. Patients then may attempt dental implants at significant cost, (to the NHS or private) and many of them fail, far more than in the general population. Poor dental health affects not just physical health, but also emotional health, as patients are embarrassed by their missing or damaged teeth, and feel judged by others who don't know that the dental issues are not their fault.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

Emotional and social impact as a child

For a child with spontaneous XLH growing up can be an overwhelmingly lonely experience, whose siblings and peers who do not have the condition may be taller and more active. Children are strong individuals with little fear but one of their first significant experiences of symptoms is typically not being able to keep up with their friends when playing at school, or partaking in the school sports day and tiring easily from physical activities. The biggest reason for this is that their legs are still severely bowed, so much so that a football could fit between their knees while their ankles are still touching. It's this coupled with a large or protruding forehead that can be some of the worst and unfortunate symptoms to have as a child. When a child has such physical differences they'll experience other children and adults staring, which is obviously a nasty, demoralising feeling. Children also have to deal with other negative social situations, such as children and parents asking "what happened", the stigmatizing term rickets being thrown around or other adults being quick to quiz your parent "if they've been eating properly". Of course you'll cower away and it's this struggle that has an effect on your confidence growing up that impacts your adult life in many ways.

Negative physical, practical and emotional impact of surgeries on the family unit and an individual's everyday life

We must also point out the significant difficulties parents have when a child or children inherit XLH from a parent who already has the condition. The burden is now amplified, as you're not only thinking about your own care as you get older, but to manage the care of your children. It's not uncommon for siblings to have corrective surgeries at the same time, however the impact this can have on the family unit is significant since it's likely if the children are to have corrective surgeries on their lower limbs they might return home dependent on wheelchairs. This is obviously going to impact that family's life. For instance through accessibility around the home, accessibility at school and even something as simple as getting two wheelchairs in a car is challenging for most, let alone for a parent who also has XLH with compromised skeletal issues.

Today, typical corrective surgeries of Ilizarov/Spatial frame and external fixation are also followed up by the insertion of an IM nail down the bone to ensure the bone doesn't bow back to its previous shape. Going through these procedures would require a minimum of 4 surgeries to fix on, 4 surgeries to remove off, and 4 surgeries to have nails in, totalling 12 surgeries (assuming all were without complications), all

between the ages of 7 and 17. There are also situations where patients who had these surgical interventions often have to be repaired or replaced during adulthood.

As you can see, the impact of surgery alone throughout childhood is hugely disruptive to that individual's attendance at school, time with friends, being able to stay active to keep healthy and lead a normal life. We have also seen that once surgery has happened in childhood there is evidence of the orthopaedic fractures still showing up in x-ray's later in life, and so the patient must be careful to not have even a low impact accident such as falling over or off a step since you can easily suffer from a fracture at the same site, that may require emergency attention and further surgery and disruption.

Financial and practical impact on adult lives and choices
Historically the condition has been viewed purely as a childhood disorder, but it is a myth that the condition should be thought of in this way. A number of factors contribute to this myth: many of the experts in the field are paediatricians; there is no natural history of the condition that extends past the closing of growth plates; and virtually all research has been limited to paediatric subjects. As a result, public literature contains misleading statements such as the following: "Apart from the short stature of most affected adults, the prognosis for a normal lifespan and normal health is good." Unfortunately, we know this is not true. Adults, even those who have had good success with childhood treatment, so that their bones are straight and the rickets are healed, subsequently go on to have extensive issues when treatment is terminated, including widespread calcifications in the spine and joints, bone pain, muscle dysfunction and extreme fatigue.

The condition can also have an impact on a patient's choice of work. Generally speaking, heavy lifting and general labour work is definitely unsuitable as it's not just bones, but also muscle function and strength, as well as energy levels, are all affected by low levels of phosphorus. As a patient ages, the impact of the condition on their body is obviously increased and many patients may find themselves making career changes because they're physically unable to do their current job. This coupled with having to learn new skills for a new profession is tricky and will obviously have emotional effects and financial pressures on their own and their family's wellbeing. I've seen many patients who approach their 50's that find it too difficult to continue with a Monday-Friday job and will either retire and seek disability allowances or depend on relations and carers to cook, clean and simply be with them.

The condition's impact on height and movement may also require adaptations, particularly as patients age, such as not being able to drive a conventional car (adapted) or to use a conventional kitchen/bathroom. Many patients will take the necessary steps to move into bungalows or ground floor flats, or live on the ground floor of their homes. Customising the home by lowering the kitchen is also not uncommon, although taking steps to build ramps, lower kitchens and widen doorways is met with significant costs.

Social and emotional impact on adult lives
It's important to recognise the relationship between physical disability and depression among teenagers and adults since depression is a significant symptom and common

when living with some of the condition's most physically demanding symptoms. To live life as a person with physical disabilities means developing extraordinarily strong self-esteem and the self-assurance of your value. The significant amount of pain and fatigue can contribute to depression, draining patients' energy and lessening their ability to deal with the normal setbacks of life.

The effect of the condition as an adult starts as early as the impact on decisions to do with family planning. Individuals might choose not to have children knowing that women have a 50% chance of your newborn inheriting the condition. In the case of a male who has XLH they know that a daughter will 100% inherit XLH as the daughter will inherit the mutated X chromosome. Having a child or children who goes through so many surgeries or being an adult who could be classified as being disabled has a huge impact on the wellbeing, mental health, and personal relationships of those patients. This could also affect the parental attitudes toward one's actual or possible disabled child or children. Parents are also concerned about the impact of the condition and being disabled on a variety of relationships, in particular doubts expressed by many about the capacity of adults with disabilities to become friends, lovers, and parents. As it's suggested that if individuals with the condition do have severe disabilities they could appear to be unhappy, unhealthy, or socially isolated, primarily due to their physical differences and being able to fit with social norms. Love and friendship, are for most people an essential ingredient of the life they want for themselves, something to value for their own sake as well as for the support they provide during stressful times. However, many people see their physical differences, such as a pronounced forehead, bowed legs and or severe gait as an obstacle to friendship, romantic love, and rewarding family life.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Less frequent need to take new treatment
The frequency at which patients with XLH currently take medicine dosages is very high, this is usually in the region of 4-6 times a day; taking phosphate & calcitriol - sometimes to be woken during the night to take these.

No stomach irritation/unpleasant taste compared to current treatment
The new treatment is administered by injection, around once every two weeks. This contrasts with the current medicines which need to be taken multiple times a day and cause an upset stomach resulting in diarrhoea, gastrointestinal pain and or unpleasant gassiness for most. This obviously has an impact on your school and work, to frequently be excused to take toilet breaks. The phosphate supplements tend to be high in sodium as well, so patients get more sodium than is recommended, which isn't good for blood pressure and cardiac health. The

phosphate also makes you thirsty requiring the need to ensure you're drinking enough water.

Improvement in energy
Generalised muscle weakness and fatigue are common symptoms in adults whereas children complain of tiring easily. We've seen that both adults and children have reported improvements to levels of fatigue and tiredness when using the new technology.

Improvement/reduction of physical symptoms of the condition
Improved symptoms as a child - reversed and improved evidence of bowing in the lower limbs, there has also been height improvements among children.
Improved symptoms as a adult - reversed and improved evidence of being able to heal fractures, microfractures, and non-unions, improvements in osteomalacia, and a delay in calcification of tendons and ligaments and major weight bearing bones and joints (spine, hips, and knees). These are shown to improve the patient's gait, their potential height, reduction in bone pain, ability to stay mobile for longer, have greater flexibility and ultimately slow the progressive nature of the condition.

We've seen that children on the new technology see major improvements of the debilitating physical symptoms as described earlier (bowed legs, distinctive gait, pronounced forehead, and short stature). That will achieve four differences; 1) No or reduced requirement for corrective surgery; 2) Improved emotional wellbeing and self-esteem 3) Be on a better trajectory as that child enters adulthood. 4) To lay quality bone and tooth formation to reduce the frequency of dental abscessing without trauma.
The current treatment of phosphorus supplements led to wide swings in the phosphorus levels in the bloodstream, so that they went below normal levels every few hours. It isn't known exactly what effect that had on patients, but it was bound to be less than ideal, and contribute to energy swings and possible less than ideal bone mineralisation. The new technology provides for a constant normal level of phosphorus for weeks at a time, rather than a few hours at a time.

Fewer doctors' visits and medical tests.
The current treatment required a delicate balancing of phosphorus and calcitriol, with no really well-defined dosages. Accordingly, treatment is a matter of trial and error, starting with a low dose, running blood and urine tests a few weeks later, adjusting the dose, more tests, more adjustments. Plus the risk of nephrocalcinosis during treatment means annual (or more frequent during childhood) kidney ultrasounds to watch for calcifications. With the new treatment, the dosage is reasonably uniform, requiring fewer adjustments and fewer blood/urine tests. Also, it appears not to present any significant risk of nephrocalcinosis, so kidney ultrasounds would not be required, either at all or at least not as frequently as with current treatment.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms

- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

It is the long term gains where we would expect to see the most improvements and have the biggest impact on a patient and their family's life. As the new technology has shown to reverse the abnormal phosphate metabolism and the resulting skeletal effects; specifically patients are seen to improve bone quality; with improvement of stiffness, pain and physical functioning along with evidence of fracture healing. The skeletal improvements in children is significant because it could result in children not requiring the traumatic corrective surgeries, head and leg braces at night, or spend the months and sometimes years needed to recover from each of those surgeries. This would also suggest that those same patients when older won't be suffering from a recurrence of refracturing or suffering from microfractures because of poor quality bone and unbalanced gait. They'd also be less likely to require knee and hip replacements at a much earlier age than the general population. Currently, patients in their thirties and forties may require joint replacement. If those same patients are without the physical symptoms, then you can only imagine how their mental health and quality of life will improve. That current financial burden to ensure your home is adequate when older, to install an accessible washroom, a modified kitchen, ensure the bedroom is downstairs, or even move from a house into a bungalow. Some patients become reliant on government disability benefits, and rely on local councils to provide suitably adapted homes. The new technology has the potential to not only change the lives of children growing up with skeletal deformities, but change the path of adults suffering daily today.

This would mean that children who have been on the medication to be an improved generation of the population as they come into adulthood. Many not experiencing bowed legs, or traumatic corrective bracing and orthopaedic surgery. These people might even expect to see improved or no psychological/emotional issues, or to not feel the need to make life changing decisions (job changes, home relocation) as I stated earlier. A patient with XLH's decision to have children themselves may also be altered in the knowledge that there is a treatment with better outcomes for their child than the treatment that they experienced themselves.

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)

- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

To inject yourself to administer the new technology might be difficult at first for children to accept. Additionally patients might have discomfort with the tissue at the site of injection. However children and adults are asked for frequent blood tests upon every visit to the GP/specialist hospital, so should not be concerned at the procedure of an injection.

Taking trips to the hospital to see your specialist for regular monitoring to establish the right dose in the beginning isn't significant if it's to prevent the same regular trips to the same specialist centre to see a surgeon for pre, post and operation visits.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

Patients in the UK are not necessarily all aware of the new technology, and are only likely to know about it if they had a child with XLH who fit the criteria of the trials for the new technology. Those that have had long term exposure of the new technology have seen significant improvement in their child's skeletal development, especially on correction of the bowed legs, height improvements, gait, and energy.

We've not known anyone who has said they wouldn't be interested in the new technology if recommended by a clinician.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

We believe all XLH patients will benefit from burosumab throughout their lives. Some patients have more severe symptoms and will accordingly benefit more, but all patients require phosphorus for healthy bones, teeth, muscle and energy. The only patients who may not benefit are those who may have an adverse reaction to the treatment. We are not aware of any such adverse reactions that outweigh the benefits of treatment.

In addition, starting any treatment as early in life as possible is the key to a better outcome and may contribute to having less severe symptoms. It's important because the demand for phosphorus when growing is high and so monitoring blood work is vital to take advantage of the growth spurt to maximise the growth opportunity.

However there is a fair argument that adults who have problems in healing fractures would also have significant benefit.

I would also say that the period of a patient's life when adult teeth are developing that they should consistently have the normal range of phosphorus in order to have quality development of adult teeth and so prevent the onset of abscessing later in life.

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Current treatment is usually phosphate sandoz (dissolved in water) that tastes bitter and sour and is gaseous and then calcitriol which is in the form of a small capsule. The phosphate is to be taken as much as can be tolerated (due to side effects; upset stomach, diarrhea) which is usually between 4-6 times equally spaced through the day. It's advised that the phosphate should not be taken within 30 minutes of consuming the calcitriol (or the milk on your breakfast), because if taken together the first medication of the day becomes ineffective (due to a binding in the stomach/intestine). Therefore the number of times you're to take medication is 5-7 times per day, equally spaced. This is including in the middle of the night, so the parent has to get up and wake the child to make the child drink the phosphate.

Can you imagine what that does to a child's (and family's) life? Not just getting the child to settle down for meals, but to settle down an hour before breakfast to take the calcitriol, then back to the table for breakfast an hour later. and some of the doses needing to be during school or social events. Even without being quite that rigorous, going with just four times a day, skipping the middle of the night one, and no calcitriol, that's still pretty disruptive for everyone, child and family alike.

It is clearly burdensome to patients and families, and does compromise compliance.

Patient cooperation with a 4-6 dose daily regimen is challenging at all ages (and of course it tastes terrible, so no one wants to take it), and since phosphorus has such a short lifespan in the bloodstream, it means that there's bound to be missed doses and therefore significant periods when the phosphate is lower than optimal for child's growth. Therefore it's hard to really expect 100 percent adherence to that kind of regimen, day in, day out, year after year, even with the best of intentions. So the every-two-weeks dosing for the new technology is going to vastly improve the odds of a patient sticking to the regimen, in addition to the fact that the new technology itself maintains the phosphate at a good level consistently, instead of constantly going up and down every few hours.

The current regime of phosphate and calcitriol must also be monitored closely as the current treatment requires balancing the benefits of treatment with complicated monitoring and potential risks. The major risks of long-term treatment with calcitriol and phosphorus: hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis, and potentially, chronic kidney disease. Careful monitoring of bloodwork and kidney ultrasound is essential in order to minimize these risks.

We have also seen some pediatricians in addition to the above, prescribe a much more “Victorian” approach; whereby they have very young children wear a type of hard-hat and leg braces at night in attempt to reshape their soft skull and lower limbs into a corrected position to reduce the effects of a pronounced forehead and leg bowing. These are clearly traumatic for both the child and parents as it attempts to reshape the parts of the body which are soft enough to be manipulated.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

We’ve seen evidence where several of the most troublesome symptoms of XLH have been significantly reduced; bone pain, stiffness, healing of non-union fractures and pseudofractures and the best improvement within children is their legs that have showed signs of straightening out or have straightened out.

As noted above, compliance with treatment is much simpler with the new technology, which should result in better outcomes. It also has none of the side effects of prior treatment, gastrointestinal distress and the risk of nephrocalcinosis.

There are currently no treatments available that address the ability to heal fractures, which cause significant bone pain. There are also no treatments that address the stiffness around the hips, spine, and knees. There is also nothing to prevent the calcification and ossification around the body so patients are only really permitted to take standard pain relief for long-term use.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We're not aware of any worsening of XLH, its symptoms as a result of the new technology.

There is merit that children may find the injection uncomfortable at first however, like we've mentioned before, children with XLH are frequently having their blood drawn for testing, which would not need to be done as often with the new technology and so I wouldn't believe it wouldn't cause too much of a concern. I would also insist that this outweighs taking current medicines 4-6 times a day, compared with the suggested once every two weeks for the new technology.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

I have heard patients mention that they didn't know how bad they felt until they started on the new technology.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

I'm not aware of any.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

I wouldn't be able to provide a new material.

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

If made available, the differences I'd expect to see would be most significant when a child is taking the new technology at the earliest age, and to continue that treatment long term as I expect we'll find that those most traumatic symptoms to not be present or be reduced. Bowed legs, enlarged joints, pronounced forehead, and finally you'll have a child who is on a better trajectory so that by the time they approach adulthood, they may not need to have the corrective surgery, or realignment of joints or have to deal with a problematic gait or the relentless dental issues. I'd expect then those adulthood symptoms to be somewhat easier than those adults who are suffering so much today.

I would also expect to see the new generation of patients who grow into adulthood to be overwhelmingly in a better emotional place, with more confidence, more energy, have more fulfilling careers, and ultimately lead better lives as individuals, without having a negative impact on those close to them. I'm also highlighting the time parents need to take off work to travel to hospital appointments for surgeries, for dental visits, for physiotherapy sessions. The time it takes to care for those individuals, and the time and effort it takes to care for those who are elderly.

To summarise, this would mean being able to drive a car that doesn't require modification, to be able to use a kitchen that hasn't been modified, to not be interrupted by taking constant doses through the day, to not experience the side effects of current treatment, and to not have to live with the constant bone pain and not being able to walk without taking pain inflammation medication to counter the stiffness and pain.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

It is clear that childhood and adult symptoms are different, as a child you're faced with physical deformities then the symptoms get progressively worse as you grow older. If the technology is not available, then we're going to see 1:20,000 new births a year in the UK where children will be taking what is merely a vitamin and mineral substitute which tastes revolting, causes stomach upsets, requires frequent monitoring all for something that is believed to be not a hugely effective treatment at all.

We must also mention the impact on having an inheritable condition that is X-linked. X-linked dominant inheritance means that the gene causing the condition is located on the X chromosome. (as we know females have two X chromosomes, while males have one X and one Y chromosome). Females who have one copy of the mutation will have a 50% chance of passing that mutated gene to their child (male or female). Males who have one copy of the mutation will have 100% chance of passing to a female, while 0% chance of passing to a male.

Therefore family planning is carefully considered among those patients who have the condition and may seek a geneticist for guidance. Unfortunately, many genetic counselors are misinformed about the condition and patients are told things like XLH is not a genetic disorder and therefore cannot be passed on, or that only males can inherit XLH or that the odds are very low (rather than closer to fifty percent for women and a hundred percent for fathers of daughters). It is also worth noting the Human Fertilisation Embryology Authority approved the condition for Pre-implantation Genetic Diagnosis (which can be used by people who have a serious inherited disease in their family to avoid passing it onto their children). However many might not fit the criteria for IVF.

On this, patients might feel more confident if they knew there was a treatment option that would minimise symptoms of the condition when making their decision to have children or not.

As already mentioned many patients, especially as children find the current treatment difficult to be compliant with. However even where the current medicine is taken as prescribed; it's clear that the symptoms experienced are still hugely significant and have a high negative impact on a patient's life:

Severe lower limb deformities (bowing or knock-kneed)
Skull development issue such as craniosynostosis
Waddling gait
Short stature and slower growth rate
Muscle pain and weakness
Frequent dental abscesses in the absence of trauma or hygiene neglect.

As an adult, all of the above are issues but include additional daily challenges:
Fracturing
Inability to heal fractures
Fear of falling & fracturing
Arthritis
Calcification of tendons and ligaments (spine, hips, knees, ankles)
Osteomalacia
Hearing issues including vertigo
Stiffness in joints
Fatigue

The new treatment is a step change for patients and should the treatment not be made available the condition will continue to have a hugely negative impact on individuals' lives. Patients and their families who have already had access to the new technology via trials have spoken of not ever wanting to return to current treatments -

We now have the technology that tackles the problem at the root cause and has the potential to eliminate significant physical and emotional challenges through the delivery of an injection, (administered once every two weeks) with no known adverse effects Vs. the current course of phosphate supplements (taken 4-6 times a day) with adverse effects and suboptimal results, is going to be life changing for the population of those suffering daily with X-linked Hypophosphatemia.

(iii) Are there groups of patients that have difficulties using the technology?

Those that live in areas of the country that are difficult for patients travel to see a specialist to monitor and receive the new technology.

Travelling when you have the condition may also be challenging for those patients. They may need to take slower routes that are more comfortable, or stay in a hotel to rest.

However these challenges are not new and may already be a factor for those who currently see specialists for general monitoring of their condition.

(iv) Are there any situations where patients may choose not to use this technology?

I have spoken to parents of children on the new technology, and not one of them wants to go back to the old treatment.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

I couldn't answer this question accurately.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Appendix D – NHS organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a commissioners perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation British Paediatric & Adolescent Bone Group (BPABG)

Please indicate your position in the organisation:

I am a Consultant Paediatric Endocrinologist with specialist expertise in the management of children with Metabolic Bone Disorders. I am one of the founding members of the BPABG which has been in existence as a speciality group within the RCPCH for 20 years. It represents paediatricians in the UK who look after children with Metabolic Bone Disease.

Links with, or funding from the tobacco industry - please declare any direct or indirec links to, and receipt of funding from the tobacco industry:

I have no links with or funding from the tobacco industry.
I received funding (approx. £250) last year from Kyowa Kiran to attend an international conference on Fibrous Dysplasia.

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Most children with X-linked Hypophosphataemic Rickets (XLH) are currently treated by specialists familiar with the condition eg paediatric endocrinologists or nephrologists.

There is no alternative at present to current standard therapy consisting of Phosphate supplements given 4 to 5 times daily and a Vitamin D analogue such as One Alpha given once daily. These medications are all given by mouth. This treatment can be associated with side effects – these include the development of calcification in the kidneys (nephrocalcinosis) and hyperparathyroidism. Despite current treatment some children develop deformities of the legs requiring corrective surgery by an orthopaedic surgeon.

It is anticipated that patients receiving Burosumab would be seen in tertiary paediatric centres such as the recognised centres in the Bone European Reference Network (BOND).

Currently there is not significant geographical variation in provision.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

Burosumab is currently only being used in children in the context of two clinical trials

The standard therapy is currently given to children from diagnosis (eg from age 6 months) until the cessation of growth at 14 to 16 years of age. Only a small minority of children continue on treatment beyond final height.

Although the current standard therapy has been used in children with XLH for the past 35 years it is not officially licensed for this indication.

The proposed technology is an attractive alternative to current standard treatment and targets the pathophysiology that occurs in XLH. It is known from current experience of it's use in children in the clinical trials that it is effective and appears to be safe and allows treated children to discontinue the oral medication which is the current standard of treatment.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

It is likely that the patients would require more frequent outpatient visits in the first three months with need for blood tests at these visits. This will be required to ensure that the dose of the drug is titrated to the desired response.

An additional requirement will be the need to train the parents in the performance of the subcutaneous injections which will be required every 2 weeks.

There will be a reduced requirement for the patients to take multiple drug doses each day. Currently this is required 4 to 5 times daily. The current regime may be associated with side effects such as diarrhoea and abdominal pain.

Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment) to enable this technology to be used?

There will be a need for additional specialist nursing support in the initial titration phase for more frequent patient visits and the need for blood tests. It is likely that the initial injections during the titration phase will be delivered by nurses either in hospital or in the patients home.
There will be a need for nursing staff support to train the parents in subcutaneous injections.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

It is not currently known what is the likely cost of Burosumab – however it is likely to be more expensive than current standard therapy for the condition.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

It is unlikely that implementation of this technology would have resource implications for other services

Would there be any need for education and training of NHS staff?

There would be a need to educate and train specialist nurses who would be involved in the initial education and training of parents in drug administration.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

The proposed technology is unlikely to have an impact on equality

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this highly specialised technology?

To review the current available data from the clinical trials of Burosumab in children and adolescents

Appendix D – NHS organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a commissioners perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation **Royal Manchester Children's Hospital, Manchester University Hospital's NHS Trust**

Please indicate your position in the organisation:

- commissioning services in general? **No**
- commissioning services specific to the condition for which NICE is considering this technology? **No**
- responsible for quality of service delivery (e.g. medical director, public health director, director of nursing)? **No**
- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)? **No, but I occasionally cover duties of my colleague , who is the PI for the Burosumab (KRN23) trail in Children**
- other (please specify) **I am the UK lead for the XLH directory**

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: **No**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

To what extent and in which population(s) is the technology being used in your local health economy?
Burosumab is only used to treat patients participating in clinical trail at our centre

- is there variation in how it is being used in your local health economy?
See my answer above
- is it always used within its licensed indications? If not, under what circumstances does this occur?
As mentioned above, Burosumab is only used to treat trial patients

- what is the impact of the current use of the technology on resources?
Burosumab is provided free of charge to patients on clinical trial
- what is the outcome of any evaluations or audits of the use of the technology?
Too early for evaluation/audit
- what is your opinion on the appropriate use of the technology?
Results of Phase II trial in children suggest that treatment with fortnightly subcutaneous injects of Burosumab in children helps to near -normal serum levels of phosphate & 1,25(OH)2D, heals rickets, promotes linear growth and improves muscle function.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

Burosumab treatment involves giving fortnightly subcutaneous injects. Parent(s)/guardian can be trained to administer this treatment.
Patient would not have to take inorganic phosphate, which cause nausea, abdominal pains & diarrhoea, 5 X a day. Better healing of rickets, improved linear growth, less fatigue and fewer surgical operations to correct lower limb deformities.

Appendix D – NHS organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Burosumab for treating X-linked hypophosphataemia [ID1151]

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- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which treatment will be licensed; **No**
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; **No**

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities. **No**

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts. **No sure.**

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this highly specialised technology?

Not base on limited Phase II trial data that are in public domain.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Burosumab for treating X-linked hypophosphataemia [ID1151]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- 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 13 pages.

About you	
1. Your name	**Professor Nick Shaw**
2. Name of organisation	**Birmingham Women's & Children's NHS Foundation Trust**

3. Job title or position	**Consultant Paediatric Endocrinologist**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
The aim of treatment for this condition	
5. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment for this condition is to ensure that adequate healing of rickets takes place to allow normal growth in height and to ensure that the legs do not develop any significant deformity. Without treatment children would not achieve a satisfactory height and are likely to require orthopaedic surgery to correct deformity of the legs that will impact on mobility.
6. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Evidence of healing of rickets on X-ray and blood tests Normal rate of growth with satisfactory adult height and no significant leg deformity

x cm, or a reduction in disease activity by a certain amount.)	
7. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Current treatment although effective can result in suboptimal outcomes eg with growth and limb deformity and may be associated with side effects. In my opinion there is a need for a more effective treatment for the condition with a reduced risk of adverse effects
What is the expected place of the technology in current practice?	
8. How is the condition currently treated in the NHS?	It is currently treated with oral phosphate supplements given 4 to 5 times per day and a Vitamin D analogue such as Alfa Calcidol once daily
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no specific clinical guidelines but many clinicians managing affected patients would use the following article: A Clinician's Guide to X-linked Hypophosphatemia by T.O.Carpenter et al published in J Bone Miner Res 26:1381-1388.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The current standard of treatment is fairly well defined with little variation or differences of opinion amongst clinicians

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The technology would significantly change the pathway as there would no longer be the need for taking medication 4 to 5 times daily
9. How will burosumab be used in NHS clinical practice?	To treat growing children (age 6 months to 16 years) with X-linked Hypophosphataemic rickets who are the patients who would benefit the most from such treatment
• How does healthcare resource use differ between the technology and current care?	The new technology would involve a subcutaneous injection given every 2 weeks without the need for any daily oral medication
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics within tertiary paediatric hospitals
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be a need to train parents in the administration of the subcutaneous injections
10. Do you expect the technology to provide clinically	Yes I expect the technology to provide advantages in comparison to current clinical care

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	There should be no impact on length of life in this condition
• Do you expect the technology to increase health-related quality of life more than current care?	It is hoped that the technology will improve quality of life in comparison to current care – however currently there is a lack of good evidence to demonstrate this.
11. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As previously commented the technology will have the most benefit in growing children.
The use of the technology	
12. Will the technology be easier or more difficult to use for patients or healthcare	I think the technology will be easier to use than current care.

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.)	It is likely that patients will need more frequent blood tests in the first three months to ensure that the drug dose is titrated against the plasma phosphate
13. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are currently no clear guidelines re commencing treatment. Treatment is likely to stop when a child stops growing between the ages of 13 to 16 years.
14. 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	I suspect that the technology may reduce the need for orthopaedic surgery for the correction of leg deformity – this may not be included in the QALY calculation.

quality-adjusted life year (QALY) calculation?	
15. 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?	The technology appropriately targets the underlying pathophysiology of the condition and is therefore innovative. It will be an improvement on current care by reducing the need for frequent daily medication.
• Is the technology a 'step-change' in the management of the condition?	Yes this does represent a step change for a condition in which there have been no advances in management for 35 years
• Does the use of the technology address any particular unmet need of the patient population?	Not that I am aware of
16. How do any side effects or adverse effects of the technology affect the	The technology appears to have minimal side effects identified to date

management of the condition and the patient's quality of life?	
Sources of evidence	
17. Do the clinical trials on the technology reflect current UK clinical practice?	The current Phase 3 clinical trial is comparing current standard practice with the new technology
• 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?	Important outcomes are growth in height and leg deformity which are being monitored in the trials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No surrogate outcomes are being used
• Are there any adverse effects that were not apparent in clinical trials	Not that I am aware of

but have come to light subsequently?	
18. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The drug company may have some additional clinical data that may not be identified by a systematic review
19. How do data on real-world experience compare with the trial data?	The drug is currently not being used outside the clinical trials
Equality	
20a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues
20b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
21. Please provide an estimate of the prevalence of XLH in England.	
21a. Could burosumab maintenance doses be given through a homecare service (if appropriate arrangements were made)?	Yes this could be managed through a home care service
21b. If yes, would there be any barriers to implementing this service?	No significant barriers as various other current medications eg growth hormone are provided in this manner
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your statement.

- The technology appropriately addresses the underlying pathophysiology of the condition
- The evidence from the current clinical trials is that the technology is effective and safe
- The technology would reduce the need for frequent daily medication
- The technology is likely to have less side effects than the current standard of care
- Longer term data from the Phase 3 clinical trial will demonstrate how the technology compares with current care

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Burosumab for treating X-linked hypophosphataemia [ID1151]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Zulf Mughal**
2. Name of organisation	**Royal Manchester Children's Hospital (Manchester University Hospital's NHS Trust)**

3. Job title or position	**Consultant in Paediatric Bone Disorders & Honorary Clinical Professor of Child Health**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
The aim of treatment for this condition	
5. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• Promote healing of rickets • Prevent limb deformities • Improve growth rate • Improve dental health • Improve myopathy • Reduce bone pain • Avoid complication of treatment e.g secondary hyperparathyroidism & nephrocalcinosis • Reduce of disease related complications arising in adulthood – arthritis, enthisopathies • Avoid cranio-facial abnormalities
6. What do you consider a clinically significant treatment response? (For example, a	• Healing of rickets – judged biochemically & radiologically • Prevention of limb deformities • Improvement of growth velocity & final adult height

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	• Fewer dental complications , e.g dental abscesses, tooth loss, maxilo-facial infections • Improvement in muscle function & independent mobility , e.g judged by 6-minute walk test & jumping machography • Less use of medications to control bone pain
7. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes - Current medical treatment consists of oral phosphate supplements administered up to 5 times a day, together with active form of vitamin D (alfacalcidol or calcitriol) administered once or twice a day orally. Unfortunately, oral phosphate supplements have an unpleasant taste. It also causes nausea, abdominal pains and diarrhoea. Therefore adherence to treatment is often poor. Meticulous monitoring is necessary, e.g. every 3 to 4 monthly, to avoid side effects of treatment: hypercalciuria, hypercalcaemia, nephrocalcinosis., secondary and tertiary hyperparathyroidism and impaired renal function. Surgical correction of lower limb deformities is often necessary.
What is the expected place of the technology in current practice?	
8. How is the condition currently treated in the NHS?	• See above
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• Not for Rx of XLH in Children & Adolescents
• Is the pathway of care well defined? Does it vary or are there	• Having worked in 3 Paediatric bone centres in the UK, I have noticed subtle variations in treatment & monitoring regimens.

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?	• It will improve adherence • Phase II trial data has shown: (1) improved healing of rickets, (2) improvement in growth rate & (3) improved muscle function.
9. How will burosumab be used in NHS clinical practice?	• Burosumab is administered by subcutaneous injections every fortnightly – no other oral medication required.
• How does healthcare resource use differ between the technology and current care?	• Yes –see my answers in section 7 & 9.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	• Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities,	• Minimal – training parents & older children to administer subcutaneous injections

equipment, or training.)	
10. Do you expect the technology to provide clinically meaningful benefits compared with current care?	• Yes, but outcomes (endpoints) evaluated in the Paediatric trial to date have been limited. For example, no assessment of limb deformities & dental problems associated with XLH. No XLH-specific QOL assessment undertaken in the trials to date.
• Do you expect the technology to increase length of life more than current care?	• Not sure
• Do you expect the technology to increase health-related quality of life more than current care?	• Unfortunately, XLH-specific QOL assessment has not undertaken to best of my knowledge
11. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• Besides XLH, burosumab may benefit patients with Fibrous Dysplasia and Tumour Induced hypophosphataemic rickets.
The use of the technology	

12. 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.)	Much easier – please see my answers in section 7 & 9
13. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Severe local or generalised reactions to burosumab. Lack of response to treatment Not in Paediatric patients
14. 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?	I am not in position to answer this question
15. 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?	Yes – improved adherence compared with conventional therapy for XLH. Phase II trial data suggests better healing of rickets, linear growth and muscle function.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes

16. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I am only aware of local (injection site) reactions.
Sources of evidence	
17. Do the clinical trials on the technology reflect current UK clinical practice?	NO - as mentioned previously, current treatment of XLH in children involves administration of oral phosphate supplements up to 5 times a day, together with active form of vitamin D (alfacalcidol or calcitriol) once or twice a day **orally**. Burosumab is administered by subcutaneous injections every fortnightly.
• If not, how could the results be extrapolated to the UK setting?	Children from 3 centres (London, Birmingham & Manchester) participated in Phase II trial of Burosumab.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Healing of rickets & improvement of linear growth
• If surrogate outcome measures were used, do	

they adequately predict long-term clinical outcomes?	Not to my knowledge
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	High doses of Burosumab have the potential for causing soft tissue calcification.
18. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Only data from Phase II trial available so too early to undertake systematic review at this stage.
19. How do data on real-world experience compare with the trial data?	In my opinion trial endpoints are somewhat limited: biochemical improvement, rickets healing, growth rate & muscle function Important 'real life end points', such as correction of deformity, dental issues, QOL, etc have not been evaluated in the phase II trial.

Equality	
20a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of any equality issues
20b. Consider whether these issues are different from issues with current care and why.	See above -
Topic-specific questions	
21. Please provide an estimate of the prevalence of XLH in England.	Incidence ranges between 1/20,000 to 1/60,000
21a. Could burosumab maintenance doses be given through a homecare service (if appropriate arrangements were made)?	Yes, but I think it could be administered by parents after appropriate training

21b. If yes, would there be any barriers to implementing this service?	No

Key messages

- 22. In up to 5 bullet points, please summarise the key messages of your statement.
- Current treatment has to be administered 4 to 5 times a day, is unpleasant and therefore adherence is often poor, especially among adolescent patients
- Meticulous monitoring is necessary to avoid side effects of treatment
- Treatment of XLH with burosumab results in biochemical improvement, healing of rickets healing, improvement in the growth rate & muscle function
- Important end points, such as correction of deformity, dental issues, QOL, etc have not been evaluated in the phase II trial

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Burosumab for treating X-linked hypophosphataemia [ID1151]

Thank you for agreeing to give us your 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.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Miss Margarita Vidal**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☒ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	I believe CLIMB have put my name forward.
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☒ I have other relevant personal experience. Please specify what other experience: I visited the XLH patient day in Manchester where I learned about the new treatment Burosumab. I am also a carer of 2 young children, age 2.5 and 10 years old so as well as being a sufferer of XLH, I care for 2 children with XLH, and I have 2 sisters and a nephew and father who have XLH. ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this	I was misdiagnosed at 18 months of age as having Rickets so given Alphacalcidol drops only. At around 10 years of age, I was diagnosed with XLH. I already had severe bowing by this age; I continued with the current treatment, Phosphate and Alpha in my teens but my legs still continued to bow and I had to have 2 major surgical procedures to straighten both legs. I now have live with some bowing of both legs and arms and suffer with varying pain of arms and legs as well as my back due to this condition. I may require surgery on my arms which are deteriorating year on year but at this time have chosen to live with it for now as it is difficult to have such a long time off work and would cause financial problems for us as I would not be able to work full time for 3-6 months for each operation.

you and your family?	My two children who I care for were tested at birth so have been receiving the current treatment of Phosphate and Alphacalcidol from around 2-3 months of age. Despite this, both have leg bowing, my boy who is 2.5 years old already has 4-5cm bowing, my daughter has K bowing (6cm inward bowing causing knock knees and feet to move further apart) and both are well below average height. My boy complains regularly of knee pain. My daughter who is 10 is also restricted in school with PE and suffers pain if she walks too much or does too much PE. Both suffer with Diarrhoea and stomach pains regularly after taking Phosphate solution.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally,	I have been emotionally and physically impacted by this condition. People stare at me due to my legs being bowed and being very small with very short legs despite having had corrective surgery to reduce bowing of both legs. This is still upsetting and I this is something I've experienced all my life. I live with pain as do many other members of my family. 7 out of 10 of my immediate family live with XLH and this has therefore had a huge impact on our family as my father who is now elderly is totally immobile (bedbound) due to this condition causing spinal stenosis and his leg bowing being so severe that he can no longer walk at all. This means we have to help care for him as well as deal with our own symptoms. My 2 sisters, one who suffers with chronic pain on a daily basis due to this condition also relies on her family to help her with daily activities such as shopping, cleaning etc. Her son also has XLH so suffers physical pain as well as emotional strain from having this condition which includes bullying at school, feeling different, people staring etc. All these factors have led to depression for me and other members of my family. I suffer daily pain in my legs, arm and back which sometimes mean that I am unable to do my job. My children suffer with pain and emotional upset at having this condition. My daughter is regularly upset at not being able to take part in sports for example and comments from other children about her height and her knock knees. Many other members of my immediate family suffer with it. My nephew has been bullied at school due to his legs being bowed and his short stature. He has missed a lot of school due to pain meaning he's unable to attend, also long periods of time off school due to operations (he's had 4 major surgeries and now requires 2 more major surgeries this year). My 2.5 year old boy is not yet aware of his condition of course, but he regularly complains of pains in his legs which is very upsetting for him and also for me, as I feel responsible for passing this condition to my

form friends and participate in school and social life. What is the effect on any siblings?	children, which also leads to more upset/depression for me as I live with the guilt of passing this on to my children. My life and the life of 6 other members of my immediate family have been dominated by this condition and continue to be.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	The current medication, Phosphate and Alphacalcidol has caused all members of my family including myself varying degrees of Diarrhoea including stomach pain which is very unpleasant to deal with. As well as the pain it often causes, the Phosphate is extremely bitter/sour so very unpleasant and difficult to administer to young children in particular. I try to administer this 6 times per day but this is very difficult to do when you're trying to go about everyday life so often means I actually give this 4 times a day at best, which is still hard work especially as the Joulies Solution (Phosphate) my children take has to be kept cold so refrigerated. This makes it really difficult on days out and holidays. Despite my commitment to ensuring my children take their medication regularly and never miss their medication, it is very upsetting as despite having the treatment almost since birth, my two children both have bowing legs, both are not growing normally (both have very short legs and my son has waddling gait) and both still suffer pain so based on all 7 experiences I have including my own, the treatment has not worked to prevent the symptoms. In summary, I would say it is better than nothing as giving some phosphate and alpha does help but based on my own personal experience and that of 6 members of my family, I do not believe this treatment is effective at stopping the symptoms and the way it needs to be stored and administered is not practical either.
11. Is there an unmet need for patients with this condition?	Yes there is a need to give XLH patients the best possible treatment to improve their lives by reducing deformities, improving growth, reducing pain and also providing a treatment that is more practical to be administered so patients can live a normal life every day.

Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include any improvement in their ability to attend school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	The new treatment treats the underlying cause so would prevent many of the symptoms including deformity, growth etc. If we can avoid bowing and improve growth, this will mean less pain (as pain comes from bone deformities) and also improve patient's mental state as we would not be in so much pain and are less likely to be victims of bullying/feeling different/being stared at as we don't have such severe disability for others to see and our mood/mental state would be much better from this and not suffering with the pain of course. The current treatment does not work well enough based on my experience and that of 6 of my immediate family and the new treatment would be far better to reduce bowing (deformities), this in turn would improve pain. It would also improve growth which is a major impact for patients; very short with very short legs and a waddling gait, as well as walking with feet going inwards. Improving all of these symptoms as well as simplifying the administering of the treatment (fortnightly rather than 6 times per day) would have a hugely beneficial impact to XLH sufferers mental state of mind too as living with the symptoms and medication is a daily struggle.
13. How easy or difficult is it to take the treatment? What is the impact you and the family	Having to take the treatment up to 6 times a day is so impractical for everyday life, particularly for children. One injection every two weeks would be so much easier to administer than the current treatment. Also, when children become a little older (teenagers etc.) My experience is that due to Diarrhoea and stomach pain it often causes, it's foul taste (extremely bitter/sour) and the impracticality of having to take it so many times a day, many children will do all they can to avoid having to take it, especially as it can be as much

in terms or travel and receiving the treatment?	as 6 times per day. They don't think about the impact, they just don't want to be in pain or have to leave their friends at break/lunch to go for their medication, so there will be many times they don't take it. This is harder to control by parents as children get older and are in secondary school. I strongly believe that many children miss doses as they get older and an injection every 2 weeks would mean parents could be confident that their child had the correct levels of phosphate all of the time as this is out of their control as the new treatment fixes the root cause not tries to replenish the levels afterwards which does not work as it needs to. Also, as mentioned above, the Joulies Phosphate needs to be kept cold which adds further difficulties especially when travelling. My daughter has to take 2 doses at school as does my nephew. This is noticeable to the other students so this also makes them feel different and exposes them to 'feeling different' and 'bullying'. This is also a real challenge on school trips, school days out and school sporting events. It would be great if they didn't have to take a treatment so regular for these reasons also.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment	The main advantage of this treatment is that it improves the symptoms of suffers by reducing deformities and improving growth. Fixing the root cause of the problem avoids all the other symptoms that come with it so it is a huge improvement on current treatment. This is by far the most important reason that we need this new treatment but also… An injection every 2 weeks is far better to administer than an unpleasant tasting oral liquid 6 times per day which has side effects including Diarrhoea and pain. My children have to have injections every 3-6 months to monitor phosphate and other vitamin levels and are used to injections. My 2.5 year old is too young to give his opinion but I asked my daughter who is 10 and my nephew who is 14 years old and they both expressed that they would be okay to have an injection every 2 weeks and they would prefer that to taking the current treatment of Phosphate up to 6 times per day. I understand the only probable side effect of the new treatment could be getting a sore/infected injection site. This side effect which I don't believe is common, is far less damaging and affects patients far less than what we currently suffer with the current treatment which tastes very unpleasant so is challenging to get children to take, has to be kept cold which isn't very practical and also causes stomach upset

does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	including Diarrhoea and pain. I am more than happy to have injections as they are more practical but most importantly, they lead to improvement in symptoms which is the most important factor. I just want my children to have access to the best treatment which will result in the best outcome for them, physically and mentally.
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Children would benefit most as they are still in growth so can avoid bowing (less deformities) and can give them better growth as well as improving their day to day lives by reducing deformities meaning less pain, less visible deformity and therefore improving their mental state/mood. As well as of course, the benefits mentioned above of having injection every 2 weeks versus current up to 6 times a day and its side effects of course. This treatment would also benefit adults with XLH as improving phosphate levels in adults would result in less deformities in later life. My arms have bowed further in my 40s. I did not realise my bones were soft enough to bow. I am not taking any phosphate treatment as despite my phosphate levels being lower than a 'normal' person, the Endocrinologist I visit (every 6 months) advises that there is a risk of Kidney Stones in adults taking Phosphate so they only prescribe it when absolutely necessary i.e. when phosphate is very low. Had I been on the new treatment, my phosphate levels would likely have been improved so my arm bowing, which now causes significant daily pain and restricts me, may have been avoided.
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and	No

the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	Because this is X linked genetic condition, this condition impacts families so in many cases, many members of one family are affected. In mine, 7 out of 10 of us have XLH and have varying degrees of disability caused by this condition. This adds further to the strain of this condition as you cannot rely on other family members and you often have to help other family members who can be in worse state than you are. For example, in my family, my father who is now 83 years old has been on a Zimmer frame with very limited mobility since he was 70 years old. He has been bed bound for 18 months now. My sister with XLH suffers with chronic daily pain. She has a 14 year old son with the condition who has severe leg bowing and is going for his 5th and 6th major leg straightening surgeries this year. He will then need support which my sister cannot give as she is unable to due to her disabilities and pain. I have significant arm bowing now which causes me pain so when my son needs carrying as his legs are painful, it's really difficult for me as I am in pain too. Therefore considering how this clusters in close families is another really tragic outcome which means it's difficult to physically help each other as so many of us are suffering with pain and deformities due to the XLH.
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement: • XLH is a cruel and debilitating condition that affects sufferers like me and my children physically and mentally causing bone deformities, pain, poor growth etc. impacting everyday life, which often lead to mental health issues such as depression. • Current treatment does not stop the symptoms and still results in deformities even if taken from 3 months of age as is the case with my 2 children (2.5 and 10 years old) and my nephew(14 years old). • The current treatment of Phosphate is very unpleasant to take, has very unpleasant side effects and the way it needs to be administered and stored, makes it very impractical to fit in with every day normal life. • As XLH runs in families, it affects many members of close families so this makes life even harder because you are suffering but so	

are all the people who you love and are close to around you so it can be really hard to support each other.

- The new treatment is needed to help XLH patients have a better quality of life by reducing deformities (bowing), which will in turn lead to less pain. Improving growth and in turn all these improvements, giving patients a better quality of life improving physical and mental health.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Burosumab for treating X-linked hypophosphataemia [ID1151]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	David Sneaton
2. Are you (please tick all that apply):	☐ a patient with the condition? ☑ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☑ I don't know
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 didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	☑ I have personal experience of the condition ☑ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☑ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	We found our son had this condition when he was 3 years old. Due to the condition his skull had fused to early meaning he need surgery on his skull. It wasn't until after his operations that he started on posphate treatment. He would need to take this 5 times a day, this also meant we had to wake him at around midnight to take it and also eventually meant he needed to take

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	a bose to school with him. He also had to have all his teeth removed. This had a huge effect on him- he was more emotionally effected with this happening. He struggled with walking distances so we had to use a pushchair until he was arand 6years old if we was going anywhere that involved lots of walking. He has always struggled with his height and this is also emotionally draining on him as his brother has hit milestones before he has been able to. It did not effect him making friends although school were amazing at making him not feel any different by encouraging to take a friend when needed to go and take his medicine. He struggled to keep up in sports at the same level as his peers It has effected us as a family as he had needed to attend many appointments. We have had to rely on family member more as we both work full time. us as parents have had to take lots of time off work and focus more on one child over the other.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	I believe this treatment to be behind the times. if he needs to stay on this for his lifetime. there are risks that his kidneys will be effected and he will most defnatly need more surgerys. It would be very dissapointing.
11. Is there an unmet need for patients with this condition?	
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also	The new treatment has been amazing. He is now stronger, fitter and more able to do sports / walk to a better ability. The results have been incredible and he is now longer effected day to day. having 1 injection a fernight is a huge diffance to having to take a supplement daily. He is not having as much pain. and he seems to dealing better emotionally. It fits in better with family life and will limit the amount of surgery he will need in the future.

include any improvement in their ability to attend school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	He is not missing as much school and the treatment fits around his new high school timetable. He participates in more sports which he loves especially now he can keep up a bit more.
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	He has no issues in taking the treatment. We are happy to travel for him to have this treatment. The hospital have been amazing at supporting us and making sure we feel like a family unit going through this together.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they	None.

long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	children. as the sooner the treatment start the better the quality of life for the future.
Equality	
16. Are there any potential equality issues that should be taken into account when	NO

considering this condition and the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement: • new treatment is life changing. • more emotionally stable for him as he feels he can do more now. • less pain / less restrictre in terms of what he can do. • He tells us he feels normal now. •	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Burosumab for treating X-linked hypophosphataemia [ID1151]

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Information on completing this expert statement

- 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
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About you	
1. Your name	**Edmund Jessop**
2. Name of organisation	**NHS England**

3. Job title or position	**Public health adviser**
4. Are you (please tick all that apply):	**x**☐ commissioning services for a CCG or NHS England in general
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	
6. 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.)	There is no service specification for XLH, nor for rare bone disease. The pathway will depend on the knowledge and preferences of the referring condition.
7. What impact would the technology have on the current pathway of care?	The pathway would be clearer if prescribing of burosumab were to be restricted to centres with defined expertise.

The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	
9. How will burosumab be used 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 clinics.)	Prescribing should be initiated and monitored at expert centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	

• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
10. What is the outcome of any evaluations or audits of the use of the technology?	
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	
11b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	

12. Please provide an estimate of the UK prevalence of XLH.	
13a. Would it be possible to provide a homecare service for the administration of maintenance doses of burosumab?	Homecare should be possible.
13b. If yes, would there be any barriers to implementing this service?	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Burosumab for treating X-linked hypophosphataemia

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

Authors
Rob Riemsma, Review Manager, KSR Ltd, UK
Isaac Corro Ramos, Health Economics Researcher, Erasmus School of Health Policy & Management, EUR, the Netherlands
Nasuh Büyükkaramikli, Health Economics Researcher, EUR
Stephanie Swift, Systematic Reviewer, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Remziye Zaim, Health Economics Researcher, EUR
Gimon de Graaf, Health Economics Researcher, EUR
Gill Worthy, Statistician, KSR Ltd
Lisa Stirk, Information Specialist, KSR Ltd
Maiwenn Al, Health Economics Researcher, EUR
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Rob Riemsma, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

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Declared competing interests of the authors
None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Nasuh Büyükkaramikli, Remziye Zaim, Gimon de Graaf and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Stephanie Swift acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance on the health economics part of the project. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

ABBREVIATIONS

1,25(OH)2D	1,25-dihydroxyvitamin D
6MWT	Six minute walk test
ADHR	Autosomal dominant hypophosphataemic rickets
AE	Adverse events
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ARHR1	Autosomal recessive hypophosphataemic rickets type 1
ARHR2)	Autosomal recessive hypophosphataemic rickets type 2
BALP	Bone-specific alkaline phosphatase
BBS	Brittle Bone Society
BI	Budget impact
BIC	Bayesian information criterion
BNF	British National Formulary
BPABG	British Paediatric and Adolescent Bone Group
BPI	Brief Pain Inventory
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CS	Company submission
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
EQ-5D-5L	Euroqol 5-dimension 5-level questionnaire
ERG	Evidence Review Group
ERN-BOND	European Reference Network on Rare Bone Disorders
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
FGF23	Fibroblast growth factor 23
GEE	Generalised estimating equations
HPO	Human Phenotype Ontology
HR	Hypophosphataemic rickets
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HS	Health state
HST	Highly Specialised Technologies
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
IgG1	Human immunoglobulin G1
iPTH	Intact parathyroid hormone
ITT	Intent to-treat
IWRS	Interactive web response system
KSR	Kleijnen Systematic Reviews
LLN	Lower limit of normal
LS	Least squares
LVH	Left ventricular hypertrophy

MHRA	Medicines and Healthcare Products Regulatory Agency
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme
PbR	Payments by results
PCS	Physical component summary
PD	Pharmacodynamic(s)
PDMA	Pharmaceuticals and Medical Devices Agency
PHEX	Phosphate-regulating endopeptidase homolog, X-linked (phosphate-regulating gene with homology to endopeptidases located on the X chromosome)
PIM	Promising Innovative Medicine
PK	Pharmacokinetic(s)
PODCI	Pediatric Outcomes Data Collection Instrument
POSNA	Pediatric Orthopedic Society of North America
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSS	Personal social services
PTH	Parathyroid hormone
Q2W	Biweekly, once every 2 weeks
Q4W	Monthly, once every 4 weeks
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised control trials
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
RUDY	Rare and Undiagnosed Diseases Study
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDS	Standard deviation scores
SE	Standard error
SF-10	SF-10 Health Survey for Children
SF-36	36-Item Short Form Survey
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class (for adverse events coding by MedDRA)
SPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TmP/GFR	Ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR)
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VUS	Variant of unknown significance
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphataemia

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1. SUMMARY

1.1 Background

X-linked hypophosphataemia (XLH) is a rare, genetic, chronically debilitating and deforming disease that profoundly impacts the affected individual's day to day functioning and health-related quality of life (HRQoL). As a genetic disease it can affect whole families and consequently have a wide impact on the quality of life of generations of families.

In XLH, genetic mutations result in an inactive phosphate-regulating enzyme and lead to high levels of circulating fibroblast growth factor 23 (FGF23). Excess FGF23 leads to increased urinary phosphate excretion, reduced 1,25-dihydroxyvitamin D (1,25(OH)2D) synthesis, and hypophosphataemia.

1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology

XLH is characterised by dysfunction of mineral metabolism (serum phosphate, serum calcium), endocrine function and renal function. The corresponding clinical manifestations of XLH include delayed walking, waddling gait, leg bowing, enlarged cartilages, bone and/or joint pain, craniosynostosis, spontaneous dental abscesses, growth failure, fractures, mineralisation defects (rickets and osteomalacia), severe dental anomalies, hearing loss and fatigue. Rickets, the hallmark of XLH in children, is associated with substantial skeletal deformities that cause daily pain and impair physical functioning. Children may be severely limited in their daily activities, such as walking, due to deformity and antalgic gait. When these deformities become permanent, people with XLH suffer lifelong disability and pain.

Children with XLH often have trouble performing age-appropriate gross motor activities, such as walking, running, and jumping, due to bowing of the femur, tibia, and/or fibula and the rotation of the tibia that causes the feet to turn in toward each other. This impaired functionality from an early age can inhibit a child's participation in physical, educational and social activities. In adults, osteomalacia and skeletal deformities lead to development of early osteoarthritis and enthesopathy that cause pain and continue to limit physical function.

The long-term goal of therapy in children with XLH is to improve or heal rickets and prevent or correct the skeletal abnormalities associated with it, to prevent the ongoing mechanical dysfunction associated with chronic weight bearing on poorly aligned bones and joints, and to reduce the child's pain and disability.

Burosumab is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the activity of FGF23. By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney and through the production of 1,25(OH)2D enhances intestinal absorption of calcium and phosphate. Burosumab improves phosphate homeostasis and its major pathologic consequences (rickets and osteomalacia), and consequently aims to resolve the skeletal and non-skeletal manifestations of XLH.

The European Medicines Agency (EMA) awarded burosumab conditional marketing authorisation on 23 February 2018. The full indication is: "Crysvita is indicated for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons." It is proposed that Crysvita be prescribed by physicians experienced in the management of patients with metabolic bone diseases.

1.3 Critique of the decision problem in the company's submission

Most of the evidence is presented as single arm studies including either treated patients (two studies, both with extensions that are still ongoing) or historical control patients (one study, with patients from one single centre, radiographic analysis set ([redacted])). The historical control study (CL002) included patients aged from five to 14 years and can therefore only serve as a control group for study CL201 (children aged five to 12 years). For patients with XLH aged one to four years old, the CS only presents a single arm burosumab study (CL205), no control data for this age group were provided.

A randomised controlled study comparing burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) is currently ongoing. [redacted]. These results will considerably reduce the uncertainty surrounding the clinical effectiveness of burosumab relative to conventional therapy in children with XLH aged between one and 12 years. They will provide a direct estimate of clinical effectiveness and will be more reliable and up-to-date than the current results based on propensity score matching between a single-arm and historical cohort study.

1.4 Summary of clinical effectiveness evidence submitted by the company

The studies included in the submission focus on the following populations and studies:

- Paediatric patients with XLH, five to 12 years old: Study CL201 (open-label RCT comparing different doses of burosumab (biweekly or monthly administration of burosumab doses 0.1 to 2.0 mg/kg))
- Paediatric patients with XLH, one to four years old: Study CL205 (open-label study to assess the safety, pharmacodynamics and efficacy of burosumab (biweekly administration of burosumab at a target dose of 0.8 mg/kg))
- Paediatric Patients with XLH, five to 14 years old: Study CL002 (A retrospective longitudinal study of skeletal outcomes in children with XLH. No burosumab administered; however, study inclusion required the use of conventional therapy (oral phosphate/active vitamin D))

Results from CL201 show that burosumab significantly improves rickets at week 40 and week 64, compared to baseline. The primary endpoint, the rickets severity score (RSS) was reduced from baseline by 61% at week 40 ($p<0.0001$) by 58% at week 64 ($p < 0.0001$) with biweekly burosumab. Burosumab treatment also resulted in healing of rickets as assessed by Radiographic Global Impression of Change (RGI-C) scores. The RGI-C score at Week 64 was +1.62. At Week 64, [redacted] of children treated with biweekly burosumab had healing of rickets (RGI-C global scores ≥ 1.0). Furthermore, [redacted] of children treated with burosumab had substantial healing of rickets (RGI-C global scores ≥ 2.0). Growth velocity increased by [redacted]) in children treated with burosumab every two weeks, with a corresponding least-squared (LS) mean change in standing height z-score of [redacted]). Biweekly burosumab also resulted in improved functional assessments and patient-reported outcomes in CL201. Walking ability, as assessed by LS mean distance walked in the six-minute walk test (6MWT), increased from baseline by [redacted] at week 64 [redacted]. Functional disability was assessed using the Pediatric Orthopedic Society of North America - Pediatric Outcomes Data Collection Instrument (POSNA-PODCI). Biweekly burosumab treatment increased scores for sports/physical functioning and pain/comfort into the normal range seen in healthy children; LS mean scores showed improvements of [redacted] and [redacted] at week 64, respectively.

Results from CL002 show that RSS was reduced by [redacted] (over a median period of 102 weeks) after long-term conventional therapy. The RGI-C score was [redacted] with conventional therapy in Study

CL002 (median 102 weeks). Furthermore, [redacted] of children treated with conventional therapy in Study CL002 had substantial healing of rickets (RGI-C global scores ≥ 2.0). After long-term treatment with conventional therapy in Study CL002, [redacted].

In study CL205 (13 children with XLH aged one to four years), burosumab treatment for 40 weeks significantly reduced RSS total score at week 40 by 59% (LS mean change of -1.73, $p < 0.0001$, ANCOVA model).

No patient died or discontinued from CL201 or CL205 for any reason; all patients continued treatment on study as of the data cut-off dates.

The most common adverse drug reaction reported in paediatric patients up to 64 weeks treatment with burosumab was injection site reactions (57%), headache (54%), pain in extremity (42%), vitamin D decreased (28%), rash (23%), toothache (19%), tooth abscess (14%), myalgia (14%), and dizziness (11%). Approximately 57% of the patients had an injection site reaction. The injection site reactions were generally mild in severity, occurred within one day of medicinal product administration, lasted approximately one to three days, required no treatment, and resolved in almost all instances.

In study CL201, one patient experienced serious TEAEs, and [redacted] All 52 patients (100%) experienced at least one TEAE during the study. The most frequent TEAEs (>30% incidence) in study CL201 were [redacted].

The most frequent TEAEs (> 30% incidence [four or more of 13 patients]) in study CL205 were [redacted]

Adverse events of treatment with conventional therapy have not been reported. Therefore, it is not possible to assess the relative safety and toxicity in relation to the comparator.

1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS states that a systematic review search was undertaken for clinical effectiveness and adverse events evidence using a combined search for all of these areas. The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. Of main concern to the ERG was the limited search conducted, which included few XLH synonyms and an unnecessarily restrictive use of a study design filter.

The main limitation of the efficacy data reported in the CS is the study design of the included studies. Due to the absence of a control group in most studies it is not possible to make any direct comparisons between burosumab and conventional therapy. As stated by the company, the "burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).

For children between one to four years old, only one study is presented in which all children received burosumab (CL205, N=13). A comparison with "established clinical management without burosumab" is not possible in this group of patients.

For children between five to 12 years old, the CS presents a study in which all children received burosumab (CL201). In addition, the CS presents a control study (CL002) in which children aged between five to 14 years received conventional therapy (i.e. oral phosphate/active vitamin D). Results of these two studies are mainly presented as a naïve comparison, simply reporting individual results from each study side by side. In addition, the company presents comparisons of 'rickets healing' with conventional therapy (Study CL002) versus burosumab (Study CL201) using propensity analysis matching.

In the CS, the company uses the terms 'healing' and 'substantial healing of rickets'. These are defined using RGI-C global scores, where scores ≥+1.0 indicate 'healing of rickets' and scores ≥+2.0 'substantial healing of rickets'. The company does explain that "Healing in this context indicates improvement in the radiographic abnormalities and does not imply that complete healing was observed" (CS, page 100). However, throughout the report the term 'healing of rickets' is used without any explanation of the degree of healing (minimal, substantial or complete). Moreover, it should be noted that RGI-C global scores and RSS scores do not capture all clinical aspects of XLH.

The naïve comparison is unreliable because there are important differences between the inclusion criteria in both studies. Inclusion criteria for patients in studies CL201 and CL002 are similar in that patients in both studies were diagnosed with XLH and were of similar age. However, children in study CL201 also had: biochemical findings associated with XLH, standing height < 50th percentile for age and gender and radiographic evidence of active bone disease including rickets in the wrists and/or knees, and/or femoral/tibial bowing, or, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read. In other words, study CL002 included all children with XLH, while study CL201 included children with more severe symptoms of XLH. This is also reflected in the relatively [redacted] standing height and [redacted] rickets severity score for children in study CL201 when compared to children in study CL002.

The adjusted comparison, using propensity analysis matching, is unreliable because of the limitations associated with these methods, in that the matching can only include those variables measured in both studies. Randomisation in a clinical trial creates a balanced group for both measured and unmeasured variables. In observational studies, the most important factors which are predictive of the outcome may not have been measured and any treatment comparisons using observational study data may be biased. In the CS the company only included three variables in the propensity score matching (PSM): age, gender and RSS total score at baseline. The rationale for variable selection was not provided other than whether they seemed similar or not between the two study populations. No details were provided of how this similarity was judged. The ERG found no statistically significant differences in age and gender between the two groups and considered that only including three variables in the creation of the propensity scores may have been too few.

1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The company conducted a systematic review of cost effectiveness studies of burosumab and other studies including costs, resource use and any HRQoL measure associated with XLH. A total of eight full-text studies were assessed for eligibility but none of them were deemed relevant to the economic evaluation of burosumab.

The company submission included a model-based cost-utility analysis comparing the use of burosumab with standard of care (SoC) to treat XLH patients with radiographic evidence of bone disease aged one year or older with growing skeletons.

Multiple sources of evidence were used to inform the parameters of the economic model. The proportion of males/females at baseline, the initial distribution of patients per disease severity stratified by age and the transition probabilities for burosumab were derived from the clinical studies CL201 and CL205. Transition probabilities for the SoC arm were derived from a UK chart review in the base-case analysis and from the study CL002 in a scenario analysis. General population weight data (UK growth charts) were used for the weight distribution. Mortality rates were obtained from the national life tables for England, for the period 2014 to 2016, as published by the Office of National Statistics. Utility values for the health states of the model were derived from a vignette study conducted by the company. Additionally, age specific multipliers were used based on the general population.

The price of burosumab was provided by the company. Burosumab is available in 10 mg, 20 mg and 30 mg vials. In the CS, it was stated that the Summary of Product Characteristics (SmPC) recommends dose rounding to the nearest 10 mg. Based on this assumption, annual patient costs by age and weight were estimated in the base-case analysis. Resource use for burosumab monitoring was based on expert opinion, while unit costs were taken from NHS reference costs. Standard of care treatment costs were estimated based on the dose recommended in clinical guidelines and the summary of product characteristics. Unit costs were taken from the British National Formulary (BNF). Resource use for surveillance costs was based on expert opinion and unit costs were taken from NHS reference costs. Physiotherapy resource use was based on published literature and complemented by expert opinion. Unit costs taken from PSSRU. A number of different sources were used for the estimation of orthopaedic intervention costs. Resource use was based on the prevalence observed in CL201, published literature and expert opinion. Unit costs were mostly sourced from the NHS reference costs, except the unit costs for osteotomy, which were based on published literature.

A deterministic one-way sensitivity analysis was conducted for key clinical and economic parameters in the model. A probabilistic sensitivity analysis was also conducted. A number of scenario analyses were also performed to assess the robustness of the model results to changes in structural assumptions made by the company.

The company's analysis estimated that patients treated with burosumab gained 10.304 more discounted quality adjusted life years (QALYs) compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When discounting was not applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

1.7 Summary of the ERG's critique of the value for money evidence submitted

The CS states that a systematic review search was undertaken for economic, cost and resource use and HRQoL evidence using a combined search for all of these areas. The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. Of main concern to the ERG was the narrow search conducted, which included few XLH synonyms and an unnecessarily restrictive use of study design filters.

The ERG identified several issues in the company's analyses. The ERG main concerns were related to the method used by the company to estimate the transition probability matrices for burosumab, the source of utilities used by the company and the assumption of lifelong treatment effects of burosumab. The choice of the discount rate was also challenged by the ERG.

The results of the ERG base-case resulted in an ICER increased by [redacted] compared to the company's base-case ICER. Most of the total increase in the ICER (despite the effect of applying the 3.5% discount rate) was due to assuming a treatment effect duration for burosumab of 20 years instead of lifelong as

assumed by the company. The ERG also conducted a new probabilistic sensitivity analysis (PSA) and additional scenario analyses exploring the impact of choosing prior distributions for the burosumab transition matrices. The latter was proven to be crucial and in the several scenarios provided by the ERG, the ICER ranged from [redacted] to [redacted].

Based on the ERG results, it is expected that, from the payer perspective, the decision uncertainty related to burosumab value for money would be low, given that the ICER estimates from all ERG analyses are above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

A budget impact model to estimate the costs to the NHS for a period of five years of adopting burosumab in England was also included in the CS. The results presented by the company suggested that the net budget impact of implementing burosumab (with an estimated prevalence of [redacted] patients) will be [redacted] in the first year and will rise to [redacted] in the fifth year. The cost of burosumab at year 5 amounts to [redacted]. The estimated total number of patients eligible for burosumab treatment after five years is [redacted] and the uptake of burosumab rises from 40% in year 1 to 90% in year 5.

The CS did not include any estimates of costs (savings) or benefits incurred outside of the NHS and PSS associated with of burosumab. The company indicated that at this stage this was not possible to quantify. However, the company expects significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health related benefits

The ERG considers the assumptions made in the budget impact analysis questionable. There are concerns about the theoretical population size and the expected uptake rate of burosumab in England. In the CS, it was reported that the size of the patient population ([redacted]) is not expected to change over time. This estimate is based on an assumption that the patients are only treated if they have growing skeletons. In the CS, it was stated that XLH is not associated with an increased risk of death, compared to the standard population. The potential (and theoretical) population size is assumed to remain constant.

Since real-world data suggest that there could be [redacted] XLH patients between one and 17 years of age in England, using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab. The cost of burosumab at year 5 would then amount to [redacted]. The company indicated that burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by the company and will therefore not have any additional financial or resource impact on the NHS.

The ERG considers it inadequate that the impact of XLH on costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab was not identified prior to the submission to NICE.

1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

The company's submission provided sufficient details for the ERG to appraise the database searches, which were generally transparent and reproducible. An adequate number of online resources were searched and a good range of additional searches were conducted for grey literature. However, the population facet for each search conducted included few synonyms, and therefore may have missed relevant literature. Given the small number of references retrieved from the search, study design filters were not essential, and may have been unnecessarily restrictive.

The main limitation of the efficacy data reported in the CS is the study design of the included studies. Due to the absence of a control group in most studies it is not possible to make any direct comparisons between burosumab and conventional therapy. As stated by the company, the "burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).

For children between one to four years old, only one study is presented in which all children received burosumab (CL205, N=13). A comparison with "established clinical management without burosumab" is not possible in this group of patients.

A randomised controlled study comparing burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) is currently ongoing. [redacted]. Results from this study will considerably reduce the uncertainty surrounding the clinical effectiveness of burosumab relative to conventional therapy in children with XLH aged between one and 12 years.

A range of relevant economic information was incorporated in the CS, including a QALY-based cost effectiveness model and an assessment of the expected costs to the NHS and PSS in England. However, the CS lacks information about the long-term effects of treatment with burosumab and about the treatment effects of burosumab in adults. The available evidence is limited, which makes the model results highly uncertain and sensitive to key assumptions. The CS also lacks an analysis of the wider societal (non-health) benefits associated with burosumab.

There is substantial uncertainty about the long-term effects of burosumab. The company conducted their analysis upon the assumption that these effects would be lifelong, despite treatment being stopped at the age of 16 in females and 17 in males, but there is no evidence to support that assumption. This assumption was proven to be crucial and one of the main drivers of the cost effectiveness results. Additional uncertainty is generated when translating the clinical outcomes to QALYs since the evidence on HRQoL was based on a vignette study describing the health states of the economic model that were valued by (only six) clinical experts. Since there is no direct or indirect evidence comparing burosumab to SoC, the assumed treatment effect of burosumab, as reflected by the transition probability matrices, is also very uncertain.

The ERG considers that the uncertainty around the reported ICERs is likely to be larger than suggested by the PSAs presented in this report. Given that a PSA only addresses parameter uncertainty, other sources of uncertainty, like the ones mentioned above, could not be included in the PSA.

1.11 Summary of exploratory sensitivity analyses undertaken by the ERG

The main changes made by the ERG to the company's model included the use of alternative transition probabilities for burosumab, sourcing utilities directly from the vignette study report (and not from the company submission) and the operationalisation of the treatment effect of burosumab. Minor changes

included discounting costs and health outcomes at 3.5%, although this was proven to have a major impact on the model results.

The results of the ERG base-case, before applying the 3.5% discount rate on costs and health outcomes, resulted in an ICER increased by [redacted] compared to the company's base-case ICER. After applying the 3.5% discount rate, the ICER increased by [redacted]. Although sourcing the utilities from Lloyd et al. had a substantial impact on the ICER (increased by [redacted]), most of the total increase in the ICER (before applying the 3.5% discount rate) was due to the assumption of reducing the utilities of burosumab patients 20 years after the end of treatment. Since there is uncertainty on whether this value of 20 years will be observed in real life, the ERG assessed the impact of assuming a different duration for the burosumab treatment effects on the cost effectiveness results. The difference between assuming 20 years duration of treatment effect (ERG) and lifelong treatment effects (company) was that the ICER increased by approximately [redacted] under the ERG assumption. Assuming smaller values for the duration of the burosumab treatment effect increased the ICER. In particular, when this was assumed to be five years, the ICER was [redacted].

The ERG was concerned that the PSA results presented by the company were underestimating the uncertainty associated with the transition probabilities for burosumab. For that reason, a new PSA and additional scenarios exploring the impact of choosing prior distributions for the burosumab transition matrices were conducted by the ERG. The latter was proven to be crucial and in the several scenarios provided by the ERG, the probabilistic ICER ranged from [redacted] to [redacted].

Based on the ERG results, it is expected though that, from the payer perspective, the decision uncertainty related to burosumab value for money would be low, given that the ICER estimates from all ERG analyses are above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

2 BACKGROUND

2.1 Introduction

This report provides an overview of X-linked hypophosphataemia (XLH) and its management. The content of this chapter is based on relevant literature, information provided by clinical advisors to the Evidence Review Group (ERG) and information presented in the background sections of the submission (CS),[1] with additional information provided in the company's response to clarification letter.[2] For additional information on the aetiology, epidemiology, health impact, prognosis and management of XLH, please see the CS (pages 32-57).

2.2 Description of health problem

2.2.1 Paediatric XLH

X-linked hypophosphataemia (XLH) is a rare and often genetic (hereditary) disorder. In XLH, high levels of circulating FGF23 lead to excess urinary phosphate excretion and subsequent hypophosphataemia. Since phosphate is required to build and maintain bones, patients typically develop bone deformities, defective tooth mineralisation and experience growth problems.

The major pathologic consequences of XLH in the bone are rickets (in children) and osteomalacia (in adults). Rickets, the hallmark of XLH in children, is associated with substantial skeletal deformities that cause daily pain and impair physical functioning, such that a young child may be limited in his/her daily activities and will suffer lifelong disability and pain as these deformities become irreversible when growth ceases. Children with XLH often experience difficulty performing age-appropriate gross motor activities, such as walking, running and jumping, due to bowing of the femur, tibia, and/or fibula and the tibia rotation that causes the feet to turn in toward each other. In addition, children experience muscle weakness, fatigue, and other physical functioning deficits that are likely caused by the diverse physiological impacts of hypophosphataemia, which may be independent of rickets. Bowing of the legs in children with XLH can be substantial and severe. Defects in the growth plate also lead to impairment in growth and growth potential. The combination of height loss caused by the bowing of the legs and the growth plate defects can lead to a permanent loss of growth potential and short stature which can have psychosocial consequences for the individual.[3]

Over time, symptoms may progress to include bone pain, joint pain caused by hardening (calcification) of tendons and ligaments, and dental pain. Some people with XLH may also experience hearing loss.[4, 5] In addition to the substantial impacts on skeletal disease, low serum phosphorous in XLH patients may contribute to muscle dysfunction, reduced mobility and physical functioning, and fatigue. Because XLH is a lifelong disease, bone and joint damage, osteomalacia and reduced mobility acquired during childhood, are continued into adulthood.

Rickets is typically measured using radiographs as the gold standard. The Rickets Severity Score (RSS), is a radiographic scoring method developed to assess the severity of nutritional rickets. The RSS provides the absolute score of epiphyseal/distal metaphyseal abnormalities in the wrists and knees based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected.[6] The RSS is a 10-point scoring method, where a score of 0 indicates no rickets and a score of 10 indicates the highest severity of rickets. The usual range of RSS total scores in XLH is between 0 and 6.5 but reflects only the epiphyseal/distal metaphyseal portion of the skeletal abnormalities that are common in affected children, as there are other aspects of XLH not fully captured in the RSS. These other findings include coxa vara (a hip deformity that causes leg length discrepancies and gait abnormalities), tibial

torsion (a twisting of the shins that causes the feet to turn inward), and genu varum (bowing) or genu valgum (knock knees).

The Radiographic Global Impression of Change (RGI-C) is an alternative radiographic scoring method for rickets. This indicates the change in abnormalities and deformities between time points. The RGI-C provides a complementary method to RSS that allows for comparison with previous radiographs. Together, both measures provide a broader insight into bone disease than any one score alone.

ERG comment: The current submission focusses on paediatric XLH, which is defined as XLH in children aged 1-17 years. Of note, the comment that "other [clinical] aspects of XLH are not fully captured in the RSS" (CS, page 41) has to be considered in the context of the economic model in the CS, which only considers RSS score alone as a clinical outcome measure. The diverse physiological impacts of hypophosphataemia, which may be independent of rickets, are not captured at all in this submission. This is acknowledged as a limitation in the CS.

Only RSS scores are used in the model; RGI-C scores are not considered, despite the company considering these to represent more sensitive readouts of rickets severity and having this information available from each of the clinical studies used to inform the economic model (CL201, CL205 and CL002).

2.2.2 Epidemiology

2.2.2.1 Prevalence of XLH

The CS contains three key references that estimate the prevalence of XLH. One published study reports on prevalence in Denmark,[7] one unpublished draft study manuscript reports on prevalence in the UK,[8] and one real-world dataset commissioned by Kyowa Kirin through the British Paediatric and Adolescent Bone Group and the European Reference Network on Rare Bone Disorders (BPABG/ERN-BOND) provides the number of XLH patients currently in selected treatment centres in the UK.

The Danish published study estimates the incidence of XLH to be 3.9 per 100,000, based on 0.57 cases being diagnosed out of 14,558 children born in Denmark in one year.[7] The estimation that this would equate to 26 new patients annually in England appears valid against a mean number of 663,157 births in England over the same incidence period (1982 to 2002).[9] Given the size of the total prevalent population [ ], this is considered by the company to be implausible.

[redacted] (based on Delmestri et al 2018[8] and a personal communication from this study's authors to Kyowa Kirin). This prevalence was applied to the general population for England in children aged between one and 17 years[10] to estimate [redacted] children with XLH (Table 2.1, below; Table 60 in the CS). However, it remains unclear how this prevalence value has been calculated (e.g. the denominator, how the 522 test cases were originally identified etc.). There is further uncertainty around this figure since, as the company have acknowledged in their clarification letter response, "[redacted]".[2] Consequently, the estimate provided from this preliminary, unpublished dataset must be interpreted with caution.

[redacted]

[redacted] Based on the information from BPABG plus information obtained through re-engaging [redacted] in England in the 1-17 age range in the company's response to clarification letter (question A5[2]). Since eligibility for treatment with burosumab requires radiographic evidence of bone disease in children and adolescents, Kyowa Kirin considers it unlikely that such patients would be undiagnosed and therefore not in treatment at one of these centres, as this degree of disease is likely to be symptomatic. According to the CS, the size of the patient population is not expected to change with time as patients are only treated if they have growing skeletons i.e. each year there may be new patients but there will also be a similar number of patients ceasing treatment.

In the company's statement in their response to clarification letter, they report that [redacted][2] [redacted] of these [redacted] patients appear to be currently treated in ERN-BOND centres. However, it is not clear if all ERN-BOND centres in England have been included in this analysis. Additional ERN-BOND centres (Oxford University Hospitals and Sheffield Teaching Hospitals[11]) do not appear in the list provided in Table 5 of the company's response to clarification letter[2]; thus, this real-world dataset may represent an underestimation of the real-world prevalence of XLH in England.

Since real-world data suggests there are [redacted] confirmed XLH patients between one and 17 years of age in England, there is a discrepancy between the Danish study's estimated values and BPABG/ERN-BOND real-world values (we would expect 26 new patients per year based on an incidence of 3.9 per 100,000,[7] but have identified an average of [redacted] new patients per year based on a real-world confirmed patient dataset). In their response to clarification letter,[2] the company questioned whether the methods used by Beck-Nielsen et al. 2009[7] may have overestimated the incidence of XLH. However, the ERG finds the methods described by Beck-Nielsen to be acceptable (patients diagnosed with rickets were identified from medical records, and the entire medical record was subsequently reviewed for biochemical and clinical parameters, similar to the methods described by Delmestri et al. 2018[8]).

Ultimately, the ERG is not confident in the data provided to support the proposed prevalence or incidence values for XLH in children aged one to 17 years the UK. This is further compounded by the suggestion that the number of cases in certain age ranges in a key study in the UK were subject to unexpected fluctuations,[8] as highlighted in the company's response to clarification letter (question A18, part IV[2]), which does not support the idea of the population of XLH remaining constant. These nuances have not been fully captured in any of the presented data.

Table 2.1: Derivation of number of XLH children on treatment in their first year

Parameter	Value	Reference
Population of females aged 1-16 years in England (2016)	5,695,613	Office for National Statistics 2016[10]
Population of males aged 1-17 years in England (2016)	5,110,255	Office for National Statistics 2016[10]
Prevalence of XLH	[redacted]	Draft abstract[8]
Number of patients eligible for burosumab per year	[redacted]	
Source: CS, Table 60		

2.2.3 Aetiology

Most XLH patients inherit their disease (i.e. have a genetic form of XLH), but a proportion (approximately 20%) develop the disease through new de novo somatic mutations.[12, 13]

The genetic form of the disease is an X-linked disorder caused by a defect in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) peptidase which is part of the phosphate sensing system in osteocytes. Only one mutated copy of the gene is enough to cause the condition in both males and females, therefore a female with XLH has a 50% chance of passing along a mutation to each of her children. Since males only have one X-chromosome, a male with XLH will pass along the condition to all of his daughters, but to none of his sons.

ERG comment: The described aetiology of the disease is in line with the description in the literature.

2.2.4 Pathogenesis

The aetiology and pathophysiological mechanisms behind XLH remain largely unknown. Patients with XLH carry mutations in the PHEX gene, which leads to an erroneous signal in the phosphate sensing control system and an inappropriate excess of FGF23. However, the mechanism through which PHEX disruption results in elevated FGF23 is still unclear.

Excess FGF23 drives the pathophysiology of XLH, leading to impaired conservation of phosphate by the kidney and consequent hypophosphataemia.[14, 15] FGF23 also suppresses 1,25(OH)2D production,[16] resulting in decreased intestinal absorption of calcium and phosphate, further impairing the body's phosphorus supply.[17] As a consequence, patients with XLH have defective bone mineralisation, resulting in low bone turnover and poor quality bone.[18] In addition, many patients have muscle function deficits[19, 20] that may be related to insufficient quantities of adenosine triphosphate (ATP) as a consequence of chronically low concentrations of extracellular phosphate.[19, 21] The musculoskeletal effects of chronic hypophosphataemia further lead to the clinical manifestations and morbidities seen in both children and adults with XLH.

XLH is characterised by biochemical imbalance, in particular regarding:

- Measures of mineral metabolism (serum phosphate, serum calcium)
- Measures of endocrine function (serum values of FGF23, 1,25(OH)2D, insulin-like growth factor I, alkaline phosphatase (ALP), osteocalcin, growth hormone)
- Measures of renal function (urinary calcium to creatinine ratio, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate (TmP/GFR)).

Serum ALP activity is elevated in children with XLH, to two to three times the upper limit of normal.[22] The magnitude of total and bone-specific ALP elevation correlates with the magnitude of rickets.[3] These parameters are commonly used as indicators of the presence and severity of rickets and is one of the primary methods used by physicians managing conventional therapy of XLH as a tool to assess results, since repeated X-rays are not advisable for children. Healing rickets by normalising ALP is the primary objective in children.[23]

ERG comment: In terms of normalising serum ALP, which is indicated throughout the CS to represent a primary objective towards healing rickets in children, it is important to note that only a proportion of children with XLH appear to present with elevated serum ALP while some remain within the normal reference range.[22]

The CS states that, "the magnitude of total and bone-specific ALP elevation correlates with the magnitude of rickets" and provides Carpenter 2011 as a reference.[3] However, this study does not describe a proportional relationship between ALP and rickets severity. Since normalising ALP is defined as the primary therapeutic objective in children with XLH, it would be of clear clinical relevance to include ALP as a clinical outcome in the economic model. Currently, RSS is the only clinical outcome that is used to inform the economic model. It is important to note that there is no evidence presented in the CS that rickets severity is a useful proxy marker that correlates with serum ALP; therefore, its relevance to the stated primary therapeutic objective in XLH patients remains unsupported.

2.2.5 Clinical features

The most important clinical features of paediatric XLH are reported to include: skeletal deformities, growth defects and dental issues.

Skeletal abnormalities include bowing of the femur, tibia/fibula, gait disturbance, joint pain, bone pain and restricted range of motion. Such deformities are severe enough to require at least one surgery in approximately 30% of paediatric XLH patients.[24] Skeletal abnormities, including bowing of the legs, and the associated misaligned joints, disproportionate growth and difficulty walking, persist despite treatment from an early age with conventional therapy (oral phosphate and active vitamin D).[25]

Growth failure appears frequently in children with XLH. The combination of height loss caused by the bowing of the legs and growth plate defects can lead to a permanent loss of growth potential despite the fact that children with XLH experience a normal pubertal growth spurt.[3] In the burden of illness study, CL001, diminished height was reported for (57/71 [80%]) of children.

Children with XLH who are on conventional treatment with alfacalcidol or calcitriol and phosphate show progressive stunting and body disproportion during childhood that is mainly due to diminished growth capacity in legs.[26] 25–40% of patients with well-controlled XLH show linear growth failure despite optimal treatment and have a final height under -2 standard deviation scores (SDS).[27-35] In a study of 28 XLH patients from 1971 to 2011, a significant difference was found between the initial stature and the final stature in only six patients who were treated with vitamin D and phosphate.[36]

Dental disease includes delayed dentition and dental abscesses, which are thought to arise from the limited mineralisation of the dentine compartment of the tooth. In study CL001, [redacted] of children and adolescents had previously had dental surgery.[37] Oral findings in 10 young patients with XLH and an average age of nine years have been enamel and dentine abnormalities, high pulp horns, large pulp chambers, and some cases of periapical abscesses related to teeth without caries or traumatic injuries.[38] A further study of 53 patients (adults and children) with confirmed hypophosphataemic rickets (HR) found that endodontically affected teeth are common, and the number of affected teeth increased significantly with age.[21] Hence, the need for endodontic treatment among HR patients is comprehensive.

Other studies were included in the CS to describe dental disease in XLH patients, but only focussed on adult patients alone, and therefore were not relevant to this appraisal.[4]

Clinical heterogeneity among XLH child and adult patients has been frequently reported.[3, 23] The clinical expression of the disease is widely variable, ranging from a mild abnormality, the apparent isolated occurrence of hypophosphataemia, to severe bone disease.[22] Varied clinical findings are reported even among siblings with the condition.[39]

ERG comment: Growth failure is reported in 25–40% of patients with well-controlled XLH despite optimal treatment, resulting in a final height under -2 standard deviation scores (SDS).[27-35] It is

presumed from this value that the remaining 60-75% of patients with well-controlled XLH achieve normal growth rates with conventional therapy. Other research has indicated that height velocity commonly increases during the first year of conventional therapy, and after two years of successful treatment, can be restored to its maximal potential in the majority of patients, although adult height usually remains compromised.[3, 23]

Dental disease in XLH patients is highlighted in the CS with a study by Anderson 2012 that assesses 53 patients with hypophosphataemic rickets.[21] Sixteen out of 53 patients were <18 years of age and therefore represent the population of interest for the burosumab indication described in the CS. Of these 16 patients, the mean number of endodontically affected teeth was 0.3 (standard deviation (SD) 0.9), while the median number was 0 (first and third quartile: 0.0 and 0.0). No comparisons were provided either in the referenced study, in the CS[1] or in the company's response to clarification letter (question A17[2]) for the number of endodontically affected teeth that would be expected in a healthy age-matched population. Based on the current information, the need for endodontic treatment among paediatric HR patients cannot be considered comprehensive, although it appears clear that dental issues are prevalent in adult XLH patients.

Clinical heterogeneity, which the CS highlights has been frequently reported for XLH patients, is a core issue that may impact burosumab treatment. Some patients with a PHEX mutation who are diagnosed with XLH retain residual gene activity.[17] In practical terms, this may mean that further dose-titrations are necessary that take into consideration not just weight but also residual gene activity. It is unclear if there is a validated test available to determine PHEX activity.

2.2.6 Diagnosis

Diagnosis of XLH is typically based on clinical findings, radiographic findings, biochemical testing and family history. Family history remains critically important to the early recognition of inherited forms. Although, genetic testing is increasingly used to confirm the diagnosis of XLH, radiographs have been the gold standard for the diagnosis and evaluation of rickets for several decades.[18, 40-42] The radiographic characteristics of rickets include lucency in the metaphyses, physeal widening, fraying and cupping.[6, 42] These diagnostic radiographic features of rickets typically reflect the impaired mineralisation and ossification affecting the growth plate. Bone manifestations are best seen in the metaphyses of rapidly growing bones, including the distal radius and ulna, distal femur, proximal and distal tibia and proximal humerus.[6, 42]

Paediatric patients with XLH are managed by paediatric endocrinologists and paediatric nephrologists. There are a limited number of expert clinicians with the necessary training and experience in rare metabolic bone diseases to appropriately manage children with XLH. It is anticipated that treatment would be initiated and monitored by specialist centres and clinicians.

2.2.7 Prognosis

As an update from the CS, which stated that no empirical evidence documenting the impact of XLH on mortality has been identified and that XLH is not thought to have an impact on the life expectancy of patients, a new analysis provided in the company's response to clarification letter stated that

[redacted]

[redacted].[2]

ERG comment: The original statement (that XLH had no impact on life expectancy) was unlikely to be accurate given the extensive pathological manifestations associated with the disease. The updated information that mortality is impacted in XLH patients has been updated in the company's economic model and [redacted].

2.2.8 Impact on patients' health-related quality of life (HRQoL)

2.2.8.1 Impact on paediatric HRQoL

As a rare, orphan disease area, XLH has not been the subject of extensive quality of life studies. Systematic reviews have identified very few studies including empirical evidence documenting the impact of XLH on quality of life; such studies are predominantly conducted in adult XLH patients.

From a young age, XLH has a detrimental impact on the quality of life of patients and families which continues throughout aging to adulthood. Familial cases are particularly burdensome since many members of the family may have the condition, such that a patient may also be a caregiver and vice versa.

As children grow up, they may notice the ways in which they are different from their peers; this can become more apparent to them when they go to school and can result in teasing and bullying by their peers. These differences could be associated with physical appearance, as their legs may develop 'bowing,' or their ability to join in with sports or at playtime. Even if physical appearance is not an issue, the child may begin to question why they have to take regular medication when their peers do not.[43] Difficulties may also be experienced in gross motor skills such as walking, running and jumping, due to symptoms such as bowing of the femur/tibia and/or fibula and the rotation of the tibia which causes the feet to turn inwards.

In an online survey to characterise the burden of illness in people with XLH (CL001), high levels of pain and limitations in mobility were reported by paediatric respondents with POSNA-PODCI scores for the Sports and Physical Function and Pain and Comfort domains below the normative healthy population mean. In CL001, the mean SF-10 physical health score of 35.5 was 1.5 standard deviations below the general population norm of 50. Similarly, in the phase 2 burosumab study (CL201), in children five to 12 years of age who received conventional therapy for an average of seven years, 55% had substantial functional impairment at baseline, defined as the POSNA-PODCI Global Functioning score <40, with particular functional impairments in the Sports/Physical Functioning and Pain/Comfort domains.[44] In Study CL201, the mean SF-10 physical health score at baseline was ([redacted]), below the population norm of 50. In particular, children with more severe rickets at baseline [redacted].

A further online survey, carried out in January 2018, collected background data regarding the impact of XLH and treatments that the child had received to help manage their condition.[45] [redacted].

ERG comment: It is clear that there is a paucity of data available to inform the question regarding HRQoL in the paediatric population. In the interim analysis of [redacted] in the UK, it is not clear how many children are being analysed. In the absence of comparative data with healthy age-matched children, it is also not clear if the number of missed school days or the number of days when patients could not take part in sports or other events is higher than the population norm or is directly related to their illness. HRQoL, as assessed in studies CL201 and CL205, was not used in the economic model.

2.2.8.2 Impact on family and carer HRQoL

Having a child with medical needs such as XLH requires full attention, with families and carers providing support and reassurance through the child's life progression. Frequent medication, hospital visits and tests can be overwhelming not only for the patient but for their carer as well. Regular blood tests, ultrasound scans to monitor kidneys, X-rays to check the development and condition of bones, frequent dentist visits and even orthopaedic surgery and osteotomies are required from an early age. Only the family and carers of a patient with XLH can assist with these issues. Emergency situations may also occur periodically as bone fractures or increases in pain severity are common between patients with XLH.[43] Parents of children with XLH often suffer from the condition themselves. In a UK survey, [redacted].[45]

2.3 Current service provision

Kyowa Kirin is not aware of any published NICE, NHS England, other national or expert guidelines for the diagnosis, treatment or management of XLH. XLH is listed amongst Rare Metabolic, Sclerosing and Dysplastic Bone Diseases in the National Health Services England (NHSE) document entitled "A13/S/a 2013/14 NHS STANDARD CONTRACT FOR SPECIALISED RHEUMATOLOGY SERVICES (ADULT)." There is no specialised service specification for children.

Guidelines on the diagnosis and management of XLH have been produced by a group of clinical experts in the USA.[3, 46] These guidelines provide specific recommendations for management of XLH in children and adults. This guidance also aligns with the proposals of an expert panel of the Japanese Society for Bone and Mineral Research,[47] as well as a review by UK clinicians that provides guidelines on diagnosis and management of rickets, including a short section on XLH.[48]

The CS states that most children with XLH currently receive conventional therapy, consisting of oral phosphate (divided in aliquots every four to six hours due to rapid excretion by the kidneys) and active vitamin D analogues (usually alfacalcidol in the UK, once daily).[23] Use of an active vitamin D analogue helps prevent secondary hyperparathyroidism that can be induced by phosphate administration. Calcitriol is an alternative; however, it requires multiple dosing and is only available as a capsule, making it less suitable for infants and young children.

The goal of therapy with oral phosphate and active vitamin D analogues in children is to provide just sufficient phosphorous to allow partially improved mineralisation of bone and improve skeletal outcomes, without providing so much that there is ectopic calcification. This approach aims to alleviate bone or joint pain, preventing skeletal deformities caused by rickets and improving growth. For the majority of paediatric patients with XLH (98.6%), treatment with conventional therapy (phosphate and vitamin D metabolites) does not adequately heal rickets, and improvements in serum phosphorous following administration of oral phosphate are transient, with a peak in serum phosphorus after each administration and then a return to baseline levels.[37, 49]

For children, treatment is initiated at the time of diagnosis and continued until long bone growth is complete. Almost all children with XLH require therapy until growth is complete, although the effectiveness on the skeleton is variable, and surgery is often necessary to correct lower extremity deformities. In Study CL001, over 30% of the children surveyed had already undergone at least one surgical procedure[24] and the majority (80%) had reportedly experienced bone or joint pain in the previous year.

Conventional therapy requires individualised dosing adjustment based on tolerability, evidence of secondary complications, changes in body size, growth velocity, and skeletal mineralisation.[3, 23] Frequent monitoring of height, serum calcium, alkaline phosphatase, parathyroid hormone, phosphate serum concentrations, and urinary calcium and creatinine is necessary to prevent tertiary hyperparathyroidism, induced by phosphate overdose and hypercalciuria with nephrocalcinosis and renal insufficiency, resulting from vitamin D metabolite overtreatment.[23]

UK clinicians stated that the following monitoring is required with conventional therapy:

- Monitor serum calcium, phosphorus, potassium and creatinine levels monthly until stable and thereafter every three months
- Monitor ALP, PTH and urine calcium and creatinine levels every three months.
- Perform renal ultrasonograms (to monitor nephrocalcinosis) every one to two years.

Frequent daily dosing and gastrointestinal distress and diarrhoea may compromise treatment persistence/compliance,[46] and as a result the therapeutic benefit of conventional therapy. Suboptimal therapy in childhood can result in lifelong disability. In adults, the reduced bone quality from chronic osteomalacia increases the risk for non-traumatic pseudofractures and causes bone and joint pain,[18] while ongoing skeletal deformities lead to the development of early osteoarthritis and stiffness that cause pain and continue to limit mobility and physical function.

Conventional therapy fails to address the underlying mechanism of the disease, as these supplements do not enhance proximal tubular phosphate reabsorption.

ERG comment: In describing a Japanese national survey conducted in 2010, the CS reports mean serum phosphate levels in a genetic hypophosphataemia group, and states, “Improvements in serum phosphorous following administration of oral phosphate are transient, with a peak in serum phosphorus after each administration and then a return to baseline levels”.[49] However, these values are derived from a mixed patient population that includes not only XLH but also autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets type 1 (ARHR1) and type 2 (ARHR2) patients. These values therefore cannot be considered representative of XLH patients. Thus, the ERG considers that this statement is not accurate, and simply highlights the heterogeneity of the disease.

2.4 Description of the technology under assessment

2.4.1 Burosumab (KRN23, Crysvita™)

Burosumab (tradename: Crysvita™) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody manufactured by Kyowa Kirin that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23), which is produced in excess in most XLH patients. The inhibition of FGF23 is reported to improve tubular reabsorption of phosphate from the kidney and increase levels of 1,25 dihydroxy-vitamin D (1,25(OH)2D) in the serum (leading to enhanced intestinal absorption of calcium and phosphate). Normalising phosphate levels is reported to ameliorate the bone-related symptoms (e.g. rickets) associated with XLH.

Since the aetiology and pathophysiological mechanisms behind XLH remain largely unknown, the mechanism-of-action of burosumab must be considered as ameliorating the symptoms rather than treating the underlying cause.

2.5 Current usage in the NHS

Burosumab is not currently in use in the NHS. The MHRA granted burosumab a 'Promising Innovative Medicine' (PIM) designation on 31 January 2017, and the EMA awarded burosumab conditional marketing authorisation on 23 February 2018. Burosumab is expected to be used in line with the anticipated marketing authorisation in children and adolescents with XLH from the age of one year old who have radiographic evidence of bone disease.

Burosumab is a monotherapy, meaning oral phosphate and vitamin D analogue therapy should be discontinued one week prior to initiation of treatment. Concurrent use of oral phosphate and vitamin D analogues is contraindicated with burosumab. Burosumab is administered every two weeks by subcutaneous injection.

Clinical expert opinion has suggested that patients responding well to burosumab treatment are likely to have a diminishing frequency of consultant visits over the longer term. In addition, burosumab will either prevent or improve skeletal abnormalities, and reduce the need for corrective surgery. Routine treatment with burosumab should also remove the need for additional supplementation with growth hormone in a small subset of patients where this is required.

The following ongoing monitoring is recommended with burosumab (Summary of Product Characteristics (Crysvita), 2017):[50]

- Monitoring for signs and symptoms of nephrocalcinosis, e.g. by renal ultrasonography, is recommended at the start of treatment and every six months for the first 12 months of treatment, and annually thereafter.
- Monitoring of plasma alkaline phosphatases, calcium, PTH and creatinine is recommended every six months (every three months for children 1- 2 years) or as indicated. Monitoring of urine calcium and phosphate is suggested every three months. Patient's fasting serum phosphate level should be monitored due to the risk of hyperphosphataemia. To decrease the risk for ectopic mineralisation, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age. Dose interruption and/or dose reduction may be required.
- Increases in serum parathyroid hormone have been observed in some XLH patients during treatment with burosumab. Periodic measurement of serum parathyroid hormone is advised.

The high burden of frequent monitoring when the drug is first introduced will tail off once the patient is on a stable dose, and the overall burden of monitoring is expected to be reduced compared with that required for conventional therapy.

ERG comment: Kyowa Kirin aim to treat a paediatric and adolescent population of XLH patients from 1-17 years of age who have radiographic evidence of bone disease. After the age of approximately 17, when growth plates fuse, it is indicated that burosumab will be discontinued as it will no longer be required to stabilise rickets symptoms. Based on the therapeutic target of burosumab (FGF23) and the largely unknown pathological mechanisms of XLH, there is no evidence presented that burosumab therapy in childhood has long-term therapeutic consequences in adulthood following treatment cessation. Bone metabolism is an ongoing and dynamic process that will continue to be subject to the pathological consequences of hypophosphataemia. Thus, the ERG considers it unlikely that the diverse pathologic and phenotypic consequences of XLH will be ameliorated without therapeutic intervention beyond the age of ~17 years, particularly with respect to progressive bone weakness. It is likely that it will continue to be necessary to treat and manage XLH patients who have received burosumab during childhood.

The economic model assumes that patients who receive burosumab and transition to the healed rickets state will remain healed. However, there is some suggestion in the literature that long-term treatment of XLH with FGF23 neutralising antibodies (in mouse models) incompletely rescues the mineralisation defect.[51]

As per the company's response, which was informed by UK-based clinical experts, growth hormone is not licensed and is not used in the UK for the treatment of XLH patients. Consequently, the statement, "Routine treatment with burosumab should also remove the need for additional supplementation with growth hormone in a small subset of patients where this is required" (CS, page 54) should be disregarded and not considered in the case for burosumab.

3 CRITIQUE OF THE COMPANY'S INTERPRETATION OF THE DECISION PROBLEM

3.1 Introduction

The remit of this appraisal, as defined in the final NICE scope, is to evaluate the benefits and costs of burosumab within its licensed indication for treating X-linked hypophosphataemia for national commissioning by NHS England.[52] The final NICE scope outlines the agreed population, intervention, comparators and outcomes for the appraisal. The NICE scope also sets out wider considerations relating to the impact of the technology beyond direct health benefits and on the delivery of the specialised service, the nature of the condition, costs to the NHS and PSS and value for money.

On 14 December 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product Crysvita (burosumab), intended for the treatment of X-linked hypophosphataemia. A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is likely to provide comprehensive clinical data at a later stage. The EMA awarded burosumab conditional marketing authorisation on 23 February 2018.

The full indication is: "Crysvita is indicated for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons."[53] It is proposed that Crysvita be prescribed by physicians experienced in the management of patients with metabolic bone diseases.

3.2 Adherence to the decision problem

Table 3.1 presents a summary of the decision problem as set out in the NICE scope[52] and the company's adherence to this (based on information presented on pages 20-21 of the CS[1]).

Table 3.1: Adherence of the CS to the agreed decision problem

	Final scope issued by NICE	Deviations of submission from the scope
Population	Children and young people with X-linked hypophosphataemia	The population is in line with the licence indication: X-linked hypophosphataemia with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons
Intervention	Burosumab	The intervention is in line with scope
Comparator(s)	Established clinical management without burosumab	The comparator is in line with scope
Outcomes	The outcome measures to be considered include: • fractures • severity of rickets • pain (including bone pain, joint pain and joint stiffness) • motor skills • growth (including height) • tooth loss and pain • skull and spinal deformities • neurological complications (including increased intracranial pressure, craniosynostosis, problems with hearing and balance, and spinal cord compression) • radiographic response • 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 could not be accounted for: • fractures • tooth loss and pain • skull and spinal deformities • neurological complications (including increased intracranial pressure, craniosynostosis, problems with hearing and balance, and spinal cord compression) • mortality These outcomes were not captured in clinical studies. Quality of life data collected in the studies (POSNA-PODCI and SF-10) could not be used to derive utility data for the health economic modelling because there is no valuation set according to the company. Therefore, the company derived utility values from a UK study.
Subgroups to be considered	N/A	

	Final scope issued by NICE	**Deviations of submission from the scope**
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options	
Cost to the NHS and PSS, and Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise	
Special considerations, including issues related to equality	Guidance will only be issued in accordance with the marketing authorisation Guidance will take into account any Managed Access Arrangements	

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The population included in the submission relates to X-linked hypophosphataemia with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. This is in line with the licence indication.

The studies included in the submission focus on the following populations and studies:

- Paediatric patients with XLH, five to 12 years old: Study CL201 (open-label RCT comparing different doses of burosumab biweekly or monthly administration of burosumab (doses 0.1 to 2.0 mg/kg))
- Paediatric patients with XLH, one to four years old: Study CL205 (open-label study to assess the safety, pharmacodynamics and efficacy of burosumab biweekly administration of burosumab at a target dose of 0.8 mg/kg))
- Paediatric Patients with XLH, five to 14 years old: Study CL002 (A retrospective longitudinal study of skeletal outcomes in children with XLH. No burosumab administered; however, study inclusion required the use of conventional therapy (oral phosphate/active vitamin D))

In addition, the CS mentions the following studies for which no data have been presented:

- A randomised, open-label, phase 3 study to assess the efficacy and safety of burosumab versus oral phosphate and active vitamin D treatment in paediatric patients with XLH, one to ≤ 12 years old with open growth plates (study CL301). Data are not yet available according to the company; although, the CS states that the primary efficacy and safety analysis for study CL301 is expected to be available [redacted].[1] Completion of this study is also a post-authorisation requirement for the conditional marketing authorisation. We asked the company to provide a precise date when data are available and whether any interim data are available.[2] The company responded that "[redacted]." Although they stress that these timelines remain provisional. The company stated they "[redacted]".
- An open-label, phase 3 study to assess the safety, pharmacodynamics and efficacy of burosumab (no control), in paediatric patients under the age of one year with XLH (study CL207). This study is planned, but no data are available. In addition, it is not relevant to the scope (children under the age of one year are outside the indication).
- XLH Disease Monitoring Program (study CL401), observing disease progression and associated side effects for up to 250 children and adults with XLH. This study is planned, but no data are available.
- A natural history survey via online questionnaire to characterise the burden of illness in adults and children with XLH (No burosumab administered). This study was used in the background section of the CS (Chapter 6 of the CS), but not as part of the clinical evidence (Chapter 9 of the CS[1]).

3.3.2 Interventions

The intervention included within the CS relates to burosumab in line with its licensed indication.

In the CS (page 12 and 31) the recommended dosage regimens of burosumab are described as: The recommended starting dose is 0.4 mg/kg of body weight and the normal maintenance dose is 0.8 mg/kg, given every two weeks. The maximum dose is 90 mg. All doses should be rounded to the nearest 10 mg. Burosumab may be initiated from one year old until end of skeletal growth. Based on UK growth data, in the cost effectiveness model, girls are assumed to remain on treatment up to 16 years of age (inclusive) and boys are assumed to remain on treatment until 17 years of age (inclusive) (CS, chapter 10.1.16, page 148).

3.3.3 Comparators

The comparator is described in the CS as "established clinical management without burosumab", this is in line with the scope.

All patients in the control study (Study CL002: A retrospective longitudinal study of skeletal outcomes in children with XLH aged five to 14 years old) received conventional therapy (i.e. oral phosphate/active vitamin D)).

3.3.4 Outcomes

As specified in the Table with the Statement of the decision problem (CS, Table 1, page 20), the studies do not provide data on the following outcomes:

- fractures
- tooth loss and pain
- skull and spinal deformities
- neurological complications (including increased intracranial pressure, craniosynostosis, problems with hearing and balance, and spinal cord compression)
- mortality

These outcomes were not captured in the clinical studies.

In the CS, the company uses the term 'healing' and 'substantial healing of rickets'. This is defined using RGI-C global scores, where scores ≥ +1.0 indicate 'healing of rickets' and scores ≥ +2.0 'substantial healing of rickets'. The company does explain that "Healing in this context indicates improvement in the radiographic abnormalities and does not imply that complete healing was observed" (CS, page 100). However, throughout the report the term 'healing of rickets' is used without any explanation of the degree of healing (minimal, substantial or complete). Moreover, RGI-C global scores and RSS scores do not capture all clinical aspects of XLH. That is of particular importance in the context of the economic model, which only considers RSS score alone as a clinical outcome measure. The diverse physiological impacts of hypophosphataemia, which may be independent of rickets, are therefore not captured as outcomes in the economic model.

In the response to the clarification letter the company described the vignettes for the various health states that informed the economic model in detail (Clarification Letter Response Question B7, Table 10). However, each health state was defined in such a way that there appears to be a perfect association between the RSS score and other clinical descriptors of the health state. For example, as the RSS score decreases so does the risk of fracture and the presence of deformity. However, this does not appear to be realistic in that it seems likely that there might be some resolution of the bone disorder such that the

RSS score decreases, but that this resolution only occurs after incurring deformity, which cannot be completely resolved and with some continued increased risk of fracture.

In addition, the model currently assumed that the effect of burosumab, although stopped at age 16 (women) or 17 (men) lasts for the rest of their lives. This also seems unrealistic, the effects of burosumab on stature, bowing of the legs, joint deformity etc. are likely to persist fairly long but may wane as osteomalacia itself and the resulting fractures may lead to associated problems in later life. Effects on bone strength will wane quicker, therefore repeated fractures and badly healing fractures after 10 or 20 years are likely to occur. Effects of burosumab on symptoms caused by hypophosphatemia itself will disappear as soon as therapy is stopped. Therefore, we have assumed in the ERG base-case that patients will experience a decline in quality of life 20 years after the end of treatment, which was operationalised by moving to the utility value of the next worse health state (see section 6.2.3 in this report).

In addition, quality of life data collected in the studies (POSNA-PODCI and SF-10) could not be used to derive utility data for the health economic modelling because there is no valuation set according to the company. Therefore, the company derived utility values from a UK study.

3.3.5 Cost to the NHS and PSS, and value for money

The CS includes a cost-consequence model in which the primary health outcome is valued in terms of incremental QALYs gained. In general, the scope was followed when assessing the costs of burosumab to the NHS and the value for money it provides.

4 IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The ERG has presented only the major limitations of the search strategies in the main report. Further minor criticisms can be found in Appendix 1 of this report.

Section 9.1.1 of the CS states that MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched for the identification of clinical effectiveness evidence. Search strategies were reported in detail in Appendix 17.1 of the CS and in the response to clarification. MEDLINE and Embase were searched using the Ovid interface from the earliest date available for each database until the end of October 2017. CENTRAL was searched for all available years until January 2018. The searches were also intended to identify studies on adverse events not already known to the company.

A wide range of additional searches were conducted, including the EU Clinical Trials Register, ClinicalTrials.gov, online patient organisations, online case reports and clinical studies. Three main journals in the field were hand-searched, and reference checking was carried out. Experts and clinical specialists were also consulted.

Following a request for clarification, full search strategies were provided for MEDLINE, Embase and CENTRAL. Strategies were not included for the trials register searches.

ERG comment:

- The selection of databases searched was adequate and searches were clearly reported and reproducible. The database name, host, date range and date searched were provided for the majority of the searches. A good range of additional resources were included.
- The main concern of the ERG is that the search terms used for the population facet of the strategy were insufficient. Only one indexing (MeSH/EMTREE) term was used, combined with one free-text term. Numerous synonyms are available for X-linked hypophosphataemia and use of these terms would have increased the retrieval of potentially relevant records.
- Given the small number of papers retrieved for this topic, the ERG believes that use of study design filters in the searches was unnecessarily restrictive. The ERG suggests that a single-facet search for XLH (and additional synonyms) without a study design filter would have adequately addressed all areas of interest, including clinical effectiveness, adverse events, cost-effectiveness, HRQL and resource use without retrieving unmanageably high numbers of records. See Appendix 1 for example MEDLINE, Embase and CENTRAL searches run by the ERG.

4.1.2 Inclusion criteria

The eligibility criteria for the review are described in Table 4.1 (CS, Table 7, page 60).

Table 4.1: Eligibility criteria

Inclusion criteria	
Population	Children or adults with XLH.
Interventions	Any
Outcomes	Reported statistical findings on clinical outcomes (either benefits or adverse effects).
Study design	Studies with a quantitative analytical approach and a study design of case comparison or interventional design (experimental or observational), including: Randomised Control Trials (RCTs), cluster RCTs, non-randomised controlled studies (including controlled before and after studies) and interrupted time series studies (with time points before and after the intervention to establish an underlying trend in the outcome).
Language restrictions	English
Search dates	Database inception to October 31st 2017 (Embase and Medline) and to December 2017 (Cochrane Register of Controlled Trials)
Exclusion criteria	
Population	None
Interventions	None
Outcomes	None
Study design	Animal studies or biochemical or cellular level investigations. Studies with a qualitative design, review articles or articles that investigate the genetic characteristics of XLH.
Language restrictions	Languages other than English.
Search dates	None
Source: CS, Table 7, page 60 XLH = X-linked hypophosphataemia	

ERG comment: The only criticism regarding the inclusion criteria is the language restriction used by only including English language studies.

4.1.3 Critique of data extraction

Methods for the systematic review process have not been reported. Therefore, there is no information regarding the number of reviewers involved in the study selection process and the data extraction process. It is common practice in systematic reviews that every step in the review is performed by at least two reviewers to minimise bias and to prevent mistakes. In this case there is no guarantee that the data extraction process was correct.

The CS does mention that "Data was extracted from included studies using a specially designed data extraction form" (CS, page 59); however, the form used was not presented.

4.1.4 Quality assessment

The risk of bias of included studies was evaluated using an adapted version of the Centre for Reviews and Dissemination (CRD) checklist for CL201,[54] and an adapted version of the Critical Appraisal Skills Programme (CASP) checklist for CL002 and CL205.[55] It was not reported how many reviewers were involved in the risk of bias assessment.

ERG comment: The company used appropriate risk of bias tools for different study types. However, the process of quality assessment was not fully described.

4.1.5 Evidence synthesis

As stated by the company, the "burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).[1]

For children between one to four years old, only one study is presented in which all children received burosumab (CL205). A comparison with "established clinical management without burosumab"[52] is not possible in this group of patients.

For children between five to 12 years old, the CS presents a study in which all children received burosumab (CL201). In addition, the CS presents a control study (CL002) in which children aged between five to 14 years received conventional therapy (i.e. oral phosphate/active vitamin D). Results of these two studies are presented as a naïve comparison, simply reporting individual results from each study side by side (See CS, Table 17, page 94). In addition, the company presents comparisons of 'rickets healing' with conventional therapy (Study CL002) versus burosumab (Study CL201) using propensity score matching. Further details of the methods and results of the naïve and propensity score matched comparisons are provided in section 4.3. As there were no controlled studies of burosumab meta-analysis was not performed.

ERG comment: Full details of the numbers of reviewers involved in the study selection, data extraction and quality assessment stages of the systematic review were not reported. Due to a lack of comparative studies meta-analyses were not possible. The lack of detail about the review methods means it is not possible to judge if appropriate steps were used to reduce the risk of reviewer error and bias. Restricting the review to studies only published in English means that some studies may have been missed, although this is unlikely due to the small amount of evidence available for burosumab.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The CS includes two studies of burosumab in children aged 5-12 years (Study CL201) and in children aged 1-4 years (Study CL205). Study CL201 is an ongoing, multicentre, dose-finding Phase 2 study which included 52 children (10 from three clinical trial sites in the UK) with XLH aged 5-12 years and compared two dosing frequencies of burosumab: once every two weeks (n=26) or once every four weeks (n=26). Study CL205 is an ongoing, multicentre, single-arm, Phase 2 study in 13 children from one to four years old with XLH who are naive to therapy or have previously received conventional therapy with oral phosphate and active vitamin D to assess the safety, pharmacodynamics, pharmacokinetics, and efficacy of burosumab administered via subcutaneous (SC) injection once every two weeks (Q2W) for a total of 64 weeks.

In addition, the CS includes a historical control study. Study CL002 is a retrospective radiographic and medical chart review study designed to evaluate the long-term safety and efficacy of oral phosphate/active vitamin D therapy. The children in CL002, aged five to 14 years old, had received long-term (approximately eight years) conventional therapy with oral phosphate and active vitamin D (n=[redacted] in the Radiographic Analysis Set). All [redacted] patients who contributed the radiographs for RSS and RGI-C analyses were enrolled at a single US site, Shriners Hospital in St. Louis, Missouri. The study is ongoing and additional data from three other sites in the United States, France, and Canada are anticipated to add to the body of evidence. Historical images will be collected from up to 100 children.

A total of [redacted] children had been enrolled in the CL002 study at the time of the latest data cut (August 2016). One child had not received conventional therapy and was not included in the analysis. The remaining [redacted] children (98%) who met the study inclusion/exclusion criteria and had been treated with conventional therapy were included in the Full Analysis Set. The mean duration between baseline and post-baseline radiographs was [redacted]).

Since CL002 was a US study, Kyowa Kirin also commissioned a longitudinal review of patient records from three expert UK centres to provide additional data (n=43). However, results from this UK review are not included in the CS. We asked the company in the clarification letter, and the company responded that this case review was commissioned specifically for NICE, and that the data were only made available just prior to submission. For this reason, no CSR was constructed as the data has not been submitted to regulatory agencies. Instead the company provided a synopsis with details on the rationale, methodology and results as part of the response to the clarification letter.[2] A summary and critique of these data are provided in section 4.5 of this report (Additional work on clinical effectiveness undertaken by the ERG).

Table 4.2: Included studies

Study ID	Study Title	Patient Population (Type/ Number of patients)	Intervention
UX023-CL201 Clinical Study report – week 64 Analysis, May 2017 (ongoing)	Randomised, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 antibody, burosumab, in Paediatric Patients with XLH	Paediatric patients with XLH, 5 to12 years old 52 initiated treatment	Multi-dose burosumab Biweekly or monthly administration of burosumab (doses 0.1 to 2.0 mg/kg) Repeat dose, up to 64 weeks
UX023-CL205 Clinical Study report – week 40 (Primary) Analysis, Oct 2017 (ongoing)	An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics and Efficacy of burosumab in Children from 1 to 4 Years Old with XLH	Paediatric patients with XLH, 1 to 4 years old 13 patients enrolled	Multi-dose burosumab Biweekly administration of burosumab at a target dose of 0.8 mg/kg. Repeat dose, up to 64 weeks
UX023-CL002 Clinical Study report, Nov 2016	A retrospective longitudinal study of skeletal outcomes in children with XLH	Paediatric Patients with XLH, 5 – 14 years old. Images will be collected from up to 100 children	This was not an interventional study; however, study inclusion required the use of conventional therapy (oral phosphate/ active vitamin D)
Source: CS, Tables 8 and 9, pages 63-64 XLH = X-linked hypophosphataemia			

The methodology of the three included studies is described in Tables 4.3 and 4.4, and demographic and baseline characteristics are described in Table 4.5.

ERG comment: As can be seen from Table 4.3, inclusion criteria for patients in studies CL201 and CL002 are similar in that patients in both studies were diagnosed with XLH and were of similar age. However, there are important differences between the inclusion criteria in both studies. Children in study CL201also had: biochemical findings associated with XLH, standing height < 50th percentile for

age and gender and radiographic evidence of active bone disease including rickets in the wrists and/or knees, and/or femoral/tibial bowing, or, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read. In other words, study CL002 included all children with XLH, while study CL201 included children with more severe symptoms of XLH. This is also reflected in the relatively [redacted] standing height and [redacted] rickets severity score for children in study CL201 when compared to children in study CL002 (see Table 4.5).

Study CL205 enrolled children with XLH aged between one and four years old. In this study children had to have clinical findings consistent with XLH, including hypophosphataemia and radiographic evidence of rickets (at least five patients were required to have a Rickets Severity Score [RSS] at the knee of ≥ 1.5 points at Screening), and a confirmed PHEX mutation or variant of uncertain significance (VUS). Only 13 children were enrolled. Therefore, results in this age group are very uncertain (see Table 4.4).

Table 4.3: Summary of methodology for Studies CL201 and CL002

Study name	**UX023-CL201**	**UX023- CL002**
Objectives	• Identify a dose and dosing regimen of burosumab, based on safety and PD effect in paediatric XLH patients • Establish the safety profile of burosumab for the treatment of children with XLH including ectopic mineralisation risk, cardiovascular effects, and immunogenicity profile	To characterise change in rickets severity over time with conventional therapy (oral phosphate/active vitamin D) in children with XLH ages 5 to 14 years.
Location	This study is being conducted at a total of nine centres: four in the United States, three in the United Kingdom, one in France, and one in the Netherlands	Two sites in the USA.
Design	Randomised, multicentre, open-label, dose-finding Phase 2 study assesses the PD, efficacy, and safety of burosumab in prepubescent children (5 to 12 years old) with XLH. The study consists of two Screening Visits, a 16-week Titration Period, a 48-week Treatment Period, and a 96-week Treatment Extension Period.	Retrospective radiographic and medical chart review of patients with XLH who had longitudinal historical radiographs of the wrist, knee, or long leg taken between the ages of 5 and 14 years (inclusive).
Duration of study	The planned study duration is 160 weeks (approximately 3 years): 16 weeks in the Titration Period, 48 weeks in the Treatment Period, and 96 weeks in the Treatment Extension Period.	This is a retrospective study. The mean duration between baseline and post-baseline radiographs was [redacted] weeks]).
Sample size and Patient population	Approximately 30 paediatric patients with XLH and radiographic evidence of bone disease (“pre-expansion patients”) were planned for enrolment under the original study protocol. The study was expanded per amendment 3 of the protocol to include additional patients (“expansion patients”) who were required to have rickets severity of at least 1.5 at the knee (per the Rickets Severity Score [RSS] method), for a total of approximately 50 patients planned overall.	[redacted] paired wrist and knee images) Children with a confirmed diagnosis of XLH who have radiographic images for at least two time points taken between the ages of 5 and 14 years.

Study name	**UX023-CL201**	**UX023- CL002**

Inclusion criteria	• Male or female, aged 5 – 12 years, inclusive, with open growth plates
	• Tanner stage of 2 or less based on breast and testicular development
	• Diagnosis of XLH supported by ONE of the following:
	  o Confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance
	  o Serum FGF23 level > 30 pg/mL by Kainos assay
	• Biochemical findings (based on overnight fasting [minimum 4 hours] values collected at Screening Visit 2) associated with XLH including:
	  o Serum phosphorus ≤ 2.8 mg/dL (0.904 mmol/L)
	  o Serum creatinine within age-adjusted normal range
	• Standing height < 50th percentile for age and gender using local normative data. (Criterion was changed to "< 50th percentile" [from "< 25th percentile"] per Protocol Amendment 1)
	• Radiographic evidence of active bone disease including rickets in the wrists and/or knees, AND/OR femoral/tibial bowing, OR, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read (The inclusion criterion of RSS ≥ 1.5 for patients enrolled with the expansion of the study was added per Protocol Amendment 3)
	• Willing to provide access to prior medical records for the collection of historical growth, biochemical and radiographic data, and disease history
	• Provide written or verbal assent (if possible) and written informed consent by a legally authorised representative after the nature of the study has been explained, and prior to any research-related procedures
	• Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule and comply with the assessments
	• Females who have reached menarche must have a negative pregnancy test at Screening and undergo additional pregnancy testing during the study. If sexually active, male and female patients must be willing to use an acceptable method of contraception for the duration of the study. (This inclusion criterion added per Protocol Amendment 1)
		• Male or female, with radiographic images from at least two time points taken between the ages of 5 and 14 years, inclusive
		• Diagnosis of XLH based on a confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance, or a clinical diagnosis of XLH based on biochemical profile and clinical symptoms

Exclusion criteria	• Use of a pharmacologic vitamin D metabolite or analog (eg, calcitriol, doxercalciferol, alfacalcidol, and paricalcitol) within 14 days prior to Screening Visit 2; washout took place during the Screening Period • Use of oral phosphate within 7 days prior to Screening Visit 2; washout took place during the Screening Period • Use of calcimimetics, aluminium hydroxide antacids, systemic corticosteroids, and thiazides within 7 days prior to Screening Visit 1 • Use of growth hormone therapy within 3 months before Screening Visit 1. (Criterion was changed to "within 3 months" [from "within 12 months"] per Protocol Amendment 2 • Use of bisphosphonates for 6 months or more in the 2 years prior to Screening Visit 1 • Presence of nephrocalcinosis on renal ultrasound graded ≥ 3 based on the following scale: o 0 = Normal o 1 = Faint hyperechogenic rim around the medullary pyramids o 2 = More intense echogenic rim with echoes faintly filling the entire pyramid o 3 = Uniformly intense echoes throughout the pyramid o 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period • Hypocalcaemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits (based on overnight fasting [minimum 4 hours] values collected at Screening Visit 2) • Evidence of tertiary hyperparathyroidism as determined by the Investigator • Use of medication to suppress parathyroid hormone (PTH) within 2 months prior to Screening Visit 1 • Presence or history of any condition that, in the view of the investigator, places the patient at high risk of poor treatment compliance or of not completing the study • Presence of a concurrent disease or condition that would interfere with study participation or affect safety • Previously diagnosed with human immunodeficiency virus antibody, hepatitis B surface antigen, and/or hepatitis C antibody • History of recurrent infection or predisposition to infection, or of known immunodeficiency	• Currently or previously treated with burosumab in Ultragenyx protocol UX023-CL201 (images and data from patients in the current study were collected as a part of UX023-CL201)

Study name	**UX023-CL201**	**UX023- CL002**
	• Use of a therapeutic monoclonal antibody within 90 days prior to Screening Visit 1 or history of allergic or anaphylactic reactions to any monoclonal antibody • Presence or history of any hypersensitivity to burosumab excipients that, in the judgment of the investigator, places the patient at increased risk for adverse effects • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments	
Interventio n(s) (n =) and comparator (s) (n =)	Burosumab, n=52: Pre-expansion Patients • Dose Cohort 1, [redacted] (0.1 mg/kg Q2W [redacted] 0.2 mg/kg Q4W [n[redacted]) • Dose Cohort 2, n[redacted] (0.2 mg/kg Q2W [redacted] 0.4 mg/kg Q4W [n[redacted]) • Dose Cohort 3, n[redacted](0.3 mg/kg Q2W [redacted] 0.6 mg/kg Q4W [n[redacted] Expansion Patients • Dose Cohort 3, [redacted] (0.3 mg/kg Q2W [redacted] 0.6 mg/kg Q4W [redacted]	Not applicable (patients had been on conventional therapy for approximately 6 years prior to study enrolment).
Baseline differences	Demographic characteristics were similar for patients randomised to the Q2W and to the Q4W dose regimens.	Not applicable
Duration of follow-up, lost to follow-up information	All patients completed at least 64 weeks on study. No patient discontinued from the study, and all patients are continuing in the study as of the data cut-off date.	Patients were not followed up as this was a retrospective study. The mean duration between baseline and post-baseline radiographs was [redacted])
Statistical tests	No formal hypothesis was tested to compare treatment groups (Q2W and Q4W) in this study. Changes from baseline in efficacy parameters were tested. Statistical analyses were reported using summary tables, figures, and data listings. Statistical tests were 2-sided at the alpha=0.05 significance level, and 2-sided 95% confidence intervals (CIs) were used. All p-values were presented as nominal p-values. No adjustment on multiplicity was made. For the primary efficacy endpoint of change in RSS total score, the difference between the two dose regimens (Q2W and Q4W) was summarised with 95% CIs. For repeated measures, the generalised estimating equation (GEE) approach was used for assessing the change over time. The GEE model included regimen, study visit and interaction between regimen and study visit as categorical variables. Model-based estimates of changes from baseline and corresponding 95% CIs were provided along with	Retrospective radiographic, biochemical, growth, and conventional therapy data collected from all patients in this historical cohort were summarised by both event incidence and patient incidence. No formal hypothesis was tested in this study. The primary evaluation in the current study was the change in rickets severity, as evaluated by 2 different methods (RSS and RGI-C). Rickets was assessed based on radiographic changes from radiograph pairs that were 1 to 2 years apart, with the earlier pair considered the baseline radiograph. For each radiograph pair, growth and

Study name	**UX023-CL201**	**UX023- CL002**
	P-values for assessing statistical significance. As exploratory analyses, covariates such as baseline measures, gender, and age were considered for adjustment within GEE models. Continuous variables were summarised with means, standard deviations (SD), standard errors (SE), medians, interquartile ranges (Q1, Q3), minimums, and maximums. Categorical variables were summarised by counts and by percentages of patients in corresponding categories. No imputation on missing data was made, unless stated otherwise. All data obtained from the Case Report Forms (CRFs) as well as any derived data were included in data listings. Efficacy results were analysed by subgroups defined by RSS total score at baseline. The "higher RSS" subgroup consisted of patients with RSS total scores at baseline ≥ 1.5; the "lower RSS" subgroup consisted of patients with RSS total scores at baseline < 1.5. The value of 1.5 was based on the median RSS total score of the study population at the interim analysis of the first 12 patients. Results also were analysed by subgroups defined by degree of functional impairment: for 6MWT results by percentage of predicted 6MWT (abnormal: < 80%, or normal range: ≥ 80%) at baseline, and for the POSNA-PODCI questionnaire by Global Functioning scale score (abnormal: < 40, or normal range: ≥ 40) at baseline.	biochemical data were linked to baseline and post-baseline radiographs by time of measurement and changes in growth and biochemical parameters were summarised. RSS, growth, and biochemical data were also summarised by event incidence in addition to paired incidence; the details of assessment plan for each endpoint are provided in. Subgroups were also prespecified based on rickets severity of the baseline radiographs: baseline radiographs with RSS total score ≥1.5 were referred to as the Higher RSS subgroup and those with RSS total score <1.5 were referred to as the Lower RSS subgroup. For continuous variables, the mean, standard deviation, median, quartiles, minimum, and maximum are provided; 95% confidence intervals (95% CI) on change from baseline were calculated for paired radiographs by one sample T test. For discrete data, frequency and percent distributions are used. Analysis was performed on the analysis sets by patient incidence, by radiograph incidence, or by paired radiographs.
Primary outcomes	Primary efficacy endpoint: Change from baseline in severity of rickets as measured by Rickets Severity Score (RSS) total score The primary efficacy analysis was at week 40. Additional efficacy analysis was carried out at week 64.	Conventional therapy endpoints include the following information: • Age at the time of initiating conventional therapy • Total duration of conventional therapy • Conventional therapy treatment status at time of radiographic imaging (Yes/No) • Conventional therapy regimen at time of radiographic image taken, including medication
Secondary outcomes (including scoring methods and timings	Secondary efficacy endpoints	

Study name	**UX023-CL201**	**UX023- CL002**
of assessments)	• Change from baseline in severity of rickets as measured by RSS knee and wrist scores • Change from baseline in the radiographic appearance of rickets and bowing as measured by Radiographic Global Impression of Change (RGI-C) global, knee, wrist and long leg scores • Growth (standing height, sitting height, arm length, and leg length) • Walking Ability (Six-minute Walk Test [6MWT]) • Functional disability and pain (Pediatric Orthopedic Society of North America – Pediatric Outcomes Data Collection Instrument [POSNA-PODCI])	• names, dose and frequency of administration for both phosphate and active vitamin D • Interruptions in conventional therapy of 3 months or more and reason for interruption Radiographic measures of rickets severity were assessed by Rickets Severity Scale (RSS) and Radiographic Global Impression of Change (RGI-C. Growth endpoints include standing height (length) in cm, z-score and percentile (adjusted by gender and age). Biochemical endpoints include change over time in serum or plasma phosphorus, calcium, iPTH, 1,25(OH)2D, and ALP corresponding to dates close to the date radiographic imaging was collected, where available.
Source: CS, Tables 10 and 12, pages 66-70 and 75-77		

Table 4.4: Summary of methodology for Study CL205

Study name	**UX023- CL205**
Objectives	Primary objectives: • Establish the safety profile of burosumab for the treatment of XLH in children between 1 and 4 years old • Determine the pharmacodynamic (PD) effects of burosumab treatment on serum phosphorus and other PD markers that reflect the status of phosphate homeostasis in children between 1 and 4 years old with XLH Additional study objectives are to assess the following in children between 1 and 4 years old with XLH: • Effects of burosumab on rickets • Effects of burosumab on growth and lower extremity deformity • Pre-dose burosumab drug concentration levels
Location	This study is being conducted at 3 centres in the USA.

Study name	**UX023- CL205**
Design	Multi-centre, open-label, single-arm, Phase 2 study in children from 1 to 4 years old with XLH who are naive to therapy or have previously received conventional therapy with oral phosphate and active vitamin D to assess the safety, PD, PK, and efficacy of burosumab administered via subcutaneous (SC) injection Q2W for a total of 64 weeks.
Duration of study	The planned duration of treatment in this study is 64 weeks. Patients who complete the study may continue into an extension study.
Sample size and Patient population	Approximately 10 paediatric patients were planned for enrolment and 13 patients were enrolled. This submission summarises the planned, primary analyses of data to week 40 for all 13 patients and additional safety data available through the data cut-off date. Patients were between 1 and 4 years old, inclusive, with clinical findings consistent with XLH, including hypophosphataemia and radiographic evidence of rickets (at least 5 patients were required to have a Rickets Severity Score [RSS] at the knee of ≥ 1.5 points at Screening), and a confirmed PHEX mutation or variant of uncertain significance (VUS).
Inclusion criteria	• Male or female, aged ≥ 1 year and < 5 years • PHEX mutation or VUS in either the patient or a directly related family member with appropriate X-linked inheritance • Biochemical findings associated with XLH including serum phosphorus < 3.0 mg/dL (0.97 mmol/L) and serum creatinine within age-adjusted normal range. (Criteria to be determined based on fasting [minimum 4 hours] values collected at baseline.) • Radiographic evidence of rickets; at least 5 patients will be required to have a RSS at the knee of at least 1.5 points as determined by central read • Willing to provide access to prior medical records for the collection of historical growth, biochemical, and radiographic data and disease history • Provide written informed consent by a legally authorised representative after the nature of the study has been explained, and prior to any research-related procedures • Must, in the opinion of the Investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule, and comply with the assessments

Study name	**UX023- CL205**
Exclusion criteria	• Unwilling to stop treatment with oral phosphate and/or pharmacologic vitamin D metabolite or analog (eg, calcitriol, alfacalcidol) during the screening period and for the duration of the study • Presence of nephrocalcinosis on renal ultrasound grade 4 based on the following scale: o 0 = Normal o 1 = Faint hyperechogenic rim around the medullary pyramids o 2 = More intense echogenic rim with echoes faintly filling the entire pyramid o 3 = Uniformly intense echoes throughout the pyramid o 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period • Hypocalcaemia or hypercalcaemia, defined as serum calcium levels outside the age-adjusted normal limits. (Criteria to be determined based on fasting [minimum 4 hours] values collected at baseline.) • Presence or history of any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study • Presence of a concurrent disease or condition that would interfere with study participation or affect safety • History of recurrent infection or predisposition to infection, or of known immunodeficiency • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments
Intervention	Burosumab, n=13
Baseline differences	Not applicable
Duration of follow-up, lost to follow-up information	All 13 patients were included in each analysis set (Efficacy Analysis Set, PK/PD Analysis Set, and Safety Analysis Set). As of the data cut-off date (20 April 2017), all patients completed week 40, no patient had discontinued from treatment or from the study, and all patients continue in the study. Additionally, 9, 7, and 4 patients have received burosumab through weeks 42, 44, and 46, respectively, as of the data cut-off date.

Study name	**UX023- CL205**
Statistical tests	The planned sample size for this study of approximately 10 patients was considered appropriate to evaluate the burosumab dose and PK/PD relationship in children aged 1 to 4 years to confirm if that relationship is similar to that observed in older children (aged 5–12 years; N=52) in Study UX023-CL201. Analyses groups included: the Safety Analysis Set (all patients who received at least one dose of study drug), the Efficacy Analysis Set (all patients who received at least one dose of study drug and have at least one post-study drug measurement), and the PK/PD Analysis Set (all patients who received at least one dose of study drug and have evaluable blood samples). Continuous variables were summarised with means, standard deviations (SDs), standard errors (SEs), medians, interquartile range, minimums, and maximums. Categorical variables were summarised by counts and by percentages of patients in corresponding categories. No imputation on missing data was made, unless stated otherwise. All data obtained from the case report forms (CRFs) as well as any derived data were included in data listings. Changes from baseline to post-baseline time points in PD and efficacy parameters were tested for statistical significance. Statistical tests were 2-sided at the alpha = 0.05 significance level and 2-sided 95% confidence intervals (CIs) were used. All p-values were presented as nominal p-values. No adjustment for multiplicity was made. An analysis of covariance (ANCOVA) model was applied to each RGI-C score (wrist, knee, global and lower limb deformity) and change from baseline in each RSS score (wrist, knee and total). The ANCOVA model for RSS scores included the change from baseline in RSS score as the dependent variable and age and RSS score at baseline as covariates. The ANCOVA model for RGI-C scores included the RGI-C score as the dependent variable and age and RSS at baseline as covariates. By-visit analyses using the Generalised Estimating Equations (GEE) model was applied for all PD parameters; the GEE model included change from baseline as the dependent variable, time as the categorical variable and adjusted for baseline measurement, with exchangeable covariance structure. By-visit analyses using the GEE model also was applied to recumbent length/standing height; the GEE model included the change from baseline as the dependent variable, visit and gender as factor, age and recumbent length/standing height z-score at baseline as covariates, with exchangeable covariance structure.
Primary outcomes	The primary efficacy endpoint is the change from baseline in serum phosphorus.

Study name	**UX023- CL205**
Secondary outcomes (including scoring methods and timings of assessments)	• Change in rickets as assessed by the Radiographic Global Impression of Change (RGI-C) global score at weeks 40 and 64 • Change from baseline in RSS total score at weeks 40 and 64 • Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as determined by the RGI-C long leg score at weeks 40 and 64 • Change in recumbent length/standing height from baseline to post-treatment study time points in cm, height-for-age z-scores, and percentiles based on age and gender. • Historical growth records may be used to evaluate change in growth velocity • Change and percentage change from baseline over time in serum alkaline phosphatase (ALP)
Source: CS, Table 11, pages 71-73	

Table 4.5: Demographic and baseline characteristics in studies CL201, CL002 and CL205

	CL201	Study CL002	CL205
	Q2W (n=26)	Radiographic analysis set ([redacted])	(n=13)
Age (years), mean (SD)	8.7 (1.72)	[redacted]	2.9 (1.15)
Sex, male n (%)	12 (46.2%)	[redacted]	9 (69.2%)
Race White Black/ African-American Other	 23 (88.5%) 2 (7.7%) 1 (3.8%)	[redacted]	 12 (92.3%) 1 (7.7%) 0
Weight (kg), mean (SD)	31.87 (7.92)	[redacted]	12.92 (1.81)
Height (percentile for age and gender), mean (SD)	[redacted]	[redacted]	[redacted]
Standing Height (z-score), mean (SD)	-1.72, 1.03	[redacted]	-1.38 (1.19)
Renal ultrasound score, (0 – 5 scale) – n (%) 0 1 2	[redacted]	[redacted]	NR
Number (%) of Patients Who Received Prior Conventional Therapy	24 (92.3%)	[redacted]	13 (100%)
Duration of Prior Conventional Therapy, mean (SD)	7.02 (2.14) years	[redacted]	16.7 (14.39) months
Age When Conventional Therapy Was Initiated (years), mean (SD)	[redacted]	[redacted]	[redacted]
Pharmacodynamic parameters, mean (SD) Serum Phosphorus, mg/dL TmP/GFR (mg/dL) Serum 1,25(OH)2 D (pg/mL) ALP (U/L	 [redacted]	 [redacted]	 [redacted]
Rickets Severity RSS Total Score, mean (SD)	1.92 (1.17)	[redacted]	2.92 (1.37)

Source: CS, Table 13, page 82.
a) At baseline paired radiograph (the earlier radiograph pair)

4.2.2 Details of relevant studies not included in the submission

CL301 is a multi-centre, randomised, open-label, Phase 3 study comparing the efficacy and safety of burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) who have radiographic evidence of rickets, open epiphyses, and have received oral phosphate/active vitamin D therapy for ≥ 6-12 consecutive months prior to screening. Approximately 60 patients will be randomised 1:1 to receive open-label burosumab administered by subcutaneous injection or oral phosphate and active vitamin D therapy for a total of 64 weeks.

The CS does not present any results for this study. Instead the CS mentions that: "The primary efficacy and safety analysis from study UX023-CL301 is expected to be available [redacted]".[1] According to clinicaltrials.gov,[56] the estimated primary completion date is July 2018. We asked the company whether or when any (interim) results are available for the committee to look at, and the company responded that
"[redacted]".[2]

ERG comment: Results from this study will considerably reduce the uncertainty surrounding the clinical effectiveness of burosumab relative to conventional therapy in children with XLH aged between one and 12 years.

4.2.3 Summary and critique of company's analysis of validity assessment

The formal appraisal of the validity of the included studies is reported in section 9.5 of the CS (CS, Tables C7 and C8, pages 87-93).

ERG comment: The main problem with the risk of bias of included studies is that none of these studies were designed for comparison of different interventions. CL201 was a randomised controlled trial comparing two burosumab dosing regimens (Q2W versus Q4W); however, only the Q2W arm was used to compare burosumab with conventional therapy. Therefore, all comparative evidence used in the submission was derived from single arm studies. This means the risk of bias of all included studies is high.

4.2.4 Summary and critique of results

4.2.4.1 Efficacy

The CS includes two studies of burosumab in children aged 5-12 years (Study CL201) and in children aged 1-4 years (Study CL205). and one historical control study (Study CL002) in children aged five to 14 years old.

STUDY CL201 - burosumab in children aged 5-12 years

An overview of the results for CL201 are shown in Table 4.6, alongside results from the historical reference study CL002. CL201 investigated dosing every two weeks (Q2W) and every four weeks (Q4W). The Q2W regimen is the expected licensed dosing frequency and are the only results presented here. Assessments of rickets, growth, and walking ability consistently showed greater improvement with the Q2W regimen as compared with the Q4W regimen.

Table 4.6: Outcomes from CL201 and CL002

	Q2W burosumab				Conventional therapy
	Week 40 (n=26)		Week 64 (n=26)		n=[redacted]
Endpoint	**Effect Size**	**p-value**	**Effect Size**	**p-value**	**Effect Size**
RSS Total Score % mean change from baseline[a] (negative is better)	-61%	< 0.0001	-58%	< 0.0001	[redacted]
RGI-C Global Score Mean (positive is better)	+1.72	< 0.0001	+1.62	< 0.0001	[redacted]
Substantial Healing by RGI-C % with RGI-C global score ≥+2.0	[redacted]	NA	[redacted]	NA	[redacted]
Growth Velocity Mean change, comparing pre- and post-treatment[c] (cm/year)	-	-	[redacted]	[redacted]	NR
Standing Height Z-score LS mean change from baseline[b]	-	-	[redacted]	[redacted]	[redacted]
6MWT Distance LS mean change from baseline[b] (m)	[redacted]	[redacted]	[redacted]	[redacted]	NR
Sports/Physical Functioning Scale (POSNA-PODCI) LS mean change from baseline[b] (10 = 1 SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR
Pain/Comfort Scale (POSNA-PODCI) LS mean change from baseline[b] (10 = 1 SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR

Source: CS, Table 17, page 94

NA = Not applicable; NR = not reported; 6MWT = 6-minute walk test; GEE = generalised estimation equation; LS = least squares; POSNA-PODCI = Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument; Q2W = every 2 weeks; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score

a) Percent change based on arithmetic means; p value based on GEE model.

b) LS mean and p value based on GEE model.

c) P-value based on one-sample t test on growth velocity change from baseline.

As can be seen from Table 4.6, for all outcomes that can be compared across studies, results are better for burosumab when compared to conventional treatment.

ERG comment: A naïve comparison of results from studies CL201 and CL002 is unreliable because of the differences in inclusion criteria and patient characteristics in both studies. As explained in section 4.2.1 of this report, there are important differences between the inclusion criteria in both studies. Study CL201 included children with more severe symptoms of XLH. This is also reflected in the relatively [redacted] standing height and [redacted] rickets severity score for children in study CL201 when compared to children in study CL002 (see Table 4.5).

RSS Total Score Change from baseline (Primary Efficacy Endpoint)

Table 4.7 shows the main outcomes from study CL201 for burosumab treatment at 40 weeks and 64 weeks follow up. In the Q2W group (N = 26), RSS total scores were reduced by 61% at week 40 (LS mean (SE) change: [redacted]), p < 0.0001) and by 58% at week 64 [redacted]), p < 0.0001).

In the primary analysis of the primary efficacy endpoint (overall population, N=52), RSS total score at week 40 was reduced by 50%, a statistically significant (p < 0.0001) least squares (LS) mean (SE) change of [redacted]. RSS total score at week 64 was reduced by 51%, a statistically significant (p < 0.0001) LS mean (SE) change of [redacted]. Mean (SD) RSS total scores were [redacted] at baseline, [redacted] at week 40, and [redacted] at week 64.

RSS wrist and knee scores (secondary endpoints)

[redacted] (see Table 4.7).

RGI-C Scores

Treatment for 40 weeks and 64 weeks with burosumab, resulted in healing of rickets as assessed by RGI-C scores. Mean global, wrist, and knee RGI-C scores at weeks 40 and 64 were > +1.4 in the overall group and in both treatment regimens (p < 0.0001 [GEE model]) (see Table 4.7).

Subgroup results by severity

Overall, burosumab showed better results for children with more severe baseline rickets scores. In the Q2W-treated higher RSS subgroup (baseline RSS total score ≥ 1.5; N = 17), RSS total score was reduced by 71% at week 40 (LS mean [SE] change: [redacted]], p < 0.0001) and by 62% at week 64 [redacted], p < 0.0001). In the lower RSS subgroup (baseline RSS total score < 1.5; N = 18), treatment with burosumab for 40 and 64 weeks [redacted].

In the Q2W dosing group, mean RGI-C Global Score was +2.08 (p <0.0001) in the higher RSS group and [redacted] in the lower RSS group at week 64.

Other outcomes

Walking ability, as assessed by LS mean distance walked in the six-minute walk test (6MWT), increased from baseline by [redacted] at week 64 (p [redacted]). In a subgroup with impaired walking ability (<80% of predicted normal; N = 14), the CS reported a "functionally meaningful increase in 6MWT distance of [redacted]at week 64[redacted]) to achieve normal mean values (≥ 80% of predicted normal)." Functional disability was assessed using the Pediatric Orthopedic Society of North America - Pediatric Outcomes Data Collection Instrument (POSNA-PODCI). Biweekly burosumab treatment increased scores for Sports/Physical Functioning and Pain/Comfort into the normal range seen in healthy children; LS mean scores showed improvements of [redacted] and [redacted] at week 64, respectively (see Table 4.7).

Table 4.7: Main outcomes from CL201 at weeks 40 and 64 (Q2W, ITT Analysis Set)

	Burosumab Q2W (n = 26)				
	Baseline, mean (SD)	**Week 40, mean (SD/SE*)**	**Mean change (SE), p-value[a]**	**Week 64, mean (SD/SE*)**	**Mean change (SE), p-value[a]**
RSS Wrist Score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSS Knee Score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSS Total Score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RGI-C Wrist Score[a]	NR	[redacted]	NR	[redacted]	NR
RGI-C Knee Score[a]	NR	[redacted]	NR	[redacted]	NR
RGI-C Total Score[b]	NR	[redacted]	NR	[redacted]	NR
6MWT Distance (distance walked [m])	[redacted]	NR	NR	[redacted]	[redacted]
POSNA-PODCI-Sports/Physical Functioning Scale (Normative Score)	[redacted]	NR	NR	[redacted]	[redacted]
POSNA-PODCI-Pain/Comfort Scale (Normative Score)	[redacted]	NR	NR	[redacted]	[redacted]

Source: CS, Tables 18-21, pages 97-105

6MWT = 6-minute walk test; Q2W = every 2 weeks; POSNA-PODCI = Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score

*) Results are mean change from baseline with SE for RSS and mean final value with SE for RGI-C. a) LS mean and p value per GEE model, which included visit, regimen, visit by regimen as factors, and score at baseline as a covariate, with exchangeable covariance structure. b) The RGI-C score was based on a 7-point ordinal scale ranging from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets).

In the Q2W group, mean (SD) growth velocity increased, from [redacted] cm/year at baseline (i.e., the two years before study entry) to [redacted] cm/year [redacted], one sample t-test). Mean (SD) standing height z-score increased from [redacted] at baseline to [redacted] at week 64, an LS mean (SE) change of [redacted]. Mean (SD) percentile standing heights were [redacted] at baseline and [redacted] at week 64.

STUDY CL205 - burosumab in children aged 1-4 years

An overview of the results for CL205 are shown in Table 4.8. Overall, burosumab significantly improved rickets and [redacted] and [redacted]. [redacted].

Table 4.8: Overview of outcomes from Study CL205

	Week 40		
Endpoint	**N**	**Effect Size**	**p-value**
RSS Total Score % mean change from baseline[a] (negative is better)	13	-59%	< 0.0001
RGI-C Global Score LS mean[b] (positive is better)	13	+2.33	< 0.0001
Substantial Healing by RGI-C % RGI-C global score ≥ +2.0	13	[redacted]	-
ALP % mean change from baseline[c] (negative is better)	13	-36.3%	< 0.0001
RGI-C Lower Limb Deformity Score LS mean[b] (positive is better)	13	[redacted]	[redacted]
Recumbent Length/Standing Height Mean change from baseline (cm)	13	[redacted]	[redacted]
Recumbent Length/Standing Height z-score LS mean change from baseline[d]	13	[redacted]	[redacted]

Source: CS, Table 24, page 109
ALP = alkaline phosphatase; ANCOVA = analysis of covariance; LS = least squares; GEE = Generalised Estimating Equations; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score
a) Percent change based on arithmetic means; p value based on ANCOVA model.
b) LS mean and p value based on ANCOVA model.
c) Percent change based on arithmetic means; p value based on GEE model.
d) LS mean and p value based on GEE model.

Impact of burosumab on bone mineral metabolism

Change in serum phosphorus (primary endpoint)

At baseline, all patients had serum phosphorus levels below normal, with a mean (SD) of 2.51 (0.284) mg/dL (0.81 [0.092] mmol/L) compared with the normal range of 3.2 to 6.1 mg/dL (1.03 to 1.97 mmol/L). Increases in serum phosphorus concentration from baseline were statistically significant at each study visit ($p < 0.0001$, GEE analysis). At week 40, mean (SD) serum phosphorus concentrations were 3.47 (0.485) mg/dL (1.12 [0.158] mmol/L); change from baseline to week 40 was 0.96 (0.439) mg/dL (0.31 [0.143] mmol/L).

Serum 1,25(OH)$_2$D

Burosumab treatment increased serum 1,25(OH)$_2$D levels from [redacted]. Increases in 1,25(OH)$_2$D from baseline were statistically significant at each study visit through week 40 ($p < 0.01$, GEE analysis).

Assessment of rickets

RSS total score (secondary efficacy outcome)

Burosumab treatment for 40 weeks significantly reduced rickets severity as assessed by RSS scores. RSS total score at week 40 was reduced by 59% ($p < 0.0001$, ANCOVA model) least squares (LS) mean (SE) change of -1.73 (0.132) (see Table 4.8). Mean (SD) RSS total scores were 2.92 (1.367) at baseline and 1.19 (0.522) at week 40. Similarly, RSS wrist scores and knee scores were reduced at week 40 by [redacted]), respectively.

RGI-C global score (secondary efficacy outcome)

Burosumab treatment for 40 weeks resulted in healing of rickets as assessed by RGI-C scores. LS mean (SE) values at week 40 were +2.33 (0.080) for RGI-C global scores; +2.26 (0.110) for RGI-C wrist scores; and +2.21 (0.153) for RGI-C knee scores ($p < 0.0001$ for all, ANCOVA model) (see Table 4.8).

Other outcomes

At baseline, mean (SD) serum ALP levels were 549 (193.8) U/L, well above the upper limit of normal (ULN) for the children in this study (approximately 297 to 345 U/L, depending on the age and gender of the child). Mean (SD) serum ALP levels decreased to 389 (84.2) U/L at week 20 (mean change: -24.8%) and to 335 (87.6) U/L at week 40 (mean change: -36.3%). Changes from baseline to weeks 20 and 40 were statistically significant ($p < 0.0001$).

Burosumab treatment for 40 weeks resulted in [redacted].

Mean (SD) recumbent length/standing height [redacted].

STUDY CL002 - historical control study

Impact of conventional therapy on bone mineral metabolism

At the time of the baseline radiographs, the mean serum phosphorus level in the overall group was [redacted], below the lower limit of normal (LLN, 3.2 mg/dL [1.03 mmol/L]) for children. At the post-baseline radiographs, mean serum phosphorous level [redacted].

Effect of conventional therapy on rickets

RSS and RGI-C score change from baseline

Prolonged treatment with oral phosphate/calcitriol therapy for a median of [redacted]. Changes in RSS total scores (wrist and knee combined) showed a mean [redacted] with continued treatment with oral phosphate/calcitriol therapy.

For the higher RSS subgroup of the prespecified analysis, mean total RSS decreased (improved) from [redacted] for the baseline radiographs to [redacted] for the post-baseline radiographs. For the lower RSS subgroup, mean total RSS score [redacted].

The RGI-C global score was [redacted] post-baseline for the overall population, [redacted] for the higher RSS subgroup, and [redacted] for the lower RSS subgroup, which translate to less than minimal healing of rickets over a median period of 102 weeks.

Lower extremity deformity

After long-term treatment with conventional therapy, the mean RGI-C lower limb deformity score was [redacted] for the overall group, indicating [redacted].

Impact of conventional therapy on growth

Observational data corresponding to the [redacted] paired baseline radiographs showed that many patients in this study had decreased height for age (mean [SD] standing height z-score of [redacted] After long-term treatment with conventional therapy, [redacted].

4.2.4.2 Adverse events

In their summary of the safety profile of burosumab, the EPAR states: "The most common adverse drug reaction (ADR) reported in paediatric patients up to 64 weeks was injection site reactions (57%), headache (54%), pain in extremity (42%), vitamin D decreased (28%), rash (23%), toothache (19%), tooth abscess (14%), myalgia (14%), and dizziness (11%)".[50]

Table 4.9 gives the adverse reactions observed from clinical trials. The adverse reactions are presented by system organ class and frequency categories, defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.[50]

Table 4.9: Adverse reactions reported in paediatric patients with XLH (N=65)

MedDRA System Organ Class	Frequency category	Adverse reaction
Infections and infestations	Very common	Tooth abscess
Nervous system disorder	Very common	Headache
	Very common	Dizziness
Gastrointestinal Disorders	Very common	Toothache
Skin and subcutaneous tissue disorder	Very common	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Very common	Pain in extremity
General disorders and administration site conditions	Very common	Injection site reaction

Investigations	Very common	Vitamin D decreased
Source: EMA - EPAR, Table 1, page 6[50]		

Injection site reactions: Local reactions (e.g. injection site urticaria, erythema, rash, swelling, bruising, pain, pruritus, and haematoma) have occurred at the site of injection. In the paediatric studies, approximately 57% of the patients had an injection site reaction. The injection site reactions were generally mild in severity, occurred within one day of medicinal product administration, lasted approximately one to three days, required no treatment, and resolved in almost all instances.

Skin reactions: In paediatric patients, the most frequent potential hypersensitivity events were rash (22%), injection site rash (6%), and urticaria (4%). The events were mild or moderate in severity.

Immunogenicity: Anti-drug antibodies (ADA) have been detected in a small percentage of patients receiving burosumab who had also tested positive for ADA prior to dosing; no adverse events or loss of efficacy was associated with these findings.[50]

In study CL201, one patient experienced serious TEAEs, and [redacted] (see Table 4.10). In study CL205, one patient experienced an SAE [redacted] considered unlikely unrelated to study drug. All 13 subjects (100%) experienced at least one TEAE during the study (see Table 4.10). [redacted].

Table 4.10: Summary of adverse events in studies CL201 and CL205 (Safety Analysis Set (SAS))

Category	Study CL201			Study CL205
	Burosumab Q2W (N = 26)	Burosumab Q4W (N = 26)	Overall (N=52)	Burosumab (N = 13)
AEs starting during screening period				4 (30.8%)
All TEAEs	26 (100%)	26 (100%)	52 (100.0%)	[redacted]
Serious TEAEs	0 (0.0%)	1 (3.8%)	1 (1.9%)	1 (7.7%)
Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious Related TEAE	0 (0.0%)	1 (3.8%)	1 (1.9%)	[redacted]
Grade 3 or 4 TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to study discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAE leading to treatment discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Source: CS, Tables 26 and 28, pages 116 and 120 Q2W, every 2 weeks; TEAE, treatment-emergent adverse event				

The most frequent TEAEs (>30% incidence) in study CL201 were [redacted]

[redacted]
(see Table 4.11).

The most frequent TEAEs (> 30% incidence [four or more of 13 patients]) in study CL205 were [redacted] see Table 4.11). [redacted]

Table 4.11: Treatment-emergent adverse events* by SOC and preferred term (SAS)

System Organ Class Preferred Term	Study CL201 Q2W (N = 26)	Study CL201 Q4W (N = 26)	Study CL201 Overall (N = 52)	Study CL205
Patients with any TEAE	26 (100.0%)	26 (100.0%)	52 (100.0%)	13 (100%)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis streptococcal	[redacted]	[redacted]	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	
Nasopharyngitis				[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	
Viral infection	[redacted]	[redacted]	[redacted]	
Lice infestation	[redacted]	[redacted]	[redacted]	
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Oral pain				[redacted]
Abdominal discomfort				[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	
Abdominal discomfort	[redacted]	[redacted]	[redacted]	
Abdominal pain	[redacted]	[redacted]	[redacted]	
Constipation	[redacted]	[redacted]	[redacted]	
Mouth ulceration	[redacted]	[redacted]	[redacted]	
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	
Injection site erythema	[redacted]	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]	[redacted]	

System Organ Class Preferred Term	Study CL201 Q2W (N = 26)	Study CL201 Q4W (N = 26)	Study CL201 Overall (N = 52)	Study CL205
Injection site swelling	[redacted]	[redacted]	[redacted]	
Pain	[redacted]	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	[redacted]	
Injection site pain	[redacted]	[redacted]	[redacted]	
Injection site rash	[redacted]	[redacted]	[redacted]	
Injection site bruising	[redacted]	[redacted]	[redacted]	
Malaise	[redacted]	[redacted]	[redacted]	
Respiratory thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract congestion				[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	
Sneezing	[redacted]	[redacted]	[redacted]	
Wheezing	[redacted]	[redacted]	[redacted]	
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypersomnia				[redacted]
Headache	[redacted]	[redacted]	[redacted]	
Dizziness	[redacted]	[redacted]	[redacted]	
Migraine	[redacted]	[redacted]	[redacted]	
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	
Back pain	[redacted]	[redacted]	[redacted]	
Bone pain	[redacted]	[redacted]	[redacted]	
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	
Injury poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Skin abrasion				[redacted]
Contusion	[redacted]	[redacted]	[redacted]	
Skin abrasion	[redacted]	[redacted]	[redacted]	
Fall	[redacted]	[redacted]	[redacted]	
Procedural pain	[redacted]	[redacted]	[redacted]	
Arthropod bite	[redacted]	[redacted]	[redacted]	

System Organ Class Preferred Term	Study CL201 Q2W (N = 26)	Study CL201 Q4W (N = 26)	Study CL201 Overall (N = 52)	Study CL205
Ligament sprain	[redacted]	[redacted]	[redacted]	
Thermal burn	[redacted]	[redacted]	[redacted]	
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	
Rash	[redacted]	[redacted]	[redacted]	
Dry skin	[redacted]	[redacted]	[redacted]	
Investigations	[redacted]	[redacted]	[redacted]	
Vitamin D decreased	[redacted]	[redacted]	[redacted]	
Blood 25-hydroxycholecalciferol decreased	[redacted]	[redacted]	[redacted]	
Immune system disorders	[redacted]	[redacted]	[redacted]	
Seasonal allergy	[redacted]	[redacted]	[redacted]	
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ear pain	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	
Vitamin D deficiency	[redacted]	[redacted]	[redacted]	
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]	[redacted]	
Skin papilloma	[redacted]	[redacted]	[redacted]	

Source: CS, Tables 27 and 29, pages 116 to 121
Q2W = every 2 weeks; TEAE, treatment-emergent adverse event
*) CL201: TEAEs occurring in ≥ 3 patients overall; CL205: TEAEs occurring in ≥ 2 patients.

ERG comment: Adverse events of treatment with conventional therapy have not been reported. Therefore, it is not possible to assess the relative safety and toxicity in relation to the comparator.

4.2.4.3 Deaths

No patient died or discontinued from CL201 or CL205 for any reason; all patients continued treatment on study as of the data cut-off dates.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.3.1 Methods

As stated by the company, "the burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).[1] However, the company provides both a naïve comparison and a matched comparison of the results from Study CL201 (burosumab in children with XLH, 5-12 years) and Study CL002 (conventional therapy in children with XLH, 5-14 years) by listing results in Table 17 (page 94) of the CS (see Table 4.6 in this report). As outlined in chapters 4.2.1 and 4.2.4 of this report, the naïve comparison is unreliable because of the differences in inclusion criteria and patient characteristics in both studies, particularly relating to rickets severity. Study CL201 included children with more severe symptoms of XLH. This is also reflected in

the relatively lower standing height and higher rickets severity score for children in study CL201 when compared to children in study CL002 (see Table 4.5).

In order to try and compensate for differences between the two studies, the company also performed a comparison of rickets severity outcomes (RSS and RGI-C) between burosumab (Study CL201) and conventional therapy (Study CL002) using propensity score matching (PSM). These analyses were carried out using the whole population of Study 201 and therefore included those who received burosumab at both doses (Q2W and Q4W). The company does mention that "the Q2W regimen showed a more stable increase in pharmacodynamic markers as compared with the Q4W regimen. Moreover, assessments of rickets, growth, and walking ability consistently showed greater improvement with the Q2W regimen as compared with the Q4W regimen, with no increase in AE's" (CS, page 93).[1] However, specific results for the Q4W regimen are not presented in the CS.

The company does acknowledge some limitations of using study CL002 as a comparator group for study CL201: "It was a retrospective radiograph and chart review study rather than a prospective natural history cohort, [redacted]." (CS, page 125).[1] There were also differences in patient characteristics between the two studies. The statistical analysis plan for the PSM provided by the company in the response to clarification stated that the two study populations were similar for race, ethnicity, and age at commencing conventional therapy but that "baseline rickets severity as measured by RSS is higher in the CL201 cohort compared to CL002. In addition, baseline age and gender for the two studies are not very comparable" (SAP, page 14).[57] However, they did not report the methods used to judge the comparability of the two studies (statistical testing or other methods). The ERG compared age and gender between the two study populations and did not find any statistically significant differences between them. For baseline age the mean was [redacted] for CL201 and [redacted] for CL002 giving a mean difference of [redacted] and for gender there were [redacted] in CL201 and [redacted] males in CL002 with a p-value = [redacted] (chi-squared test). However, the baseline total RSS score was significantly higher in CL201 (mean difference [redacted]. Therefore, the company used PSM to try and create a more comparable sample for the analysis of rickets severity between burosumab (using study CL201) and conventional therapy (using study CL002). The propensity score (PS) is the estimated conditional probability of being treated with burosumab compared to conventional therapy based on observed individual patient baseline covariates. A logistic regression model adjusting for baseline RSS total score, age and gender was used to estimate a PS value for each patient The PS values were used to adjust for differences between the patient populations of the two studies in the analyses in a number of different ways:

1. Inverse probability of treatment weighting (IPTW): in the analysis the data for each patient is weighted by their PS where patients on burosumab are given a weight of 1/PS and patients on conventional therapy are given a weight of 1/(1-PS). These weights were then included in an analysis of covariance (ANCOVA) model with change from baseline in RSS total score, of the final RGI-C global score as the outcome and adjusting for treatment group and baseline RSS total score. All subjects from both studies were included in the analysis (including Q4W burosumab).
2. Propensity score matching (PSM): patients receiving burosumab or conventional therapy where matched based on their closest PS values. Only patients who could be successfully matched were included in the analysis and the maximum tolerated difference for matching was 0.2 SD of the logit of the PS values [source SAP section 7.2.4].[57] After matching the two treatment groups were compared using the same ANCOVA model used in the IPTW analyses. Two matching methods were used:

- Matching without replacement: burosumab patients were matched one at a time to their closest control (conventional therapy patient). Once a conventional therapy patient was matched they were removed from the matching dataset and excluded from the analysis. To account for matching variability the matching was repeated 1,000 times and the order of patients in the burosumab group was randomly sorted.
- Matching with replacement: as there were fewer conventional therapy patients compared to burosumab patients matching with replacement was also used. Here a conventional therapy patient could be matched with multiple burosumab patients and they received higher weights in the analysis based on the number of times they were matched. The weights were included in the ANCOVA model.

4.3.2 Results

Details of the baseline patient characteristics of studies CL201 and CL002 before (original study data) and after PS weighting and matching are shown in Table 4.12 below. The study populations from the PSM were more comparable than those from the original studies, particularly with regards to the baseline RSS total score.

Table 4.12: Baseline characteristics in studies CL201 (burosumab) and CL002 (conventional therapy) in propensity score analysis

	Study assessment (not weighted)		Weighted by inverse probability of treatment		Propensity score matching without replacement in control		Propensity score matching with replacement in control	
	CL201	CL002	CL201	CL002	CL201	CL002	CL201	CL002
Sample size	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at baseline (mean [SD] years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (% female)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age when conventional therapy initiated (mean [SD] years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline RSS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wrist score (mean [SD])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Knee score (mean [SD])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total score (mean [SD])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 30, page 127

a) Burosumab subjects (Study CL201) receive a weight equal to 1/Propensity Score, and conventional therapy subjects (Study CL002) receive a weight equal to 1/(1-Propensity Score), where the propensity score is

estimated from a logistic regression model with treatment group as response (1 = burosumab, 0 = conventional therapy), baseline RSS total score and age as covariates and sex as a categorical covariate.
b) Mean sample size and results based on 1000 iterations of PS matching without replacement.
c) A conventional therapy subject could be selected to match multiple treated subjects. Conventional therapy subjects matched multiple times received higher weights based on the number of times matched.
d) All subjects from the intent-to-treat (ITT) analysis set were selected.
e) All subjects from the radiograph analysis set were selected; when more than one radiograph pair available for a subject, the pair with the duration between two radiographs taken closest to 64 weeks is selected; radiographs that were deemed as growth plates fused or partially fused were excluded from the analysis.

Figure 4.1: Differences in RSS total scores (LS mean ± SE) between Study CL201 (burosumab treatment) and Study CL002 (conventional therapy) from propensity score analyses

Figure redacted - AIC

Figure 4.2: Differences in RGI-C global scores (LS mean ± SE) between Study CL201 (burosumab treatment) and Study CL002 (conventional therapy) from propensity score analyses

Figure redacted - AIC

ERG comment: As there was no direct or indirect evidence available to compare burosumab with conventional therapy using evidence from RCTs, the evidence in the CS is based on a comparison of data from two single arm studies. Although the burosumab evidence is from a phase 2 trial, there was no control group and the randomisation was between different regimens of burosumab. The data for conventional therapy was obtained from a historical cohort study, which was different to the burosumab trial in terms of inclusion criteria and patient population. In order to try and adjust for differences between these two studies the company performed additional analyses which matched the two groups using propensity score matching. However, these analysis methods have major limitations, in that the matching can only include those variables measured in both studies. Randomisation in a clinical trial creates balanced group for both measured and unmeasured variables. In observational studies, the most important factors which are predictive of the outcome may not have been measured and any treatment comparisons using observational study data may be biased.[58]

The company only included three variables in the PSM, age, gender and RSS total score at baseline. The rationale for variable selection was not provided other than whether they seemed similar or not between the two study populations. No details were provided of how this similarity was judged. The ERG found no statistically significant differences in age and gender between the two groups and considered that only including three variables in the creation of the propensity scores may have been too few. Although the PSM groups were closer at baseline for these three variables compared to the original data, the results of the PSM analyses were very similar to those from a naïve comparison between the two study populations.

The company provided the statistical analysis programs used for the PSM analyses in the response to the clarification letter but not the data. Therefore, the ERG could not check the PSM analyses to establish that they could reproduce the results. Three different PSM methods were used and although they provided similar results it is not clear which PSM result should be considered the most reliable. The PSM analyses were only performed for rickets and not for any other relevant clinical or safety outcomes.

Due to the lack of a direct comparison between burosumab and conventional therapy and the limitations of using propensity score matching with data from two different observational studies the results of the rickets analyses presented by the company should be considered with caution. The results from CL301, a randomised controlled trial comparing the efficacy and safety of burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) are expected [redacted]. These will provide more reliable estimates for the clinical effectiveness and safety of burosumab compared to conventional therapy and should be given greater consideration than the naïve and adjusted analyses presented in the company submission.

4.4 Summary of evidence presented in other submissions

No other scientific evidence was submitted by other consultees.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work on clinical effectiveness undertaken by the ERG has been included in section 4.2.4 of this report. In addition, we will discuss the longitudinal review of patient records from three expert UK centres to provide additional data (n=43) commissioned by Kyowa Kirin as a UK alternative to CL002 which was a US study. The company provided a synopsis with details on the rationale, methodology and results of this UK study as part of the response to the clarification letter.[2]

The study included paediatric patients (up to age 18) with a confirmed diagnosis of XLH, as defined by radiological and clinical evidence of rickets, with documentation of a confirmed PHEX mutation. To be included in the analysis patients must have had at least two sequential radiographs. Study CL002 included paediatric patients with a confirmed diagnosis of XLH, but radiographic images from at least two time points taken between the ages of five and 14 years, inclusive, had to be available. Therefore, the UK study has a wider age range and is less comparable to study CL201in terms of age as can be seen in Table 4.13. However, the company does add that "the mean age at each RSS observation across the patients was 7.5 years, which is therefore similar to CL201 and CL002".[2]

Table 4.13: Demographic and baseline characteristics in CL201, CL205, CL002 and UK review

	CL201	Study CL002	CL205	UK Review
	Q2W (n=26)	Radiographic analysis set ([redacted])	(n=13)	Radiographic analysis (n=38)
Age (years), mean (SD)	8.7 (1.72)	[redacted]	2.9 (1.15)	[redacted]
Sex, male n (%)	12 (46.2%)	[redacted]	9 (69.2%)	[redacted]
Race White Black/ African-American Other	 23 (88.5%) 2 (7.7%) 1 (3.8%)	[redacted]	 12 (92.3%) 1 (7.7%) 0	[redacted]
Weight (kg), mean (SD)	31.87 (7.92)	[redacted]	12.92 (1.81)	[redacted]
Height (percentile for age and gender), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Standing Height (z-score), mean (SD)	-1.72, 1.03	[redacted]	-1.38 (1.19)	NR
Renal ultrasound score, (0 – 5 scale) – n (%) 0 1 2	[redacted]	[redacted]	NR	NR
Number (%) of Patients Who Received Prior Conventional Therapy	24 (92.3%)	[redacted]	13 (100%)	NR
Duration of Prior Conventional Therapy, mean (SD)	7.02 (2.14) years	[redacted]	16.7 (14.39) months	NR
Age When Conventional Therapy Was Initiated (years), mean (SD)	[redacted]	[redacted]	[redacted]	NR
Pharmacodynamic parameters, mean (SD) Serum Phosphorus, mg/dL TmP/GFR (mg/dL)	 [redacted] [redacted]	 [redacted] [redacted]	 [redacted] [redacted]	NR

	CL201	Study CL002	CL205	UK Review
	Q2W (n=26)	Radiographic analysis set ([redacted])	(n=13)	Radiographic analysis (n=38)
Serum 1,25(OH)2 D (pg/mL)	[redacted]	[redacted]	[redacted]	
ALP (U/L	[redacted]	[redacted]	[redacted]	
Rickets Severity				
RSS Total Score, mean (SD)	1.92 (1.17)	[redacted]	2.92 (1.37)	NR

Source: CS, Table 13, page 82 and Response to Clarification letter (Question A4)
a) At baseline paired radiograph (the earlier radiograph pair)

Data were collected from two participating UK expert centres (Birmingham Children's Hospital NHS Foundation Trust and Central Manchester University Hospitals NHS Foundation Trust). At the baseline visit (diagnosis) data were collected on patient demographics (age, date of diagnosis, ethnicity and gender), medical history, family history of XLH, basic parameters (weight, blood pressure, height and biochemical parameters (calcium [corrected], parathyroid hormone, phosphate and alkaline phosphatase)), current medications and rickets severity. At the follow-up visit (most recent) data were collected on significant events (for example, new comorbidities, fractures, hospitalisations, ectopic calcifications, orthopaedic surgery), basic parameters (as before), current medications and rickets severity.

Rickets severity was graded using the Rickets Severity Score (RSS; Thacher scores), as used in the burosumab clinical trial program. The same consultant radiologist based in Manchester provided RSS scores for all radiographs in the review.

Planned analyses and outcomes included the assessment of RSS at different timepoints, based on availability of radiographic data and assessment of patient weight by age and gender.

Results included data from 43 patients, diagnosed between June 1992 and August 2016. Of the 43 patient histories, data from 38 patients were included as they provided two radiographic scores.

The only results presented for the UK review are the data presented in Table 4.14 below. As such these data are not comparable to data reported in study CL002 and in the burosumab studies. It is unclear how comparable these data are to any of the burosumab data.

Table 4.14: Rickets status at x-rays from UK chart review, based on RSS

Year n+1 / Year n	Mild	Moderate	Severe	Healed	Total
Mild	12	5	4	3	24
Moderate	7	14	5	2	28
Severe	4	10	33	3	50
Healed	1	1	2	1	5
Total	24	30	44	9	107

Source: Response to clarification letter, question A4

The company states that "Due to the nature of a retrospective chart review, which provides RSS scores with varying time between visits, annualised estimates of changes in RSS score have not been analysed in detail. However, the transition matrices used in the cost-effectiveness model provide clear indication of the RSS progression amongst patients" (see Table 4.14).[2] "Nearly half of the x-rays conducted indicated that patients had severe rickets, as 50 of the 107 (47%) observations were from severe rickets. This is comparable to the baseline characteristics of the CL205 and CL201 studies, in which 43% of patients were severe. Half of the patients with mild rickets (RSS 0.5 or 1) did not have a significant change in RSS between visits, but in those that did, more deteriorated than improved (9 vs 3 patients). Few patients had healed rickets at any one time (9 of 107 x-rays) but the healed status appeared to be temporary as only one remained healed at the next x-ray".[2]

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The ERG is confident that all relevant studies (published and unpublished) of burosumab were included in the CS, including data from ongoing studies. The same applies to the historical control patients. A control study in UK patients was mentioned in the CS without any results being report in the CS. However, results were provided as part of the response to the clarification letter. The reporting of outcomes from included studies also seems complete.

A randomised controlled study comparing burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) is currently ongoing. [redacted].[2] Results from this study will considerably reduce the uncertainty surrounding the clinical effectiveness of burosumab relative to conventional therapy in children with XLH aged between one and 12 years.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

A key issue that may limit the robustness of the efficacy data reported in the CS relates to the study design of the included studies. Due to the absence of a control group in most studies, inference of treatment effects (including magnitude) may be confounded. As stated by the company, the "burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).[1]

For children between one to four years old, only one study is presented in which all children received burosumab (CL205). A comparison with "established clinical management without burosumab"[52] is not possible in this group of patients.

For children between five to 12 years old, the CS presents a study in which all children received burosumab (CL201). In addition, the CS presents a control study (CL002) in which children aged between five to 14 years received conventional therapy (i.e. oral phosphate/active vitamin D). Results of these two studies are mainly presented as a naïve comparison, simply reporting individual results from each study side by side. In addition, the company presents comparisons of 'rickets healing' with conventional therapy (Study CL002) versus burosumab (Study CL201) using propensity analysis matching.

In the CS, the company uses the term 'healing' and 'substantial healing of rickets'. This is defined using RGI-C global scores, where scores ≥ +1.0 indicate 'healing of rickets' and scores ≥ +2.0 'substantial

healing of rickets'. The company does explain that "Healing in this context indicates improvement in the radiographic abnormalities and does not imply that complete healing was observed" (CS, page 100).[1] However, throughout the report the term 'healing of rickets' is used without any explanation of the degree of healing (minimal, substantial or complete). Moreover, RGI-C global scores and RSS scores do not capture all clinical aspects of XLH. That is of particular importance in the context of the economic model, which only considers RSS score alone as a clinical outcome measure. The diverse physiological impacts of hypophosphataemia, which may be independent of rickets, are therefore not captured as outcomes in the economic model.

In the response to the clarification letter the company described the vignettes for the various health states that informed the economic model in detail (Clarification Letter Response Question B7, Table 10). However, each health state was defined in such a way that there appears to be a perfect association between the RSS score and other clinical descriptors of the health state. For example, as the RSS score decreases so does the risk of fracture and the presence of deformity. However, this does not appear to be realistic in that it seems likely that there might be some resolution of the bone disorder such that the RSS score decreases, but that this resolution only occurs after incurring deformity, which cannot be completely resolved and with some continued increased risk of fracture.

In addition, the model currently assumed that the effect of burosumab, although stopped at age 16 (women) or 17 (men) lasts for the rest of their lives. This also seems unrealistic, the effects of burosumab on stature, bowing of the legs, joint deformity etc. are likely to persist fairly long but may wane as osteomalacia itself and the resulting fractures may lead to associated problems in later life. Effects on bone strength will wane quicker, therefore repeated fractures and badly healing fractures after 10 or 20 years are likely to occur. Effects of burosumab on symptoms caused by hypophosphatemia itself will disappear as soon as therapy is stopped. Therefore, we have assumed in the ERG base-case that patients will experience a decline in quality of life 20 years after the end of treatment, which was operationalised by moving to the utility value of the next worse health state (see section 6.2.3 in this report).

Regarding the evidence synthesis, the naïve comparison is unreliable because there are important differences between the inclusion criteria in both studies. Inclusion criteria for patients in studies CL201 and CL002 are similar in that patients in both studies were diagnosed with XLH and were of similar age. However, children in study CL201also had: biochemical findings associated with XLH, standing height < 50th percentile for age and gender and radiographic evidence of active bone disease including rickets in the wrists and/or knees, and/or femoral/tibial bowing, or, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read. In other words, study CL002 included all children with XLH, while study CL201 included children with more severe symptoms of XLH. This is also reflected in the relatively [redacted] standing height and [redacted] rickets severity score for children in study CL201 when compared to children in study CL002.

The adjusted comparison, using propensity analysis matching, is unreliable because of the limitations associated with these methods, in that the matching can only include those variables measured in both studies. Randomisation in a clinical trial creates balanced group for both measured and unmeasured variables. In observational studies, the most important factors which are predictive of the outcome may not have been measured and any treatment comparisons using observational study data may be biased. In the CS the company only included three variables in the PSM: age, gender and RSS total score at baseline. The rationale for variable selection was not provided other than whether they seemed similar or not between the two study populations. No details were provided of how this similarity was judged. The ERG found no statistically significant differences in age and gender between the two groups and

considered that only including three variables in the creation of the propensity scores may have been too few.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The main uncertainty regarding the effectiveness evidence is the comparability of results from treated patients and historical control patients. Most of the evidence is presented as single arm studies including either treated patients (two studies, both with extensions that are still ongoing) or historical control patients (one study, with patients from one single centre, Radiographic analysis set ([redacted])). The historical control study (CL002) included patients aged from five to 14 years and can therefore only serve as a control group for study CL201 (children aged five to 12 years).

For patients with XLH aged one to four years old, the CS only presents a single arm burosumab study (CL205), no control data for this age group were provided. Only 13 children were enrolled in study CL205; therefore, results in this age group are very uncertain.

5 VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

The aim of this chapter is to provide an assessment of whether or not burosumab for X-linked hypophosphatemia (XLH) represents value for money for the NHS in England. This assessment is mainly based on the evidence submitted to NICE in the company submission and in the response to the clarification letter. This includes a cost effectiveness model, a description of the methods and assumptions used to inform the input parameters of the model, and the results of economic analyses performed using the submitted cost effectiveness model. This chapter starts with a review of existing economic analyses for burosumab either from the literature or elsewhere in the public domain. Afterwards, a detailed exposition and critique of the submitted model and economic analyses is presented.

5.2 Review of existing economic analyses

The company conducted a systematic review of cost effectiveness studies of burosumab and other studies including costs, resource use and any HRQoL measure associated with XLH. The details of the search strategy were provided in Section 17.3 of the CS.[1] A summary of the search strategy and the review process leading to the selection of relevant papers is given in the remaining parts of this section.

5.2.1 Searches

Section 11.1 of the CS states that a systematic literature review of the economic and health economic evidence on XLH was undertaken. Search strategies were reported in detail in Appendix 17.3 of the CS and in the response to clarification. MEDLINE, Embase, EconLit and the NHS Economic Evaluation Database were listed as the databases searched in the identification of economic evidence. All databases were searched from the earliest date available for each database until the end of October 2017. The searches were also intended to identify studies for health-related quality of life data and for resource identification, measurement and valuation studies.

The CS states (p.150) that grey literature was identified '*provided that the foundation for the reported findings is a study with a publicly available research protocol or is a study published in full manuscript form as an academic resource*'.[1] Three main journals in the field were hand-searched, and reference checking was carried out. Experts and clinical specialists were also consulted.

The company submission and request for clarification provided full search strategies for MEDLINE, Embase and EconLit. Strategies were not provided for NHS EED, so it is not clear if this search was undertaken.

ERG comment:

- The selection of databases searched was adequate and most searches were reproducible. The database name, host, date range and date searched were provided for the majority of the searches. A good range of additional resources were included.
- The ERG only presents the major limitations of the search strategies here. Further minor criticisms can be found in Appendix 1 of this report.
- The main concern of the ERG is that the search terms used for the population facet of the strategy were insufficient. Only one indexing (MeSH/EMTREE) term was used, combined with one free-text term. Numerous synonyms are available for X-linked hypophosphatemia and use of these terms would have increased the retrieval of potentially relevant records.

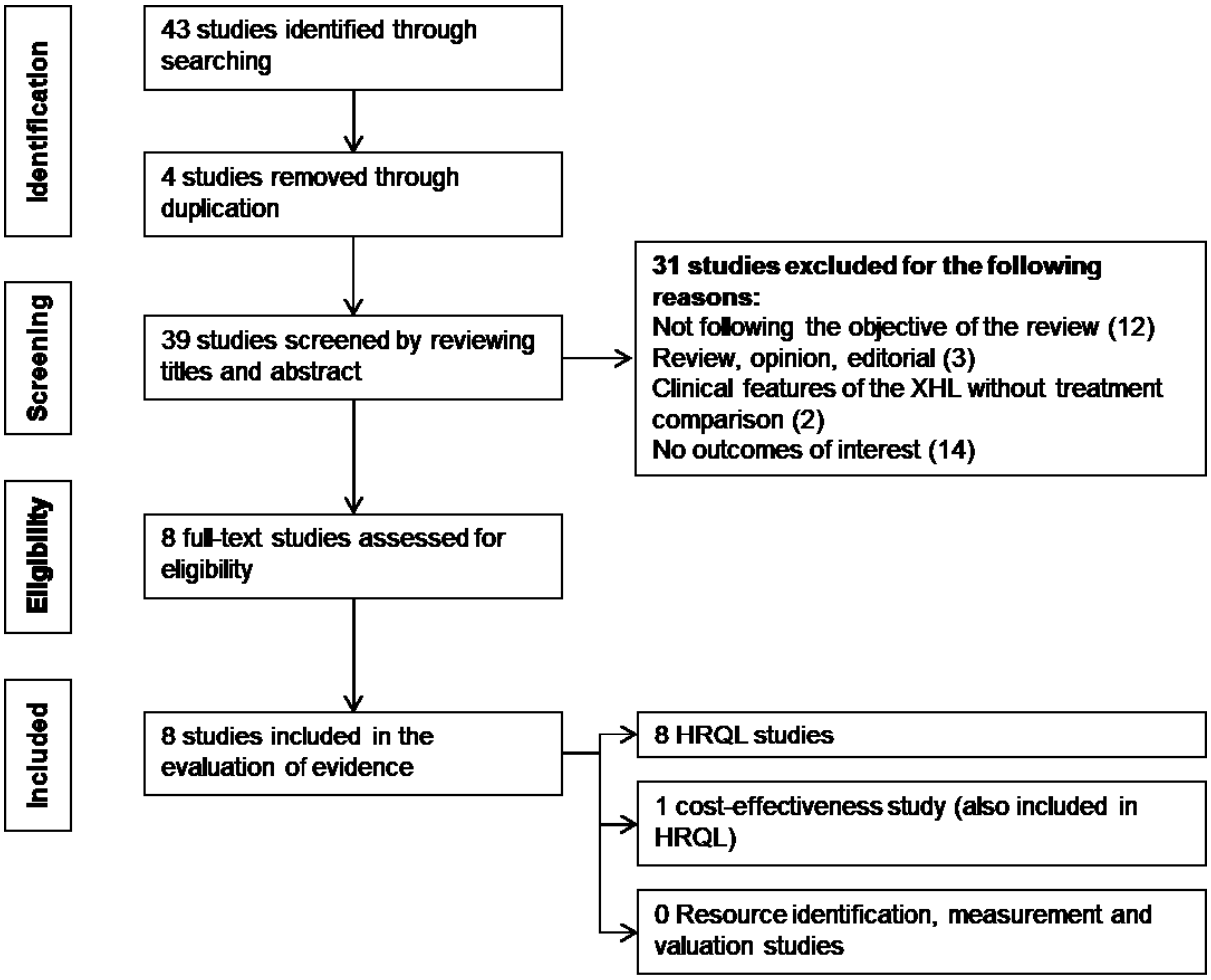
- Given the small number of papers retrieved for this topic, the ERG believes that use of study design filters in the searches was unnecessarily restrictive. The ERG suggests that a single-facet search for XLH (and additional synonyms) without a study design filter would have adequately addressed all areas of interest, including clinical effectiveness, adverse events, cost effectiveness, HRQoL and resource use, without retrieving unmanageably high numbers of records. See Appendix 1 for example MEDLINE, Embase and CENTRAL searches run by the ERG.
- The strategies provided for both MEDLINE and Embase contain repeated facets and considerable redundancy. The structure of the searches is confused; however, the final results sets appear to be correct.
- The EconLit search does not include details of the host used, database fields searched, or the number of results found. The strategy is therefore not reproducible. No strategy or results are provided for NHS EED; therefore, it is not clear whether this database was searched.

5.2.2 Review process and results

The company used broad selection criteria for the health economic evidence as reported in Table D11.1 of the company submission (CS, page 151).[1] A total of 43 publications were identified from the electronic searches. Four studies were removed due to duplication. After title and abstract screening, 31 publications were excluded as these were deemed not relevant for the research question. Thus, a total of eight full-text studies were assessed for eligibility which were included in the final evaluation of evidence. The flow of studies through the identification and selection processes is depicted in Figure 5.1.

Eight publications consisting of six studies were included in the review. An overview of the six studies is given in Section 10.1.16 of the CS.[1] The six studies were considered in terms of HRQoL but only one was related to an economic evaluation. This was the study by Forestier-Zhang et al. 2016,[59] where a cost utility simulation of 109 XLH patients (including 24 from the UK) was conducted. The paper examined various scenarios for the maximum willingness to pay threshold based on observed utility values. However, the study was not based on an economic model, considered hypothetical treatment costs, and reported only a mean EQ-5D utility (with the corresponding standard deviation), which could not be used to estimate utilities by health state in the company's model. Therefore, the study was deemed not relevant to the economic evaluation of burosumab.

Figure 5.1: PRISMA diagram for economic systematic literature review



Source: Response to clarification letter, Figure 1.[2]

ERG comment: Quality assessments, like the assessment criteria list from Drummond and Jefferson 1996,[60] for the identified studies were not included in the CS. Nevertheless, the ERG concurs that none of the identified studies are relevant to the economic evaluation of burosumab.

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

The company submission included a model-based cost-utility analysis comparing the use of burosumab with standard of care to treat patients with XLH. The patient population included in the economic evaluation were XLH patients with radiographic evidence of bone disease aged one year or older with growing skeletons. Subgroups of patients were not considered. Based on growth charts it was determined that in the UK growth is completed at the age of 16 in females and 17 in males. Therefore, treatment with burosumab was assumed to be continued until this age in the model.

Burosumab is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the activity of FGF23. By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney and through the production of 1,25(OH)2D enhances intestinal absorption of calcium and phosphate. Burosumab improves phosphate homeostasis and its major pathologic consequences (rickets and osteomalacia), and consequently aims to resolve the skeletal and non-skeletal manifestations of XLH. Standard of care (SoC) treatment is the only comparator considered in the analysis and consists

of systematic oral phosphate supplements and active vitamin D analogues in the form of alfacalcidol A, or oral or injectable calcitriol.

The economic evaluation was conducted from the perspective of the NHS and PSS in England. The model estimates cost and health consequences over a lifetime time horizon for a cohort of patients with XLH aged one to 12 years at the beginning of the simulation. The cycle length of the model is one year. The outcomes of the model are the estimated incremental QALYs, the incremental costs and the incremental cost effectiveness ratio (ICER) associated with burosumab vs. SoC for treating XLH. Cost and health outcomes are discounted at a rate of 1.5%.

ERG comment: The scope of the economic evaluation is generally in line with the scope developed by NICE. Deviations in the company's decision problem were discussed in section 3.3 of this report. The adherence of the scope of the economic evaluation to the NICE reference case was also assessed by the ERG, and it is shown in Table 5.1 below.

Table 5.1: Adherence to the reference case principles relevant to highly specialised technologies

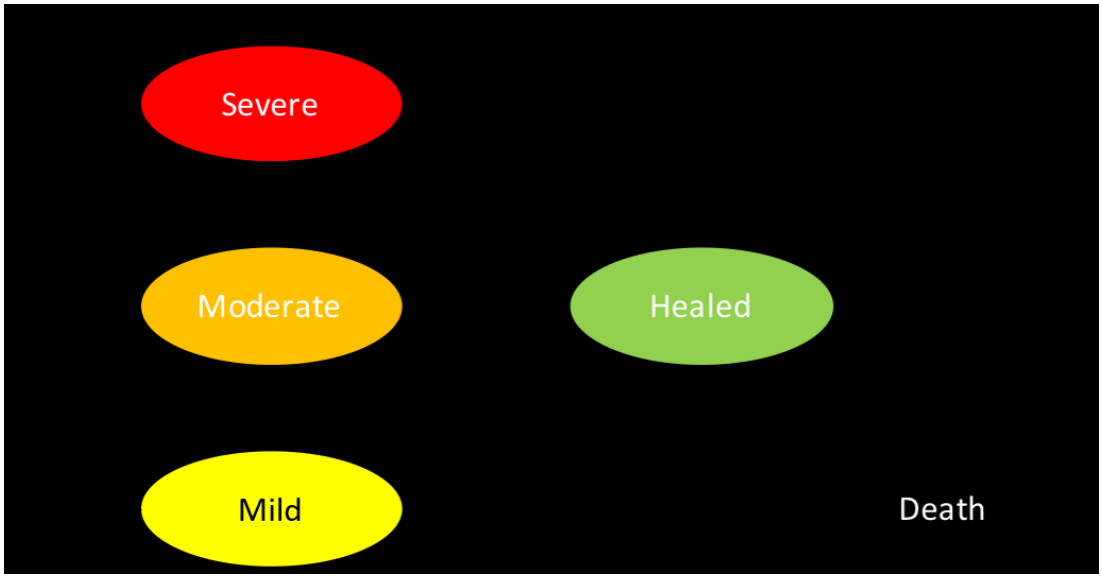
Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE	The scope of the economic evaluation is generally in line with the scope developed by NICE. Deviations were discussed in Section 3.3 of this report.
Comparator	Therapies routinely used in the NHS, including technologies regarded as the current best practice	Standard of care (SoC) is the only comparator considered. It is the established clinical management without burosumab (systematic oral phosphate supplements and active vitamin D analogues in the form of alfacalcidol A, or oral or injectable calcitriol).
Perspective on costs	NHS and PSS	NHS perspective was adopted.
Perspective on outcomes	All health effects on individuals.	Patient health benefits were included in the model. Benefits to other afflicted individuals (e.g. caregivers) were not included in the model but discussed qualitatively in the company's submission (CS Chapter 14).
Type of economic evaluation	Cost-effectiveness analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Based on a systematic review	Meta-analysis was not used, as there is no direct or indirect evidence of the effectiveness of burosumab vs. SoC available. Effectiveness data was

Element of economic analysis	Reference case	ERG comment
		obtained from single-arm studies.
Measure of health effects	QALYs and life years	Health benefits are valued in terms of life years and QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	No, the utility values associated with the model's health states were derived from a vignette study conducted with 6 UK XLH clinical experts. The valuation was based on EQ-5D, which is the NICE standard.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects.	No, costs and outcomes were discounted at 1.5%.
Equity weighting	An additional weighting can be applied for incremental QALYs above 10 years.	No additional equity weighting is applied to QALY gains.

5.3.2 Model structure

An Excel-based Markov model was developed by the company to perform the economic evaluation of burosumab for treating XLH patients in the UK. The model simulates the disease progression of XLH by using the Rickets Severity Score (RSS) as a surrogate for disease severity, which defines the different health states of the model, in patients treated with either burosumab or SoC. The impact of the disease is translated to lifetime costs and QALYs in the submitted cost effectiveness model. The model consists of four (mutually exclusive) health states representing different rickets severity levels (healed, mild, moderate, and severe) and a death state. The severity levels are defined based on the RSS, a radiographic scoring method developed to assess the severity of nutritional rickets. It scores abnormalities in the wrists and knees and is defined on a scale between 0 and 10. Healed rickets correspond to an RSS equal to 0, mild rickets correspond to an RSS between 0.5 and 1.0, moderate rickets correspond to an RSS between 1.5 and 2.0, and severe rickets correspond to an RSS larger or equal than 2.5. Transitions from every alive health state to any other alive health state are allowed in the model. Additionally, patients can move from any of the alive health states to the death state. The relation between the RSS and HRQoL and the choice of cut-offs on the RSS to define meaningful health states was based on a consensus from clinical experts. Figure 5.2 provides the graphical representation of the conceptual model as presented by the company.

Figure 5.2: Model structure as presented by the company.



Source: CS, Figure 24.[1]

It is acknowledged by the company that basing the model structure on the RSS is a limitation of the analysis because:

- Rickets and RSS do not capture all aspects of XLH symptoms and progression. Whilst rickets is the hallmark manifestation of XLH, given the heterogeneity of the condition there is a chance that someone with mild rickets may have more severe additional manifestations.
- RSS is scored independently (not compared to previous x-rays) which may result in inconsistencies in RSS scores between time points that are used to generate transition probabilities.
- The RSS can be complemented by other measures like RGI-C (as in CL201) which provides a comparison to baseline (previous x-rays). RGI-C scores are positive if there is an improvement (+3 if healed, -3 if worsening) compared to baseline. A patient showing no improvement in RSS could experience an improvement or worsening in RGI-C indicating that the patient did or did not benefit from treatment. However, this cannot be captured in the model. However, whilst the RGI-C gives an indication of change in status, it does not indicate the patient status so cannot be used to generate health states.

Despite the limitations mentioned above, the company indicated that the RSS measure provides a reasonable indication of patients' overall XLH health status because:

- Stratifying patients according to these definitions of severity reflected the reduced quality of life of the patient. Thus, the RSS is correlated with HRQoL.
- The model is built in such a way that patients in the healed rickets health state accrue costs for surveillance and drug treatment; patients in the mild rickets health state are assumed to experience additional pain and mobility problems, and associated costs; patients in the moderate and severe health states are assumed to incur orthopaedic intervention costs (in addition to costs from less severe health states). Thus, the RSS is also correlated with costs.
- Rickets severity is the primary endpoint of clinical studies as in CL201.
- In CL201 no patient's rickets worsened according to the definitions of the health states used in the model based on RSS. In addition, it was also observed that no patients' rickets worsened at Week 64 in the study, as all RGI-C scores were positive, as shown in Table 32 of the CS.[1]

Therefore, whilst the RSS is a limited measure, in CL201 it seemed to capture the treatment effect as measured by the RGI-C as well.

Transitions between the alive health states are age dependent for the burosumab arm, where two different transition probability matrices are used depending on whether the patient age is one to four years or five years and older. Transitions between the alive health states for the SoC arm are not age dependent. Only background mortality is included in the model as, according to the company, XLH is not associated with an additional mortality risk according to the available evidence. Thus, age and gender-specific background mortality risks are estimated from UK life tables. The model has a lifetime time horizon and adopted the perspective of the NHS in England. A cycle length of one year (52 weeks) with a half-cycle correction was used. The company used a discount rate of 1.5% per year for costs and effects since, according to the company, on the basis of the evidence presented, the long-term health benefits are likely to be achieved.

ERG comment: The main issues identified by the ERG within the model structure are first summarised in Box 5.1, and these issues are elaborated on afterwards.

Box 5.1: Main issues identified within the model structure in company's economic analysis

1. Appropriateness and comprehensiveness of using RSS to define health states
2. Difference of the effects of burosumab and SoC on patients younger than age five and patients older than age five.
3. Baseline weight, age and disease severity distribution
4. Appropriateness of discount factor
5. Lack of any treatment/disease related adverse events
6. Appropriateness of assuming "full recovery" in the healed rickets health state

1. Appropriateness and comprehensiveness of using RSS to define health states

The clinical rationale behind the definition of the health states in the cost effectiveness model based on the rickets severity was unclear for the ERG (healed rickets (RSS 0), mild rickets (RSS 0.5 and 1.0), moderate rickets (RSS 1.5 and 2.0) and severe rickets (RSS 2.5 or greater)). Since the RSS scale typically extends to 6.5 in a real-world XLH setting (as described on page 41 of the CS), the ERG questioned the appropriateness of allocating a RSS change of 0.5 between the first three states (healed, mild and moderate rickets) while allocating a RSS change of 4.5 (2.0 to 6.5) to the final state (severe rickets). (Question B13 in response to the CL[2]).

In their answer to the request for clarification, the company referred to pages 155-156 of the company submission[1] and the study by Mäkitie et al. 2003,[61] where rickets were graded as normal, normal/mild, mild, mild/moderate, moderate, moderate/severe, or severe rickets. Based on clinical expert opinion, the health states used in the model were simplified to healed, mild, moderate, or severe based on RSS scores. Mäkitie et al. described severe rickets as acrosteolysis, periosteal resorption, severe deformity of long bones, and/or pathological fracture. Patients with these manifestations of X-ray characteristics are most likely to be scored as 2.5 and higher. The company also indicated that resource utilisation and quality of life for patients with RSS equal to 2.5 are not expected to differ significantly compared to patients with higher RSS scores, thus yielding the definition of the severe health state in the model. Healed rickets corresponds to an RSS equal to 0. According to the RSS algorithm described in Table 6 of the CS,[1] RSS scores have intervals of 0.5.[6] Thus, the definition of mild and moderate health states had to cover the interval of RRS 0.5 to 2.0, for which an equal distribution over these health states was

assumed. Hence, the mild health state was assumed to be an RSS of 0.5 or 1 and the moderate health state was assumed to be an RSS of 1.5 or 2. Note that given this allocation, an average RSS of 1.4 would be interpreted as mild rickets, whilst an average RSS of 2.3 would be interpreted as moderate rickets.

Despite the acknowledgement by the company of the limitations of the RSS to define health states, they still assert that RSS is associated with both utility and cost, i.e. if RSS increases then so should cost and utility should decrease in a predictable way. However, as alluded to in Section 3.3.4 above and in some detail in Section 5.3.3.3 below, utilities were estimated from vignettes assuming an association between RSS and clinical characteristics that lack face validity. In particular, it is likely that RSS can improve and indeed rickets appear to be healed, but for there to be residual deformity and increased fracture risk. Since deformity and fracture risk would likely be negatively associated with utility, defining health states only by RSS is likely to overestimate any improvement due to burosumab in moving to states with a lower RSS.

2. Difference of the effects of burosumab and SoC on patients younger than age five and patients older than age five.

The health effects of burosumab are assumed to be age dependent since one set of transition probabilities was used for patients aged one to four years (CL205), whilst another set of transitions was used for patients aged between five and 12 years of age (CL201). In absence of any other source of evidence, the latter transition probabilities were also used for patients between the age of 12 and 17. From age 18 and onwards, it was assumed that patients would remain in their current health state until death occurs. For the SoC arm, the same set of transition probabilities (either the UK chart review or CL002) was used for all ages. The ERG had concerns about the different assumptions made by the company regarding the operationalisation of treatment effects in the model.

When this issue was brought up in the clarification letter (Question B17[2]), the company reiterated that transition probabilities are age dependent for burosumab but according to the ERG this answer lacked a proper justification. It seems that this assumption was made only based on the available data (CL205 for patients aged one to four and CL201 for patients aged five to 12). However, it is still unclear whether the distinction between ages 1-4 and 5-12 is due to different manifestations of the disease in those age groups or due to a different treatment effect of burosumab. If the former is correct, then a different transition probability matrix should have been used for patients 1-4 in the SoC arm as well. It should also be noted that the probabilities derived from CL205 are based on a total 13 patients only, and the probabilities derived from CL201 on a total of 26 patients. Therefore, the ERG considers that assuming such a distinction in effects between these two age groups is at least uncertain.

Transition probabilities for patients aged between five and 12 years were used for patients between the age of 12 and 17. Whilst this might be a good proxy, it is not based on any evidence. The company showed in an alternative scenario that, combining data from both age groups to estimate one set of transition probabilities for burosumab patients to be used for all ages (between one and 17), the ICER was minimally increased. Therefore, using two sets of transition probabilities for burosumab rather than one had a minimal impact on the ICER. This scenario assumed that there is no age dependent treatment effect of burosumab. However, as mentioned above, it is uncertain whether this is the case or not. Thus, a relevant additional scenario, using two different transition matrices for the SoC arm for the two age groups, could have been presented (provided that these two separate matrices could have been estimated). In such scenario, the ERG would not expect a major impact on the ICER, but the uncertainty around the model results (as presented in a PSA) would be increased.

3. Baseline weight, age and disease severity distribution

It was not clear to the ERG what the company's rationale was to select the data sources used to derive baseline weight, age and disease severity level distribution of XLH patients. Demographic parameters should be representative for the patient population expected to be treated in clinical practice, i.e. UK XLH patients. Although data from the UK chart review were available (see section 4.5 of this report), the company did not use this data source to inform the demographic parameters of the model. In the response to the clarification letter (Question B5),[2] the company indicated that due to the nature of the chart review, i.e. a retrospective study including patient histories following diagnosis, this was not considered indicative of the starting age and rickets severity distribution. Thus, combined data from CL201 and CL205 were used as proxy. Furthermore, the company compared the weights of the patients included in the UK chart review to the weights of the UK general population. Figure 2 and 3 in the response to the clarification letter suggested that the weight of XLH patients in the UK chart review was comparable to the weight of the UK general population, especially for males.[2] Females in the UK chart review seem to weigh more than females in the UK general population.

4. Appropriateness of discount factor

The ERG considers that the costs and health effects should have been discounted at a 3.5% rate, rather than at 1.5%. The NICE Technology Appraisal Methods Guide specifies that a rate of 1.5% could be considered by the Appraisal Committee if the achievement of long-term benefits is highly likely.[62] However, it is not specified that a rate of 1.5% should be applied in the base-case analysis.

The ERG considers that it is not clear from the submitted evidence that treatment with burosumab restores patients, who would otherwise die or have a very severely impaired life, to full or near full health. Throughout the CS, it is mentioned that XLH is not associated with additional mortality, and for that reason the model only considers background mortality. Thus, even though the model indicates that patients treated with burosumab will spend most of their lifetime in the healed rickets health state, it is uncertain to what extent this can be seen as full health, as discussed in section 3.3.4. More importantly, as discussed in section 3.3.4 as well, it is also uncertain whether these effects will be maintained lifelong. Therefore, the ERG will apply a 3.5% discount rate in the ERG base-case but will present a scenario analysis with a discount rate of 1.5%.

5. Lack of any treatment/disease related adverse events

Adverse events (AEs) were not included in the base-case analysis on the basis that the AEs observed in the trials are "typical for paediatric population" or frequent manifestations of the disease but not treatment related. In response to the clarification letter (Question B6 – Table 9[2]), the company presented all the treatment-emergent adverse events (TEAEs) occurring in study CL201 and classified them as typical for a paediatric population, frequent manifestation of XLH or related to treatment administration. Only "injection site reactions" were identified as related to treatment administration and were thus included as an AE in the model. AEs classified as manifestations of the disease should be captured by the model. However, the UK chart review and CL002 did not include any safety data and therefore the company did not have any evidence that could be used to model AEs in the SoC arm. Note that the AEs classified as manifestations on the disease are likely to be related to the severity of the disease. Thus, patients in more severe health states (higher RSS) are expected to experience more (or more severe) AEs. As mentioned above, only "injection site reactions" were included in the model as burosumab-related AEs, although not in the base-case analysis. Furthermore, this was considered in terms of costs only, but not in the utility calculations. The company indicated that any disutilities associated to the comparator treatments (active vitamin D and oral phosphate) are expected to be higher than those associated with burosumab (given that many children find them unpalatable). However, this statement was not based on any evidence. Furthermore, since the comparator treatments are given daily,

whereas burosumab is an injection bi-weekly, the company considers it likely that treatment-related disutilities are greater in the comparator than the burosumab arm. Finally, the company mentioned that compared to the costs and health effects currently incorporated in the model, it is likely that the inclusion of adverse events would have relatively modest impact on the model results. While the ERG agrees with the latter statement and acknowledges the challenges of incorporating AEs into the model given the available evidence, it also thinks that not incorporating AEs to the model adds an additional level of uncertainty that should be taken into account when assessing the model results.

6. Appropriateness of assuming "full recovery" in the healed rickets health state and lifelong treatment effects for burosumab

As mentioned above, the ERG considers that defining health states by RSS is likely to overestimate any improvement due to burosumab in moving to states with a lower RSS. In addition, as explained in section 4.6.2, the model currently assumed that the effect of burosumab lasts for the rest of the patients' lives, which seems to be unrealistic. Therefore, in the ERG base-case it was assumed that patients will experience a decline in quality of life 20 years after the end of treatment, which was operationalised by moving to the utility value of the next worse health state (see section 6.2.3 in this report).

5.3.3 Evidence used to inform the company's model parameters

Multiple sources of evidence were used to inform the parameters of the economic model. A summary of the evidence used to inform each group of parameters in the model is presented in Table 5.2.

Table 5.2: Summary of evidence sources used to inform key parameter groups in the company's model

Parameter group	Source of parameter values
Initial patient distribution (age, sex, weight, disease severity)	The distribution of gender and a joint distribution of age and disease severity were based on the baseline patient characteristics in the two clinical studies of burosumab (CL201 and CL205). General population weight data (UK growth charts) were used for the weight distribution.
Transition probabilities between alive states (disease severity states)	Transition probabilities for burosumab were derived from the clinical studies CL201 and CL205. SoC transition probabilities were derived from a UK chart review in the base-case and from the study CL002 in a scenario analysis. More details of these studies are shown in **Error! Reference source not found.**.
Mortality	Mortality rates were obtained from the national life tables for England, for the period 2014 to 2016, as published by the Office of National Statistics. [9]
Health related quality of life	Utility values for the health states were derived from a vignette study conducted by the company.[63] Additionally, age specific multipliers were used based on the general population.[64]
Burosumab treatment costs	The price of burosumab was provided by the company. For monitoring, resource use was based on expert opinion, while unit costs were taken from NHS reference costs.[65]

Parameter group	Source of parameter values
Standard of care treatment cost	Dosing was based on guidelines and the summary of product characteristics. Unit costs were taken from the BNF (source electronic model).[2]
Health state costs (both treatment alternatives)	For the costs of surveillance, resource use was based on expert opinion and unit costs were taken from NHS reference costs.[65] Physiotherapy resource use was based on expert opinion and a Che et al.,[66] and unit costs taken from PSSRU.[67] A number of different sources were used for the orthopaedic intervention costs. Resource use was based on prevalence observed in one of the clinical studies of burosumab (CL201), Che et al.[66] and Skrinar et al.,[68] as well as expert opinion and assumptions. Unit costs were mostly taken from NHS reference costs,[65] apart from unit costs for osteotomy, which were based on the study by Smith.[69]

An overview of the characteristics of the main clinical studies which were used to inform model parameters are listed in **Error! Reference source not found.**. No evidence from an RCT in which urosumab was compared to placebo or other relevant comparator was available. Therefore, data from separate studies were used as evidence to inform treatment effects of burosumab (two phase 2 clinical trials for different age cohorts) and standard of care (two chart review studies). These studies enrolled different populations and differed in duration of follow-up. Mortality was assumed to be the same in both treatment alternatives.

Table 5.3: Overview of studies used to inform parameters of the Markov model

Study identifier	Type of study	Evidence used in model	Number of patients	Observation interval*
CL205	Phase 2 clinical trial	Clinical effects of burosumab in children aged 1-4 y.	13	40 weeks
CL201	Phase 2 clinical trial	Clinical effects of burosumab in children aged 5-12 y.	52	64 weeks
UK chart review	Retrospective chart review	Clinical effects of standard of care.	34	Varying
CL002	Retrospective chart review	Clinical effects of standard of care.	[redacted]	2 years

* Observation interval of data used to inform model parameters
For more detailed information of the patient characteristics see Table 4.13 of this report.

5.3.3.1 Transition probabilities

Transition probabilities for standard care

A chart review study on RSS measurements conducted in the UK was used to inform transition probabilities for the standard of care alternative. Patients in this study were examined at varying time intervals. Two different approaches were employed to deal with the interval censored nature of these data. The first one assumed the last observed RSS value persisted until the next observation (i.e. if RSS=1 at Year 1 and RSS=2 at Year 3, then it was estimated that at Year 2 RSS=1), referred to as last observation carried forward (LOCF). This was used in the company's base-case. The second approach assumed a constant linear change in RSS between two time points (i.e. if RSS=1 at Year 1 and RSS=2 at Year 3, then it was estimated that at Year 2 RSS=1.5). This was included as a scenario analysis.

Observations more than three years apart were excluded from the analyses. The resulting transition probabilities for the SoC arm assuming LOCF and linear change can be seen in Table 5.4 and Table 5.5, respectively.

Table 5.4: Transition probability matrix between alive health states for standard of care treatment in base-case (estimated using last observation carried forward)

	Mild	Moderate	Severe	Healed
Mild	70%	11%	9%	9%
Moderate	18%	69%	10%	4%
Severe	5%	12%	79%	4%
Healed	7%	7%	14%	71%
Source: Table 42 in the CS.[1]				

Table 5.5: Transition probability matrix between alive health states for standard of care treatment in scenario analysis (estimated using linear change assumption)

	Mild	Moderate	Severe	Healed
Mild	51%	21%	16%	12%
Moderate	24%	52%	17%	7%
Severe	7%	19%	68%	6%
Healed	20%	20%	40%	20%
Source: Table 44 in the CS.[1]				

In a scenario analysis, the company derived transition probabilities for the SoC arm from the CL002 study.[1] This study acted as a comparison cohort for the burosumab treated population in study CL201 (thus, for patients aged five years or older).[37] During clarification, the company corrected a methodological error made when estimating this transition matrix. Therefore, the probabilities shown in Table 5.6 were obtained from the electronic model submitted by the company with the response to the clarification letter.[2]

Table 5.6: Transition probability matrix between alive health states for standard of care treatment in scenario analysis (based on CL002 data)

	Mild	Moderate	Severe	Healed
Mild	78%	7%	4%	11%
Moderate	22%	75%	4%	0%
Severe	0%	63%	37%	0%
Healed	29%	29%	0%	41%
Source: Electronic model (after clarification).[2]				

The company chose the UK chart review to derive transition probabilities for the base-case for two main reasons: it provided a better representation of the UK patient population and treatment practices (since CL002 was conducted in the US), and it was based on a longer follow-up with (on average) more observations per patient.

Transition probabilities for burosumab

Transition probabilities for the burosumab arm were estimated from two phase 2 clinical trials, one enrolling patients aged one to four years (CL201), and one enrolling patients aged five to 12 years

(CL205).[70] Since the company assumed that the treatment effect of burosumab on RSS was not the same in both trials, in the model each trial result was applied to those patients that better matched the trial population. Thus, the company assumed in the model that all patients under five would achieve the treatment effects as observed in CL205, and all patients aged five years and over would achieve the treatment effects as observed in CL201. The same methodological error mentioned above for CL002 in the SoC arm, was also corrected by the company for these transition matrices. Therefore, the probabilities shown in Table 5.7 and Table 5.8 were also obtained from the electronic model submitted by the company with the response to the clarification letter.[2]

Table 5.7: Transition probability matrix between alive states for burosumab treatment in patients aged 1one to four years

	Mild	Moderate	Severe	Healed
Mild	100%	0%	0%	0%
Moderate	59%	41%	0%	0%
Severe	50%	50%	0%	0%
Healed	0%	0%	0%	100%
Source: Electronic model (after clarification).[2]				

Table 5.8: Transition probability matrix between alive states for burosumab treatment in patients aged five years and older

	Mild	Moderate	Severe	Healed
Mild	57%	0%	0%	43%
Moderate	37%	52%	0%	12%
Severe	53%	25%	14%	8%
Healed	0%	0%	0%	100%
Source: Electronic model (after clarification).[2]				

ERG comment: The ERG does not agree with the methodology used by the company to estimate the transition probability matrices presented above. The data sources used to inform transition probabilities in the model have different observation periods (40 weeks in CL205, 64 weeks in CL201 and 104 weeks in CL002). Since the model assumed a cycle length of one year, the problem at hand was to estimate the three corresponding transition probability matrices for a different time scale (52 weeks). This was done by the company following the four steps below, as indicated on page 163 in the CS: [1]

1. Generate 40-week, 64-week, two-year and three-year transition probability matrix (based on the observe data).
2. Convert the probabilities to rates and annualise, using the formula *rate = – ln(1 – probability) / time*
3. Convert the annualised rates back to transition probabilities, using the formula *probability = 1 – exp(– annualised rate)*
4. Proportionally adjust the probabilities such that each row of the transition probability matrix equates to one.

In the recent review paper by Olariu et al. 2017,[71] the approach used by the company is summarised as well as the problem that may arise from using that approach. Thus, in order to change the time scale of a probability, the company first converted it into a rate using the formula indicated in step two above, and then calculated the re-scaled probability using the formula in step three. This is a (correct) well-known approach.[72-74] However, when a model has more than two health states, as it occurs with the

company's model, the formulae above introduces bias because these ignore competing risk between the health states of the model. This bias can have significant impact on the model results and therefore it should not be ignored.[75] A correct way to overcome this potential issue requires taking a certain root of the transition probability matrix. This method is not new, as it was described (at least) in the paper by Craig and Sendi in 2002.[76] Taking the root of a matrix is not always possible. As an alternative, Chhatwal et al. 2016 developed an algorithm to approximate such a matrix.[75] Another alternative approach would consist of choosing shorter cycle lengths in the model. That way the probability of multiple events occurring during one cycle would be reduced, thus minimising the bias.[77]

The issue described above was raised by the ERG in the clarification letter (Question B16) where the paper by Chhatwal et al. was indicated as reference.[2] However, the company did not attempt to re-estimate the transition probability matrices as suggested by the ERG. Instead of that, the company performed an exercise to quantify how large the impact of using the incorrect transition probabilities would be.

In the response to Question B16, the company made a few statements that the ERG would like to discuss. The company indicated that Chhatwal et al. "*presented an alternative approach based on finding the root of a transition probability matrix using eigendecomposition, or where that fails, a numerical approximation method*".[2] The ERG would like to emphasise that the "alternative" method of finding the root of a transition matrix is not new in the field of health economics since there is published literature on this method dating back to at least 2002.[76] The numerical approximation method seems to be indeed new. According to the company, the "*proposed methods require complex computational approaches in software such as MATLAB or Mathematica, neither of which are commonly used in economic evaluations*".[2] The ERG does not agree with this quote. Calculating the root of a matrix does not require the software mentioned by the company. In fact, the ERG has used R (as shown in Appendix 2 of this report), which is accepted by NICE. While it is true that the algorithm by Chhatwal et al. was developed in MATLAB/Mathematica, this does not mean that it cannot be translated into other language like R or VBA. In any case, "translation" was not needed because their algorithm is available online and could have been used by the company following the instructions in the link below:

http://www.mgh-ita.org/ita-tools/online-modeling-tools.html

Furthermore, the company indicated that "*despite this article being published in July 2016, no NICE appraisals have required application of this more advanced technique, rather than the commonly used method as used for the burosumab model*".[2] The ERG would like to emphasise again that this method is not new in the field of health economics. Given that it was published at least in 2002, it seems unlikely that this approach was not considered in previous NICE appraisals, although, given the time constraints, the ERG could not check this point. However, even if that would be the case and this technique was not used before in NICE appraisals, the ERG considers the company's argument still invalid since errors should be corrected at the time they are discovered independently of what has happened in the past.

Finally, the company concluded their response to Question B16 by stating that "*the approach to derive one-year transition probabilities from the trial observations seems to be valid and a multi-variate version is not required*".[2] The ERG does not agree with this statement. The company's approach is still invalid and a correct methodology, as explained above, is required. What the company has shown is that the impact of using the incorrect transition probability matrices in the model results is expected to be minor/moderate. This might be the case since the transition probability matrices are applied in the model for a relative small number of cycles.

The ERG preferred transition probability matrices are presented in section 6.2.1 of this report. The derivation and a detailed explanation of the methods used to derive these matrices can be found in Appendix 2 of this report.

5.3.3.2 Mortality

Since there is no evidence suggesting that XLH might reduce life expectancy, only age and gender specific background mortality was included in the model. Mortality rates were obtained from the national life tables for England, for the period 2014 to 2016, as published by the Office of National Statistics.[9]

ERG comment: In the clarification letter, the ERG asked the company (Question B12) about the plausibility that patients with more severe clinical manifestations of the disease were likely to have a significant reduction in life expectancy compared to an "average" UK patient. The company did not consider this implausible given the increased risk of fractures with XLH and the association between hip fractures and mortality in older healthy adults. Nevertheless, the company emphasised that there are no published articles providing evidence of this, justifying thus the assumption in the model that there is no excess mortality risk associated with XLH. In any case, the company explored an additional cost effectiveness scenario where patients in the severe health state of the model had twice the risk of dying from age 50 years and older. In that scenario, the ICER was reduced by 1% compared to the company's base-case ICER.

5.3.3.3 Health-related quality of life

The clinical trials identified by the company did not include health-related quality of life (HRQoL) measures that could be used in the economic analyses. Two studies conducted by the company included SF-36 data, but these studies did not rely on RSS (or other measures of severity). Therefore, these data could not be used to inform the company's model.[78, 79] Furthermore, as mentioned in section 5.2.2, the company did not identify any HRQoL results in the literature that could be used in the model. Thus, the company conducted a vignette study to elicit utility estimates for the health states defined in the cost effectiveness model (e.g. based on RSS). A proxy valuation of the health states with UK clinical experts was undertaken, where the experts were asked to imagine a patient as described by the vignette and to rate the impact of the health state on HRQoL by filling out the EQ-5D-5L.

Case histories (vignettes) were defined in terms of RSS and age and were created based on qualitative published studies and a series of five interviews with clinical experts. In total, 12 case histories were developed, based on four severities of rickets as defined by RSS in line with the cost effectiveness model (healed, mild, moderate and severe) and three different age categories (one to four years old, five to 12 years old and 13 years and older). The health states were validated and valuated in a series of interviews with six UK clinical experts. However, two experts did not assess the severe health state because they had no experience with patients in that condition. For each case history, the experts were asked to value the impact of the disease on different aspects of HRQoL using EQ-5D-5L. Then, the mapping algorithm developed by Van Hout et al., 2012 was used to generate EQ-5D-3L utilities.[80] Full details of the study are available in a report.[63]

The derived utilities can be seen in Table 5.9. Utility scores ranged from 0.462 (severe rickets in patients 13 years and older) to 0.969 (patients five to 12 years old). The company assumed that the utilities derived for adolescents aged 13 and over were also be applicable to adults. Moreover, it was assumed that since XLH is not associated with additional mortality, the utilities were used over the patients' lifetime, using an age decline as in the general population.[64]

Table 5.9: Utility values used in the cost effectiveness model

Health state	Utility value	Standard deviation	Source
Age 1-4			
Healed rickets	0.872	0.097*	Vignette study[63]
Mild rickets	0.774	0.094**	
Moderate rickets	0.685	0.175	
Severe rickets	0.545	0.065***	
Age 5-12			
Healed rickets	0.969	0.072*	Vignette study[63]
Mild rickets	0.757	0.119**	
Moderate rickets	0.613	0.170	
Severe rickets	0.521	0.084***	
Age 13 and over			
Healed rickets	0.862	0.105*	Vignette study[63]
Mild rickets	0.671	0.110**	
Moderate rickets	0.575	0.094	
Severe rickets	0.462	0.161***	
Utility multipliers			
Age 18-24	1.000	-	Age-decline based on the general population[64]
Age 25-34	0.992	-	
Age 35-44	0.966	-	
Age 45-54	0.930	-	
Age 55-64	0.888	-	
Age 65-74	0.851	-	
Age 75+	0.781	-	

Source: Table 31 in the CS.[1]
*This is the standard deviation around the difference between the healed and mild states. The standard error should be used in the model.
**This is the standard deviation around the difference between the mild and moderate states. The standard error should be used in the model.
***This is the standard deviation around the difference between the moderate and severe states. The standard error should be used in the model.

Given the small sample of clinical experts that valued the health states, there is significant variation around the mean values. When considering how to account for this uncertainty in probabilistic and deterministic sensitivity analysis, the company considered that using the mean and standard deviations directly would lead to implausible simulations since 'better' health states could have lower utilities than 'worse' health states. To ensure the variation was accounted for whilst generating plausible simulated utilities, the moderate health state was used as an anchor and the values for other health states were calculated based on differences to the moderate state. The moderate health state was chosen since not all clinical experts valued the healed and severe health states.

ERG comment: The ERG agrees with the company that "*the method used here to develop states and capture utilities is not the optimal source of evidence*".[1] It is a limitation that utility values were obtained

from clinical experts and not directly from XLH patients or, given that the condition affects very young children, from the parents of the patients. The latter would have been considered a more appropriate proxy for assessing HRQoL by the ERG. According to the company, "*to validate the utilities derived from the clinical experts, an ongoing study will report findings from a survey of parents of children affected by XLH. Results of this subsequent study will be reported during the NICE appraisal of burosumab and will be made available to the committee at the earliest convenience*".[1] Unfortunately, the results of this study were not available at the time this report was finished.

The utility values that the company presents in Table 31 of the CS (Table 5.9) do not match all the utility values as presented in the report about the vignette study by Lloyd et al. 2018.[63] For each age group, the value for 'healed rickets' is higher in the CS than in Lloyd et al. whereas the value for 'severe rickets' is lower in the CS than in the Lloyd et al. report. No explanation for this discrepancy was provided. In addition, it is not clear to the ERG how the standard deviations were derived that are presented in Table 5.9 for the non-moderate health states. For the three moderate health states it is unclear whether these values represent the SDs as observed from the vignette study, or the standard errors (SEs), representing the uncertainty of the mean estimate. In the electronic model, these values have been used as if they represent SEs.

At this moment, it is not possible to validate all the utility values for children reported by the company. However, the utility scores for the 'healed rickets' state can be compared to the average utility scores of the general publication. The utility values used in the model are 0.872, 0.969, and 0.862 for the 0-4, 4-13, and 13+ age-groups, respectively. In the study report by Lloyd et al. these values are substantially lower at 0.800, 0.89, and 0.811. The UK average for adults from 18-25 years, the youngest group for which a population average is available, is 0.922.[64] Thus, it appears that the utility value for 'healed rickets' in the group from four to 13 years old as used in the model is rather high, though not impossible given that the population norm is based on young adults rather than children.

However, given the rather high utility values presented in the CS compared to the report by Lloyd et al. and the lack of an explanation for the discrepancy between the two sets of utilities, the ERG considered the Lloyd-set for the ERG preferred base-case and conducted an exploratory sensitivity analysis to assess the impact of using the utility-set presented in the CS. These results will be reported in Chapter 6.

In their response to the CL (question B7), the company provided the descriptions of the vignettes that were used in the study by Lloyd et al. Per age-group, four vignettes were defined, one for each health state. The descriptions provided are strictly ordered, in that on each attribute of the vignette an equal or worse description will be given for a worst health state. For example, for the 'healed rickets' state the vignette defines five of the attributes as follows*: Patient is able to walk nearly normally for their age. They may have a slightly non-normal gait and residual bowed legs; Patient is able to complete usual activities such as dressing and playing; Patient does not experience pain associated with their XLH; Patient's mood, anxiety or sadness varies in the same way that an otherwise healthy person's would be expected to; Patient can complete school, work and many usual activities normally and doesn't have undue problems with completing tasks*.

The text for the same five attributes for 'mild rickets' reads: *Patient is able to walk nearly normally for their age. They have a slight waddling gait with some muscle weakness. They have bowed legs; Patient is able to complete usual activities such as dressing and playing. They fall over more often than other children their age; Patient does experience pain associated with their XLH, particularly in their limbs. They may need pain medication at times; Patient may be withdrawn at times and experience feelings of sadness, frustration and they may lack confidence. They may dislike the need for hospital visits. They*

may suffer teasing or bullying at school; Patient can complete school, work and many usual activities normally and doesn't have undue problems with completing tasks. They often experience quite severe tiredness or stiffness after taking part in sports.

By using experts to devise the descriptions in this very clearly ordered way, there is no possibility of improvement in one attribute with no change or even worsening of another. In contrast, more variation may be expected when patients or parents fill out an EQ-5D, as some patients with mild rickets will report e.g. moderate pain and no anxiety or depression, whereas others may report no pain and moderate anxiety or depression, thus leading to more variation in utility within one health state. Indeed, some patients with healed rickets might have considerable residual deformity, particularly if they had originally been in the severe state and still have some risk of fracture.

Treatment related adverse events were not included in the model. Whilst it is difficult to separate out some of the reported adverse events from frequent manifestations of the disease or typical for a paediatric population, this is not true for injection site reactions, erythema and swelling that were reported in [redacted], [redacted] and [redacted] of the patients, respectively. However, as indicated in section 4.2.4.2 of this report, since all injection site reactions associated with burosumab were categorised as mild in severity, the ERG agrees with the company that these are not expected to have a significant impact on the model results.

5.3.3.4 Resource use and costs included in the model

This section summarises resource use and costs presented in the CS. No studies were identified that reported resource use information. Clinical experts (Dr William G Van't Hoff and Dr Jeremy Allgrove) provided the frequencies and costs (surveillance, drugs, pain and mobility, and orthopaedic interventions) used in the CS. There is no specific healthcare resource group (HRG) or payment by results (PbR) code for XLH.

Technology and comparator costs

In the CS, it was assumed that in the first year of treatment, patients commence treatment on a recommended starting dose of 0.4 mg/kg with a stepwise increase up to 0.8 mg/kg over three months. Estimation of the treatment costs in the CS comprises a mean dose of 0.6 mg/kg for the first three months and a mean dose of 0.8 mg/kg in the subsequent nine months. The first-year dose is therefore estimated to be 0.752 mg/kg, which equates to 94% of the maintenance treatment dose. The company indicated that this assumption was in accordance with the SPC. In the CS, it was stated that the SPC recommends dose rounding to the nearest 10 mg. A scenario analysis was conducted by the company to explore the impact of rounding the dose up to the next 10-fold, rather than to the nearest as recommended in the SPC. The annual per patient cost was estimated (cost per vial) and listed in Table 5.10. Table 5.11 lists summary of acquisition costs by age and weight.

Table 5.10: Dosage and cost of burosumab

	Vial size	Cost per vial	Dose per infusion (mg per kg)
Burosumab	10 mg	£2,992	0.752mg/kg in the first 12 months of therapy, then the full dose of 0.8mg/kg
	20 mg	£5,984	
	30 mg	£8,976	
Source: CS, Table 48.[1]			

Table 5.11: Summary of acquisition treatment costs by age/weight

Age (years)	Weight (kg)	Dose (mg)	Rounded dose (mg)	Vials (10mg)	Vials (20mg)	Vials (30mg)	Annual cost
1	9.4	7.5	10	1	0	0	£77,792
2	11.8	9.4	10	1	0	0	£77,792
3	14.1	11.3	10	1	0	0	£77,792
4	16.1	12.9	10	1	0	0	£77,792
5	18.5	14.8	10	1	0	0	£77,792
6	20.7	16.5	20	0	1	0	£155,584
7	23	18.4	20	0	1	0	£155,584
8	25.9	20.7	20	0	1	0	£155,584
9	28.7	23	20	0	1	0	£155,584
10	31.8	25.4	30	0	0	1	£233,376
11	35.5	28.4	30	0	0	1	£233,376
12	39.1	31.3	30	0	0	1	£233,376
13	44	35.2	40	1	0	1	£311,168
14	49.6	39.7	40	1	0	1	£311,168
15	54.2	43.4	40	1	0	1	£311,168
16	58.2	46.6	50	0	1	1	£388,960
17	60.7	48.6	50	0	1	1	£388,960

Source: CS, Table 49.[1]

The list price of burosumab is included in the CS. [redacted]

Monitoring costs

In the CS, monitoring costs account for dose adjustments in the first year of treatment with burosumab. After initiation of treatment with burosumab, in the first month of treatment fasting serum phosphate is monitored, followed by every four weeks for the subsequent two months and thereafter as appropriate. It was indicated in the CS that if fasting serum phosphate is within the reference range for age, the same dose was maintained. In the CS, patients were assumed to require five additional blood tests and 15-minute consultations in the first year, with nurses taking blood tests to support dose titrations over the course of three months. The total monitoring cost per patient was assumed to be £126.55 (including nurse visits costs (five times for 15 minutes) of £111.25 and blood tests costs of £15.30.[65, 67]

Acquisition costs of the comparator

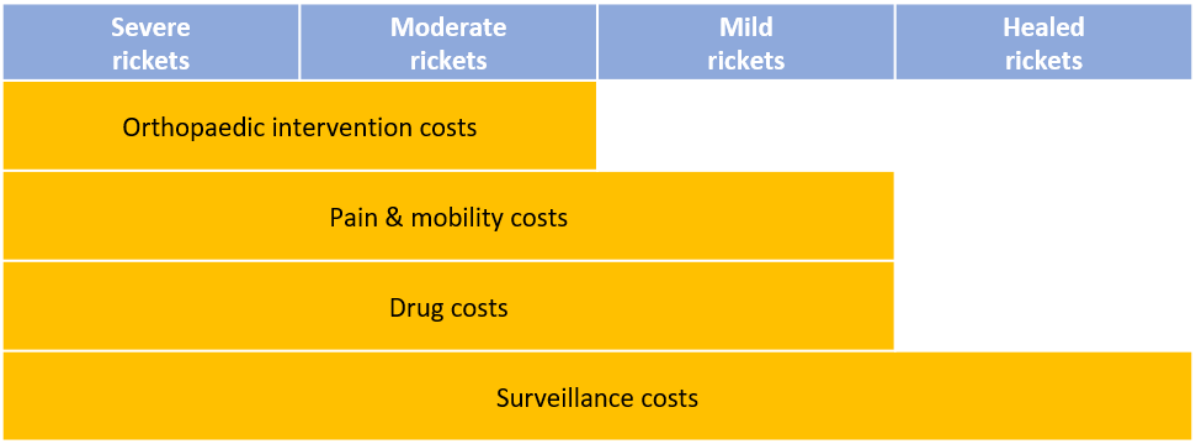
In the CS, alfacalcidol was dosed based on weight. A mean dose of 40 nanogram/kg/day was used, based on clinical expert opinion which indicates that the usual dose of alfacalcidol is 30-50 nanogram/kg/day. This is almost double the recommended dose for another vitamin D analogue, calcitriol, due to the difference in half-life between the two formulations.[3] The company indicated that the computational complexity of modelling treatment costs by age and the relatively low costs of the

comparator,[2] the mean cost of treatment across one to 17 year olds was used to estimate the average annual cost of alfacalcidol. For oral phosphate, it was assumed to be one tablet four times per day.[3]

Health state costs

In the CS, follow-up costs were categorised in four groups as shown in Figure 5.3: surveillance, pain and mobility, orthopaedic intervention and drugs (adults only). According to the CS, only patients in the moderate or severe health state are assumed to receive orthopaedic treatment. It was also assumed that patients in the mild, moderate or severe health states receive pain and mobility costs (physiotherapy). The company assumed that all patients receive the same surveillance costs regardless of health status. Only patients that have had rickets in childhood are assumed in the CS to receive the cost of vitamin D analogues and phosphate supplements in adulthood. Unit costs and resource use for all health state costs are detailed in Table 5.12.

Figure 5.3: Costs categorised by health state



Source: CS, Figure 26.[1]

Surveillance costs

In the CS, surveillance costs were assumed to be the same for all health states and in both treatment arms. Therefore, surveillance costs do not have any impact on the base-case results. In the CS, a scenario analysis was conducted in which patients who are healed at the end of childhood do not require ongoing clinical reviews in adulthood. Clinical experts could not estimate how often SoC patients would be seen in the healed health state. The details of surveillance costs are listed in Table 5.12. In the CS, surveillance costs comprise:

1. Laboratory monitoring costs, which include costs required to test serum calcium, phosphorus, potassium, and creatinine levels, ALP, PTH and urine calcium and creatinine levels.
2. A specialist consultation, which includes the costs for outpatient visits for specialist reviews.
3. Radiography, considered as the gold standard for the diagnostic and efficacy of rickets.
4. During renal ultrasonography patients are screened for signs of nephrocalcinosis, a clinical indicator for worsening XLH severity.
5. At risk of dental problems, dental outpatient appointments were assumed once every 2 years for dental examinations or minor interventions.

Drug costs

In the CS, the estimate of the costs of phosphate supplements and vitamin D analogue was based on two published studies.[66, 68] Per its SPC, the vitamin D analogue dosage was assumed to be five tablets

per day for vitamin D resistant rickets. Based on expert opinion for calcitriol a dosage of 1.125 micrograms per day was assumed.

Pain and mobility costs

In the CS, it was assumed that patients will usually use over-the-counter painkillers for pain management which would therefore not be relevant to the NHS and PSS perspective. GP visits were also excluded, as these could not be linked to specific symptoms of XLH. Thus, pain and mobility costs only consisted of physiotherapy (5% based on clinical expert opinion). It was assumed that children would receive one session (one hour) of physiotherapy per month.

Orthopaedic intervention costs

In the CS, resource use from dental abnormalities were approximated from the proportion of patients with a medical history of tooth abscess in the CL201 study.[70] The costs of the procedures were obtained from an average of dental procedures and weighted by a number of major/intermediate/minor procedures (see Table 5.12). In the CS, patients who have osteotomy procedures are assumed to require two interventions during childhood, which is applied by the company assuming that the costs occur every eight years during childhood. The same assumption was made regarding stapling of growth plates.

In the CS, it was assumed that if patients require a hip arthroplasty, the costs apply to adults only, so the cost of a hip arthroplasty was divided by 60 years to estimate an annual cost. The same calculation was used for knee arthroplasty.

Table 5.12: Summary of cost input parameters included in the model

	Age group	% of patient	Unit cost	Resource use per year	Total cost	Unit Cost Source	Resource Use Source
Surveillance costs							
Specialist Consultation	Children	100%	£249.31	4	£997.22	NHS reference costs 2016/17.[65] Using an average of consultant-led (WF01A) paediatric endocrinology (service code 252) and nephrology (service code 259) as patients are managed by both.	Clinical expert opinion
	Adults	100%	£102.33	1	£102.33	NHS reference costs 2016/17.[65] Using an average of consultant-led (WF01A) endocrinology (service code 302) and nephrology (service code 361) as patients are managed by both.	Assumption
Laboratory Monitoring	Children	100%	£4.19	4	£16.76	NHS reference costs 2016/17.[65] DAPS05 (Haematology) and DAPSS04 (Clinical biochemistry).	Clinical expert opinion
	Adults	100%	£4.19	1	£4.19		
Radiography	All	100%	£29.78	0.50	£14.89	NHS reference costs 2016/17.[65] DAPF (Direct Access Plain Film).	Clinical expert opinion
Renal Ultrasono-graphy	All	100%	£51.36	1	£51.36	NHS reference costs 2016/17.[65] IMAGDA RD40Z (Direct access ultrasound scan with duration of less than 20 minutes, without contrast).	Clinical expert opinion
Dental Check up	Children	100%	£125.39	0.50	£62.70	NHS reference costs 2016/17.[65] Outpatient attendance 142 (Paediatric dentistry).	Clinical expert opinion
	Adults	100%	£126.26	0.50	£63.13	NHS reference costs 2016/17.[65] Outpatient attendance 144 (Maxillo-facial surgery).	Clinical expert opinion
Drug costs							
Oral Phosphate	Adults	65%	£0.16 per tablet	5 tablets per day	£193.70	Cost from BNF 20th December 2017: Phosphate Sandoz effervescent tablets (100). Source electronic model.[2]	The summary of product characteristics recommends 4-6 tablets per day (using 5 average) for vitamin D resistant rickets; Che

	Age group	% of patient	Unit cost	Resource use per year	Total cost	Unit Cost Source	Resource Use Source
							et al. indicated 64.6% of adult patients receive phosphate supplements.[66]
Alfacalcidol	Adults	59%	£0.31 per 500ng capsule	Dose of 1,125 ng per day	£200.31	Cost from BNF 16th January 2018: Alfacalcitrol 500nanogram capsules (30). Source electronic model.[2]	Guidelines by Carpenter et al recommend a dose of 0.5-0.75 mcg per day for Calcitriol (another Vit D not used in UK),[22] but KOL opinion indicates that double dose is required for alfacalcidol, so a mean of 1.125 mg is used. Che et al. indicated 59.2% of adults receive a vitamin D.[66]
Pain and mobility costs							
Physiotherapy	Children	5.00%	£87 per session	1 session per month	£52.20	Cost from PSSRU 2016 (6.1).[67]	Clinical expert opinion indicated that 5% patients may request physiotherapy. Assuming one session per month.
	Adults	57.40%	£45 per hour	1 hour per month	£309.96	Cost from PSSRU 2016 (section 13). Assuming Physiotherapist specialist which is a band 8.[67]	Resource use from Che et al. [66] Assuming one hourly session per month.
Orthopaedic intervention costs							
Dental Abnormalities	Children	19.20%	£154.60	1	£29.68	NHS reference costs 2016/17.[65] Average of dental procedures in 18 years and under, weighted by the number of major/intermediate/minor procedures on the NHS (CD01B, CD02B, CD03B).	Resource use is approximated from the proportion of children with a medical history of tooth abscess in CL201 clinical study report. We assume one procedure per year.
	Adults	62.50%	£169.52	1	£271.24	NHS reference costs 2016/17.[65] Average of adult dental procedures, weighted by the number of major/intermediate/minor procedures on the NHS (CD01A, CD02A, CD03A).	The proportion of adults with dental abnormalities is sourced from Che et al.[66] The company assumed one procedure per year.
Osteotomy	Children	7.7%	£4072.99	Twice in childhood	£39.20	Smith et al.[69]	Resource use is approximated from the proportion of patients with a medical history of osteotomy in CL201 clinical study report. We assume patients have two osteotomy

	Age group	% of patient	Unit cost	Resource use per year	Total cost	Unit Cost Source	Resource Use Source
							procedures during childhood which is applied by assuming the cost occurs every 8 years as a child.
Stapling of Growth Plates	Children	17.5%	£171	Twice in childhood	£3.74	NHS reference costs 2016/17.[65] HN24E Trauma & Orthopaedics (Intermediate Knee Procedures for Non-Trauma, between 6 and 18 years, with CC Score 0).	Resource use from clinical expert opinion. In the CS, patients' growth plates are stapled twice during childhood which is applied by assuming the cost occurs every 8 years as a child.
Hip Arthroplasty	Adult	8%	£5823.53	0.017%	£7.76	Unit cost from NHS reference costs 2015-16 using the most frequent major hip procedure code (HN12F: Very Major Hip Procedures for Non-Trauma with CC Score 0-1).[65]	Resource use from Skrinar et al.[68] Once per lifetime (60 years, adulthood at approximately 20 and life expectancy approximately 80).
Knee Arthroplasty	Adult	12%	£5691.76	0.017%	£11.38	Unit cost from NHS reference costs 2015-16 using the most frequent major knee procedure code (HN22E: Very Major Knee Procedures for Non-Trauma with CC Score 0-1).[65]	Resource use from Skrinar et al.[68] Once per lifetime (60 years, adulthood at approximately 20 and life expectancy approximately 80).
Source: CS, Table 52.[1]							

Adverse event costs
No costs associated with AEs were used in the base-case analysis. In the sensitivity analysis, the impact of including costs associated with AEs (lower limit £0 and upper limit £5) were explored, using an incidence rate of 28.2% for injection site reactions based on Study CL201 and Study CL205.

ERG comment: The company indicated that all known costs and resources have been considered. The ERG requested clarification of the orthopaedic intervention costs which are only considered to occur in patients with a rickets score of 1.5 or higher, but no evidence was provided for the relevant cut-off. In the CL, it was indicated that orthopaedic interventions are only required in patients that have a need for such intervention, who are mostly likely to have more severe rickets. The assumption (confirmed by clinical experts) states that if a patient has healed or mild rickets, then it is unlikely that they would require orthopaedic interventions. The ERG also indicated that the monitoring costs are applied only in the first year of treatment (for dose adjustments). Patients up to the age of 17 are expected to see a specialist every three months, regardless of whether they receive SoC or burosumab. This is incorporated into the surveillance costs which are incurred by all patients. These consultations with clinical specialists are to monitor the disease and treatment. The company indicated that after the first three months, burosumab is not expected to require any additional monitoring over that already conducted with SoC. The ERG indicated that treatment costs of the comparator are not age specific, but an average treatment cost for all patients age one to 17 is used in the model. Given that the comparator consists of two treatments, only one of which has a cost that is age-related (alfacalcidol) and the cost of alfacalcidol is not a driver of costs, the simplification of an average cost (instead of age specific) is acceptable. These revisions have been included in the revised base-case. The revised model sent after the clarification phase comprised updated costs that reflect the same year (2016/17). Overall, the applied changes did not have an impact on the results. Surveillance costs are applicable to all patients and orthopaedic intervention costs are not drivers of the results.

In addition, the ERG had two priority questions in the CL about dosing and vial sharing of burosumab. The company indicated that vial sharing is not applied to burosumab. According to the company, if patients received their exact dose as per their weight, which could be a proxy scenario for vial sharing, the ICER would become [redacted]. Based on the SPC, if a patients' weight indicates a dose of 7.5 mg, then this will be rounded up to 10 mg. It was further stated that when patients are five years old, the calculated dose is 14.8 mg but the recommended dose to be administered is 10 mg. The recommended starting dose regimen in children, according to the CS, is based on experience in Study CL201 and Study CL205. Rounding to the nearest 10 mg was used during dose titration in Study CL201. The company indicated that when pharmacokinetic (PK) modelled dose levels were rounded to the nearest 10 mg a difference in dose of <5 mg is not expected to affect response. The maximum dose of 90 mg is recommended based on PK simulations and the practical limitation of a tolerable injection volume. It was stated that this information was presented to the EMA.

5.3.3.5 Demographic parameters included in the model

A number of demographic characteristics were considered in the model as input parameters. These included the initial distribution of patients per health state stratified by age (see Table 35 and Table 36 in the CS[1]) and the percentage of males (50.77%) at baseline. These parameters were obtained by combining the data from CL201 (all doses) and CL205. Weight by age and

gender was also included in the model as a parameter. The median weight of the general population (for each age and gender category) was assumed,[81, 82] as shown in Table 34 in the CS.[1]

ERG comment: It was not clear to the ERG what the company's rationale was to select the data sources used to derive baseline weight, age and disease severity level distribution of XLH patients. This was discussed in Box 5.1.

5.3.4 Model evaluation

The company presented the results of the health economic analyses in terms of incremental costs and incremental QALYs (combined as an ICER) for burosumab compared to standard of care. Results were obtained by performing a cohort simulation for each starting age (one to 12 years) in each treatment alternative, using the Markov model described in section 5.3.2 of this report. The results for each treatment alternative were then obtained by taking the weighted average of all the cohort simulations for that treatment alternative, using the age distribution of the treatment population. The company submission also included the results of deterministic and probabilistic sensitivity analyses (denoted by DSA and PSA, respectively), the latter consisting of 5,000 model iterations. An overview of the parameters included in the economic model is given in Table 5.13. Other parameters, like mortality or discount were not included in the sensitivity analyses. The results of a number of deterministic one-way and scenario analyses were also presented in the company submission. These are summarised in Box 5.2.

ERG comment: The company, in its response to the clarification letter, submitted an updated electronic model. The following changes were implemented to the original model in the updated version:

- For the transition probability matrices, a programming error in the original model was corrected (transition probabilities from study CL201, which has an observational interval of 64 weeks, were converted to annual probabilities as if they had an observational interval of 40 weeks). In response to Question B16 of the clarification letter, the company applied a revised method for changing the cycle length from the 40 or 64 weeks as observed in the clinical studies to the one year used in the model. As discussed in section 5.3.3.1, the company used an incorrect method to adjust cycle length, which introduced an error (by adjusting individual transition probabilities the rows of the transition matrices did not add up to one). In the original model, the error (i.e. the difference between the sum of each row of transition probabilities and 1) was resolved by dividing each element on a row by the sum of that row. In that way the error was proportionally spread over all elements. In the updated model, the error was added in full to the element on the row representing the probability of remaining in the same health state. The ERG is of the opinion that the original solution for dealing with the error introduced by the invalid method is preferred to the solution used in the updated model, because the error that is introduced is spread over multiple transition probabilities rather than just one, thereby minimizing the effects of the error. This issue has been addressed by the use of the ERG preferred transition probability matrices as discussed in section 5.3.3.1 and presented in section 6.2.1.
- An additional scenario analysis was explored, where the transition probabilities between health states for all ages was based on pooled data from both clinical studies on burosumab (CL201 and CL205).

- The adding of a factor 0.05 to the cumulative Gamma functions in the probabilistic sensitivity analysis was removed from the transition probability matrix based on the UK chart review (see section 5.4.2.3).
- Unit costs have been updated so that all costs are from 2016/17 costs/tariffs.

Table 5.13: Summary of the input parameters included in the economic model

Parameter	Mean value	Range / Distribution	Source
Baseline age and severity distribution	Table 36 in CS	Dirichlet distribution using observed values in CS Table 35.	Pooled baseline distribution from CL201 (all doses) and CL205
Percentage male	50.77%	In one-way sensitivity analysis the range is 0-100%.	Pooled data from CL201 (all doses) and CL205
Weight	Median weight of the general population in CS Table 34	A lower weight at the 25% percentile (also in CS Table 34) is tested in sensitivity analysis	Royal College of Paediatrics and Child Health[81]
Transition probabilities – treated group, age 1-4 years	CS Table 38	Dirichlet distribution using observed values in CS Table 37.	CL205 study
Transition probabilities – treated group, age 5 years and older	CS Table 40	Dirichlet distribution using observed values in CS Table 39.	CL201 study
Transition probabilities – control group, all ages	CS Table 42	Dirichlet distribution using observed values in CS Table 41. An alternative approach to missing data imputation is used in a scenario analysis. A further scenario analysis uses data from Study CL002.	UK chart review
Utilities	CS Table 31	Beta and Normal distributions using values from the UK vignette study.	UK vignette study[63]
Cost of burosumab	CS Table 48 and 49	None	Proposed list price
Monitoring costs associated with burosumab	One-off cost of £126.55 per patient at treatment initiation (CS Table 50)	Gamma distribution assuming standard error is 25% of the mean	Unit costs taken from PSSRU[67] and NHS Reference Costs 2016/17[65]
Surveillance costs and resource use Including (specialist consultations, laboratory monitoring, radiography,	CS Table 54	Gamma distribution assuming standard error is 25% of the mean	Unit costs from NHS Reference costs 2016/17.[65] Resource use taken from KOL opinion

Parameter	Mean value	Range / Distribution	Source
renal ultrasonography, dental check-ups)			Detail outlined in CS Table 52
Comparator costs (oral phosphate and alfacalcidol)	£492.57 per child and £394.01 per adult (CS Table 51 and 53)	Gamma distribution assuming standard error is 25% of the mean	Unit costs from the BNF (Source electronic model[2]) and resource use taken from Carpenter et al. for children[22] and Che et al. for adults[66]
Pain and mobility costs and resource use (physiotherapy)	CS Table 52 and Table 53	Gamma distribution assuming standard error is 25% of the mean	Unit costs taken from PSSRU[67] and resource use from Che et al.[66] Detail outlined in Table 52
Orthopaedic intervention costs and resource use Including (dental abnormalities, stapling of growth plates, hip arthroplasty, knee arthroplasty)	CS Table 52 and Table 53	Gamma distribution assuming standard error is 25% of the mean	Unit costs from NHS Reference costs 2016/17[65] Resource use and further details outlined in CS Table 52
Adverse event costs (injection-site reactions)	£0 - see section 12.3.8	Range £0 - £5	Assumed unit costs Resource use outlined in studies CL201 and CL205
Source: Table 20 in the response to the clarification letter.[2]			

Box 5.2: Deterministic sensitivity analyses and scenario analyses presented in the CS

Deterministic one-way sensitivity analyses

- Ratio between genders in treatment population
- Transition probabilities for burosumab and standard of care
- Resource use
- Unit costs
- Dosing of medication in standard of care
- Age group specific utilities of health states

Scenario analyses

- Discount rate
- Uniform age distribution at start of treatment
- Age and severity distribution based only on patients treated on Q2W schedule
- Using observed (40-week) transition probabilities for patients aged one to four years
- Using observed (64-week) transition probabilities for patients aged five and over
- Using transition probabilities based on pooled data from both clinical studies on burosumab
- Using transition probabilities for standard of care based on linear interpolation of UK chart review data
- Using transition probabilities for standard of care based on CL002 study
- Treatment is stopped at age 15 for both genders
- Treatment is stopped at age 16 for both genders
- Treatment is stopped at age 17 for both genders
- Using mean dose for burosumab from study CL201 (1.05 mg/kg) as opposed to what is recommended in the summary of product characteristics
- Rounding dose of burosumab up (as opposed to rounding to nearest 10 mg)
- Using the 25th percentile weight instead of median weight for each age
- Continuing standard of care treatment in adult patients with healed rickets
- No surveillance in adulthood for patients with healed rickets

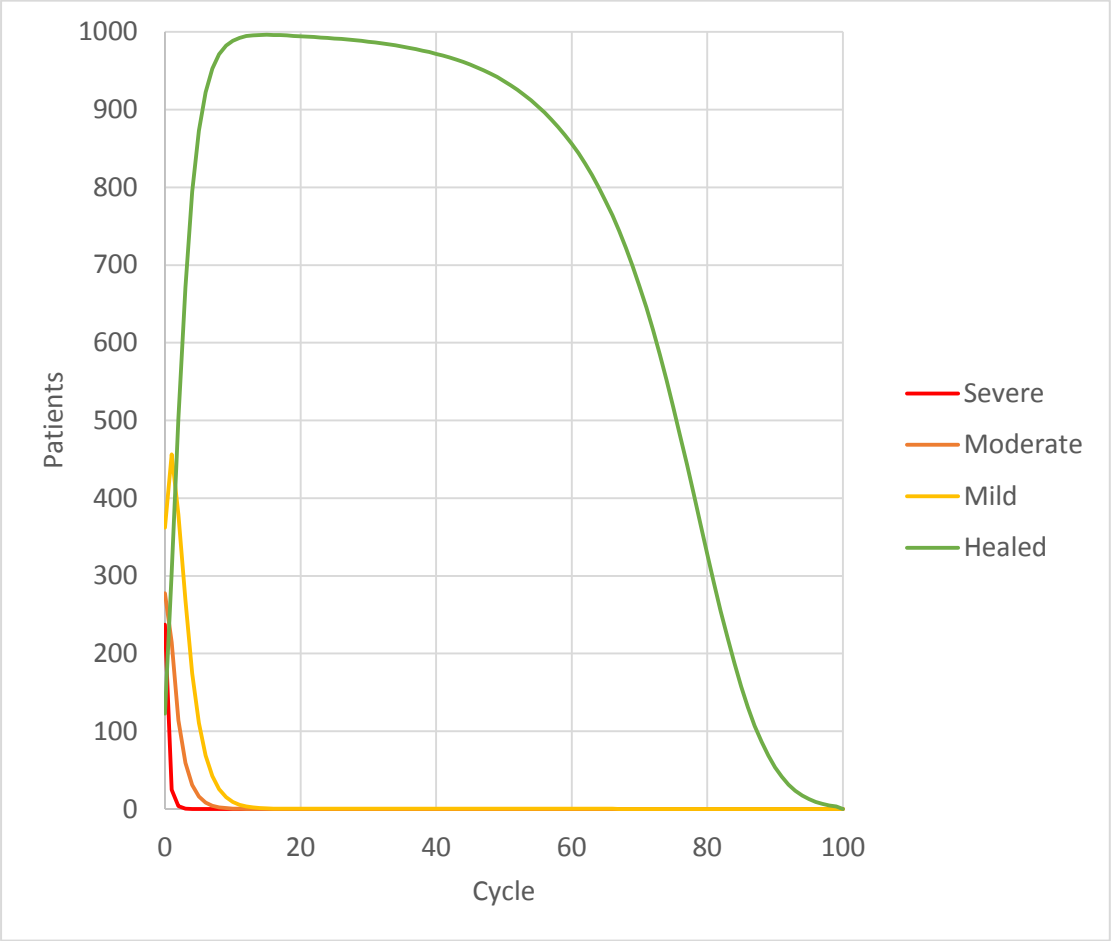
5.4 Headline results reported within the company's submission

In this section, the results of the cost consequence analysis presented by the company are summarised. During the clarification phase, the company detected and corrected two errors in the model. These are described in the response to Question B16 of the clarification letter.[2] Thus, the results described in this section are based on the version of the model submitted by the company with the response to the clarification letter. It should be emphasised that after correcting these errors the ICER increased by 1% compared to the one originally presented in the CS. Therefore, the impact on the results was minor.

The base-case Markov traces for the burosumab and SoC arms are shown in Figure 5.4 and Figure 5.5, respectively. Patients treated with burosumab are expected to spend most of their time alive in the "Healed rickets" health state. In particular, the model predicted that after six years more than 92% of the patients treated with burosumab were healed. After 13 years this was almost 100%. It is also striking that after three years of treatment with burosumab there are basically no patients in the severe health state (0.05%). In comparison, the distribution of SoC

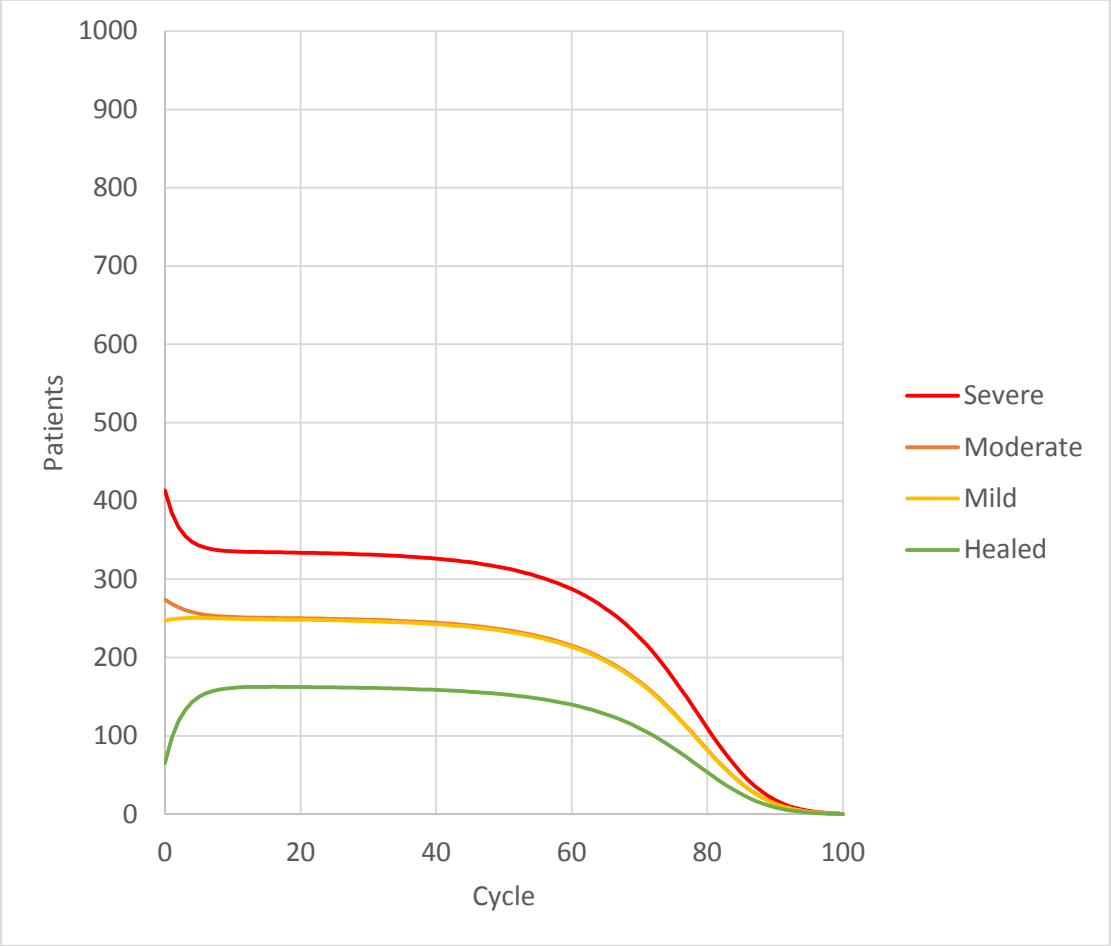
patients per health state is rather constant during most of the patient's lifetime. Approximately 35% of patients are expected to spend their time alive in the "Severe rickets" health state, 25% in the "Mild rickets" health state, another 25% in the "Moderate rickets" health state and approximately 15% in the "Healed rickets" health state. Note that there is no overall survival gain for burosumab in the base-case where the median survival is approximately 75.5 years in both arms. Differences in outcomes are thus due to the QALYs accrued over the lifetime.

Figure 5.4: Base-case: burosumab Markov trace



Source: Electronic model (after clarification).[2]

Figure 5.5: Base-case: SoC Markov trace



Source: Electronic model (after clarification).[2]

5.4.1 Headline total QALYs and total costs for burosumab versus standard care

Table 5.14 presents the results of the cost effectiveness analysis of burosumab versus SoC for the base-case scenario.

Table 5.14: Summary results of the company's base-case scenario

	Costs	QALYs	ICER	Costs	QALYs	ICER
	Discounted			Undiscounted		
SoC	[redacted]	25.989	--	[redacted]	41.786	--
Burosumab	[redacted]	36.293	[redacted]	[redacted]	58.677	[redacted]

Source: Electronic model (after clarification).[2]
Abbreviations: ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care

The company's analysis estimated that patients treated with burosumab gained 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discounting was applied, the estimated gain in QALYs was 17.008 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

Tables 5.15 and 5.16 below present a breakdown of discounted QALYs and costs for burosumab and SoC. The company's analysis suggests that under burosumab patients accrue more than 95% of the total QALYs in the "Healed rickets" health state (least severe state),

whereas for SoC, the number of QALYs accrued is similar among the four health states. This difference between the distributions of years spent in each health state, especially those spent in "Healed rickets", leads to incremental discounted QALYs of approximately 10 years.

More than 99% of the total costs for the burosumab arm are due to the treatment costs. In the SoC arm, 40% of the total costs are due to surveillance and 32% due to other medical costs. Although the burosumab arm results in cost savings in terms of pain-and-mobility ([redacted]) and orthopaedic interventions ([redacted]), the difference between burosumab and SoC is almost fully associated with burosumab treatment costs, adding up to approximately [redacted].

Table 5.15: QALY difference by health state for burosumab vs. SoC patients – base-case analysis

Health state	QALY burosumab	QALY SoC	Increment	Absolute increment	% increment
Healed rickets	34.324	5.770	28.554	28.554	61.0%
Mild rickets	1.385	7.210	-5.826	5.826	12.4%
Moderate rickets	0.444	6.230	-5.786	5.786	12.4%
Severe rickets	0.140	6.778	-6.638	6.638	14.2%
Total	36.293	25.989	10.414	46.804	100%

Source: Electronic model (after clarification).[2]
Abbreviations: QALYs = quality-adjusted life years, SoC = standard of care

Table 5.16: Costs associated with burosumab and SoC per category – base-case analysis

Cost category	Costs burosumab	Costs SoC	Increment	Absolute increment	% absolute increment
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	99%
Drug (other)	[redacted]	[redacted]	[redacted]	[redacted]	1%
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	0%
Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	0%
Pain and mobility	[redacted]	[redacted]	[redacted]	[redacted]	0%
Orthopaedic intervention	[redacted]	[redacted]	[redacted]	[redacted]	0%
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Source: Electronic model (after clarification).[2]
Abbreviations: SoC = standard of care

5.4.2 Sensitivity analyses presented within the company's submission

The company conducted sensitivity and scenario analyses. The results of these analyses are summarised below.

5.4.2.1 Deterministic sensitivity analysis

The results of the deterministic sensitivity analysis (DSA) were presented by the company as a tornado diagram where the top 20 most sensitive parameters were shown. This can be seen in Figure 5.6. It was observed that the ICER was most sensitive to changes in transition probabilities and utilities. The ICER was also sensitive to the proportion of females in the population since growth plates, and therefore treatment, stops earlier in females.

Figure 5.6: Tornado diagram illustrating results of top 20 most sensitive parameters in one-way sensitivity analysis

Figure redacted - CIC

Source: Figure 11 in clarification letter response.[2]

ERG comment: Transition probabilities were not included in the DSA in the original version of the model submitted by the company. When this issue was raised in the clarification letter (Question B32[2]), the company included transition probabilities in the DSA, by varying the probabilities within the 90% confidence interval of a Dirichlet distribution. The results are shown in the tornado diagram above (Figure 5.6) and indicate that the model results are sensitive to the transition probabilities for patients aged five and older treated with burosumab. However, the ICER was not sensitive to changes in the transition probabilities for SoC and for burosumab patients under the age of five. In particular, the ICER increased significantly when the results were obtained at the upper limit of the 95% confidence interval, which resulted in the transition probabilities shown in in Table 5.17. These results were driven around the uncertainty in patients worsening in their rickets severity since this was not observed in the trial. In particular, remaining in the healed health state was assumed to occur with probability

one in the base-case analysis. However, the company reiterated that data from the RGI-C supported that patients had sustained improvements in rickets and therefore that it is likely that a patient would remain healed once healing has occurred. According to the company, this was also consistent with the restoration of phosphate that is associated with burosumab.

Table 5.17: Simulated upper bound of 95% confidence interval for burosumab transition matrix for patients aged 5 and over

	Mild	Moderate	Severe	Healed
Mild	53%	2%	2%	43%
Moderate	36%	46%	2%	17%
Severe	44%	26%	18%	13%
Healed	7%	7%	7%	79%
Source: Table 19 in the response to the clarification letter.[2]				

5.4.2.2 Scenario analysis

The company ran a number of scenario analyses to test the robustness of the model's results to changes in structural assumptions. The results of these analyses are summarised in Table 5.18.

The ICER was most sensitive to applying a discount rate of 3.5% for costs and effects, resulting in an ICER increased by 50% ([redacted]). Using Study CL002 data for transition probabilities in the SoC arm resulted in a 15% increase to the ICER ([redacted]), due to a 14% reduction in incremental QALYs. The ICER was also sensitive to changes in burosumab cost-relating parameters like children's weight, dosage and dose rounding, ranging from [redacted] to [redacted]. Applying a linear interpolation method for handling missing data in the UK chart review data used for SoC transition probabilities resulted in a 10% reduction in the ICER ([redacted]). Finally, the ICER was also sensitive to the age of stopping treatment (between 15 and 17 years), with ICERs ranging between [redacted] and [redacted]. For the other scenarios considered by the company, the ICER barely changed (up to a maximum of 2% increase).

ERG comment: The ERG believes that additional scenarios could have been explored, especially in terms of burosumab effectiveness. Given the low number of observations in both CL201 and CL205, scenarios showing the impact of changing the transition probabilities towards the healed and severe rickets health states could have been informative.

Furthermore, in all of the analyses, there is an underlying assumption that the treatment effect would be lifelong, since after patients reach age 18 in the model they are assumed to remain in their current health state and no deterioration in the health status of the patient occurs. However, it can be a possible that the treatment effect fades away after a certain number of years, as discussed in section 4.6.2 of this report. This was not explored by the company in the cost effectiveness analyses.

Table 5.18: Results of scenario analyses

Scenario	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Difference (%) in ICER
	Burosumab	SoC	Burosumab	SoC				
Base-case analysis	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	
Discount rate (3.5%)	[redacted]	32,626	22.318	16.121	[redacted]	6.197	[redacted]	50%
Even age distribution of cohort aged 1-12 years	[redacted]	51,284	36.580	26.215	[redacted]	10.364	[redacted]	1%
Baseline age and severity distribution: using only patients that were randomised to the bi-weekly burosumab dose	[redacted]	51,259	36.564	26.187	[redacted]	10.376	[redacted]	2%
Transition probabilities, aged 1-4 years: 40-week observations	[redacted]	50,580	36.290	25.989	[redacted]	10.301	[redacted]	0 %
Transition probabilities, aged 5 years and over: 64-week observations	[redacted]	50,580	36.403	25.989	[redacted]	10.415	[redacted]	-1%
UK chart-review data for SoC transition probabilities with missing data using linear interpolation	[redacted]	53,389	36.293	24.825	[redacted]	11.468	[redacted]	-10%
Study CL002 data for SoC transition probabilities	[redacted]	51,497	36.293	27.366	[redacted]	8.927	[redacted]	15%
Treatment stops at 15 years, both genders	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	-22%

Treatment stops at 16 years, both genders	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	-7%
Treatment stops at 17 years, both genders	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	7%
Mean burosumab dose 1.05 mg/kg	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	29%
Rounding up the dosage of burosumab required, rather than rounding to the nearest 10mg	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	12%
25th percentile children weight distribution	[redacted]	50,444	36.293	25.989	[redacted]	10.304	[redacted]	-10%
Continuing SoC drug treatment in adults with healed rickets	[redacted]	53,462	36.293	25.989	[redacted]	10.304	[redacted]	0%
Children with healed rickets no longer require surveillance in adulthood	[redacted]	48,984	36.293	25.989	[redacted]	10.304	[redacted]	-0%
Source: Electronic model (after clarification).[2] Abbreviations: ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care								

5.4.2.3 Probabilistic sensitivity analysis

A PSA was conducted using the probability distributions and parameters described throughout section 5.3.3 and summarised in Table 5.13. The average results (across 5,000 simulations) are shown in Table 5.19. The probabilistic ICER is 27% higher than the deterministic one, mostly due to the incremental QALYs, which in the PSA was approximately two QALYs smaller than in the deterministic base-case analysis.

Table 5.19: Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	24.825			
Burosumab	[redacted]	36.293	[redacted]	8.120	[redacted]

Source: Table 17 in response to clarification letter.[2]
Abbreviations: ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care

The plot of the PSA outcomes in the cost effectiveness (CE) plane (Figure 5.7) shows that 99.9% of the simulations resulted in a gain in QALYs. The cost effectiveness acceptability curves in Figure 5.8 indicates that at a willingness to pay of £170,000, the probability of burosumab being cost-effective is [redacted].

Figure 5.7: PSA outcomes in the CE plane

Figure redacted - AIC

Source: Figure 9 in response to clarification letter.[2]

Figure 5.8: Cost effectiveness acceptability curves

Figure redacted - AIC

Source: Figure 10 in response to clarification letter.[2]

ERG comment: The PSA analyses were well-performed in general and the ERG agrees with most of the choices regarding probability distributions made by the company.

After clarification, the ERG detected an error in the model, which was using the standard deviation instead of the standard error when sampling random values for the utilities. The company used the following approach to obtain random utilities for the PSA: first a utility for the moderate health state is randomly drawn from a Beta distribution, with parameters estimated from the mean and standard deviation values obtained in the vignette study. That utility value for the moderate health state is then used as reference and the utilities for the other health states are calculated by randomly drawing the difference in utility compared to the moderate health state from a Normal distribution, with mean and standard deviation also obtained in the vignette study. For example, for patients aged 13 years and older (note that these utilities are applied in the model until patients die, thus for a large number of model cycles) the estimated mean utility in the moderate health state is 0.575 and 95% confidence interval (CI) is (0.417,0.727). In order to calculate utilities for the mild health state, a random value is drawn from a Normal distribution with mean 0.096 (the estimated mean difference in utility in the mild health state compared to the moderate health state) and standard deviation 0.11. With these parameters, a 95% confidence interval for the difference in utility in the mild health state compared to the moderate health state is (-0.085,0.277). Likewise, a 95% CI for the difference in utility in the healed and severe health states compared to the moderate health state is (0.018,0.364) and (-0.378,0.152), respectively. However, the company made a further assumption when modelling the utilities which was bounding the sampled utilities so that the health states with less severe rickets get always a higher or equal utility value compared to the next more severe health state (i.e. healed ≥ mild ≥ moderate ≥ severe). The ERG does not agree with this assumption as will be explained below. This assumption results in practice in uncertainty ranges for the difference in utility in the mild, healed and severe health states compared to the moderate health state that are (0,0.277), (0.018,0.364) and (-0.378,0), respectively. Note also that since the utility value

for the healed health state must be higher than the utility value for the mild health state, it is very likely that the lower limit for the uncertainty range of the difference in utility for the healed health state is higher than 0.018. Thus, in summary, according to the ERG the combination of using standard deviations (instead of standard errors) and the bounding condition introduced by the company implies that the model samples very large utility values for the mild and especially the healed health state, and very low for the severe health state. Since after 13 years the model predicts that alive patients in the burosumab arm have almost 100% chance of being in the healed rickets health state and that approximately 35% of the SoC patients are expected to spend their time alive in the severe rickets health state, the ERG is of the opinion that the current PSA results, as presented by the company, are biased in favour of burosumab.

As mentioned above, the ERG does not agree with the assumption of bounding the utilities so that the health states with less severe rickets always get a higher or equal utility value compared to the next more severe health state. When this issue was raised in the clarification letter (Question B9[2]), the company argued that it is common to adjust parameters associated with differing health states.[83] Otherwise, simulations may assign utilities to patients with mild rickets with values lower than those assigned to patients with severe rickets, which according to the company is implausible given the definition of the health states. The ERG disagrees with this latter statement. The company has acknowledged that rickets and RSS (and thus the model heath states) do not capture all aspects of XLH symptoms and progression and given the heterogeneity of the condition there is a chance that someone with mild rickets may have more severe additional manifestations, as mentioned above including in section 3.3.4. In fact, using the standard error instead of the standard deviation when sampling utilities for the health states, that should be very unlikely. In a less extreme case, the ERG does not consider it implausible that a patient with moderate rickets may have a lower utility than a patient with mild rickets, given the heterogeneity of XLH, the scale of the RSS (e.g. RSS = 1.49 is mild and RSS = 1.51 is moderate) and the uncertainty around the utility estimates. Nevertheless, as requested by the ERG, the company built a function into the model to enable the PSA to be run with or without bounded utilities. Unbounded utilities will be assumed in the ERG preferred base-case analysis in section 6.

As a first step for the calculation of the transition probabilities in the PSA, the model calculates "Cumulative Gamma functions" (see e.g. "Transition probabilities" sheet, cell Q9) where a factor 0.05 was added to the random draw of the Gamma distributions. It seems that this factor was added to account for non-observed transitions (empty cells in matrix) in the PSA (e.g. from Severe to Severe) as a sort of prior distribution, which in principle seems like an appropriate approach. However, the choice of 0.05 was arbitrary, as confirmed by the company in response to the clarification letter (Question B23[2]). The model results are sensitive to changes in that value and for that reason the ERG asked the company to provide a rationale for choosing 0.05 in the base-case and to perform sensitivity/scenario analyses on this factor. Unfortunately, the company simply responded that the choice of 0.05 was arbitrary but no further explanation was given. Furthermore, the ERG noted that when UK chart data were chosen for the comparator arm, this adjustment was not needed because all possible transitions were observed. The company corrected this in the model. The choice of a prior distribution for transition matrices is discussed in the paper by Briggs et al. 2003,[84] where an uninformative prior distribution over the rows of transition probability matrices is recommended to overcome the potential problem of zero observed counts in some of the cells of the matrices. This can be achieved for example by employing a minimally informative prior distribution like a Dirichlet(1, 1, 1, 1), which can

be interpreted as a uniform prior distribution expressing the belief that each transition is equally likely (i.e. this prior distribution assumes a 0.25 probability to all transitions with a high level of uncertainty). Given the low number of observations in the burosumab arm, using uninformative prior distributions for the transition matrices seems appropriate to the ERG and will be assumed in the ERG preferred base-case analysis in section 6.

The overall uncertainty associated with the PSA results is likely to be underestimated, not only for the reasons discussed above, but also because the following parameters were not included in the PSA:

- The initial distribution of patients per health state stratified by age was obtained by combining the data from CL201 and CL205. Despite being mentioned in Table 5.13 in section 5.3.4 that a Dirichlet distribution was used, these parameters seem to be fixed in the model.
- The percentage of males (50.77%) at baseline was also obtained by combining the data from CL201 and CL205. Given the limited number of observations in these trials, a Beta distribution could have been used.
- Weight by age and gender was also included in the model as a parameter. As discussed in section 5.3.2 (see e.g. Box 5.1), it is uncertain if these weights are representative for the XLH population (especially for females). Since the weight distribution per age is known, a probability distribution (e.g. Normal) could have been used to include weight in the PSA.

However, the impact of these parameters on the overall parameter uncertainty and on the decision uncertainty is expected to be minor. Because of this, and due to the time constraints associated to this assessment, the ERG did not include these parameters in the PSA conducted in section 6.

5.4.3 Validation

In the CS, there is hardly any reference to the validation efforts conducted on the model other than indicating that clinical experts validated the costs considered in the model, utilities were validated against the limited published literature and that cross-validation was not possible since there are no published cost effectiveness analyses in XLH. In the clarification letter, the ERG asked the company to provide details of the validation efforts conducted on the model. The company indicated then that the clinical experts also validated the conceptual model and supplemented information on the input parameters of the model. Furthermore, the company pointed out that "*continuous internal validation has been provided in the development of the model by two separate health economic consultancies for the absence for apparent bugs local code structure, appropriate translation of the conceptual model*".[2] Finally, an example of an extreme value test was provided. This indicated that when the treatment effect of burosumab was assumed to be zero (same transition probabilities in both arms), then the outcomes of the model were identical for both arms with the exception of drug and treatment monitoring costs.

ERG comment: While the ERG acknowledges that, due to the rarity of the disease, it might be difficult to validate many aspects of the model, it also deems the validation efforts reported in the CS insufficient. Although in the response to the clarification letter some more details were provided, it was not mentioned for example what kind of internal validation tests were conducted. A detailed discussion on the face validity of the results was missing in the CS and the response to the clarification letter. Given the lack of cost effectiveness studies on XLH, the

ERG feels that additional attention on the face validity of the results would have been helpful in this case. The ERG also asked the company to include in the response to the clarification letter the results of the ongoing external validation indicated on page 167 of the CS but these were not reported.

5.5 Discussion of available evidence relating to value for money for the NHS and PSS

Chapter 5 of this report focused on the economic evidence for burosumab submitted to NICE by the company. The company presented a QALY-based cost effectiveness model-based analysis comparing burosumab with SoC. The company's analysis estimated that patients treated with burosumab accumulated 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discount was applied, the estimated gain in QALYs was 17.008 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

The ERG identified several issues in the company's analyses. The most important concerns were related to the operationalisation of "full recovery" in the healed rickets health state and lifelong burosumab treatment effect and the choice of the utilities for the base-case. These seemed to bias the results in favour of burosumab. The choice of the discount rate also had a significant impact on the model's results, as shown by the company in one of the scenarios they conducted. The ERG was also concerned about some of the assumptions made by the company in their PSA since these also seemed to bias the results in favour of burosumab.

Other issues discussed by the ERG were the difference of the effects of burosumab on patients younger than age five and patients older than age five, the method used by the company to estimate transition probability matrices, the choice of baseline weight, age and disease severity distribution, and the lack of any treatment/disease related adverse events. However, all these were proven to have a minor impact on the model's results.

Some of the problems identified within the critical appraisal of the economic analyses were addressed by the ERG in the next chapter of this report. Thus, the next chapter outlines the additional analyses conducted by the ERG, which includes the development of a new base-case analysis (including a PSA) and several additional scenarios.

6 IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Introduction

The additional analyses performed by the ERG are presented in this chapter. As described throughout Chapter 5, the ERG identified several issues in the company's analyses. Issues regarding the structure of the model were summarised in Box 5.1, whilst issues within the evidence and/or the methods used to inform the company's model parameters were discussed in section 5.3.3.1 (transition probabilities), section 5.3.3.3 (utilities) and section 5.4.2.3 (PSA). The efforts of the ERG in this chapter are focussed on solving (or partially solving) these issues. In particular, the ERG expected that the largest impact on the cost effectiveness results is caused by the choice of discount rates, the operationalisation of "full recovery" in the healed rickets health state and the lifelong treatment effects for burosumab. Furthermore, given the limited evidence in this submission, the ERG considers that great uncertainty is associated with the deterministic results and therefore, extra attention will be paid to the PSA.

6.2 Changes to the company's economic model

The changes made by the ERG to the company's model are summarised in this section. Note that the version of the model used as reference is the one submitted with the clarification letter. Compared to the original version of the model, the company made the following changes (see section 5.3.4 for details):

- Correction of a programming and a methodological error in the transition probability matrices for burosumab and SoC (CL002).
- Correction of a methodological error in the transition probability matrix for SoC (UK chart review).
- Unit costs were updated to 2016/17 costs/tariffs.

Major changes included the use of alternative annual transition probability matrices for burosumab derived from the original data, sourcing utilities directly from Lloyd et al. 2018,[63] the operationalisation of the full recovery and the lifelong treatment effects. Minor changes included discounting costs and health outcomes at 3.5% and including costs for adverse events. Based on these changes, a new ERG preferred base-case was defined in section 6.3.3.

6.2.1 Transition probabilities for burosumab

The ERG preferred transition probability matrices for burosumab are shown in Table 6.1 and Table 6.2 below. The derivation and a detailed explanation of the methods used to derive these matrices can be found in the critique to section 5.3.3.1 and Appendix 2 of this report.

Table 6.1: ERG preferred annual transition probability matrix for burosumab (patients aged one to four years)

	Mild	Moderate	Severe	Healed
Mild	100%	0%	0%	0%
Moderate	59%	41%	0%	0%
Severe	59%	41%	0%	0%
Healed	0%	0%	0%	100%
Source: Appendix 2 of this report.				

Table 6.2: ERG preferred annual transition probability matrix for burosumab (patients aged five years and older)

	Mild	Moderate	Severe	Healed
Mild	57%	0%	0%	43%
Moderate	40%	50%	0%	10%
Severe	62%	35%	0%	3%
Healed	0%	0%	0%	100%
Source: Appendix 2 of this report.				

6.2.2 Source used to estimate utilities

As mentioned in the ERG critique to section 5.3.3.3, the utility values that the company presented in Table 31 of the CS (Table 5.9) do not match all the utility values as presented in the report by Lloyd et al. 2018,[63] where the vignette study is described. It was observed that for each age group, the value for 'healed rickets' is higher in the CS than in Lloyd et al. 2018 whereas the value for 'severe rickets' is lower in the CS than in the Lloyd et al. However, no explanation for this discrepancy was provided by the company. Additionally, it was not clear to the ERG how the standard deviations that are presented in Table 5.9 for the non-moderate health states were derived. For these reason, the utilities reported in Lloyd et al. 2018, as shown in Table 6.3 below, are used in the ERG preferred base-case analysis.

Table 6.3: Mean utility values for the health states captured using EQ-5D-5L.

Health state	Mean	Standard Deviation*
Age range 1-4		
Healed rickets (RSS score=0)	0.800	0.135
Mild rickets (RSS Score=0.5-1.0)	0.774	0.192
Moderate rickets (RSS Score=1.5-2.0)	0.685	0.175
Severe rickets (RSS Score>2.5)	0.610	0.184
Age range 5-12		
Healed rickets (RSS score=0)	0.890	0.113
Mild rickets (RSS Score=0.5-1.0)	0.757	0.159
Moderate rickets (RSS Score=1.5-2.0)	0.613	0.170
Severe rickets (RSS Score>2.5)	0.602	0.106
Age range 13+		
Healed rickets (RSS score=0)	0.811	0.108
Mild rickets (RSS Score=0.5-1.0)	0.671	0.154
Moderate rickets (RSS Score=1.5-2.0)	0.575	0.094
Severe rickets (RSS Score>2.5)	0.479	0.169
Source: Table 1 in Lloyd et al. 2018[63] *Standard errors should be used in the model.		

6.2.3 Operationalisation of the full recovery and lifelong treatment effects

As explained in section 4.6.2, the ERG considers that defining health states by RSS is likely to overestimate any improvement due to burosumab in moving to states with a lower RSS. In addition, the model currently assumed that the effect of burosumab lasts for the rest of the

patients' lives, which seems to be unrealistic. For that reason, the ERG assumed that the treatment effect would decline in time. Thus, it was assumed that after 20 years after the end of treatment, patients would experience a decline in quality of life which was operationalised by assuming the utility value of the next worse health state, as shown in Table 6.4.

Table 6.4: Utility values used in the ERG base-case for patients 13 years and older

Health state	Utility value (13 to 37 years)	Utility value (38 years and older)
Healed rickets	0.811	0.671
Mild rickets	0.671	0.575
Moderate rickets	0.575	0.479
Severe rickets	0.479	0.479

6.2.4 Minor changes

Minor changes included the following:

- Discounting costs and health outcomes at 3.5% (instead of 1.5% as assumed by the company).
- Including adverse events costs. These were assumed to be £0 in the base-case analysis. The CS does not report any estimation about what these costs could be. The only reference to this can be found in the electronic model where a range between £0 and £5 was used. For the ERG base-case, it was conservatively assumed £5 for the adverse event costs.

6.2.5 PSA-related changes

As discussed in the ERG critique of section 5.4.2.3, the following adjustments were made by the ERG in the PSA:

- Using the standard errors instead of the standard deviations when sampling random values for the utilities.
- Unbounding utilities so that the health states with less severe rickets do not always get a higher or equal utility value compared to the next more severe health state.
- Using a Dirichlet(1, 1, 1, 1) prior distribution for all possible transitions in the burosumab transition probability matrices.

6.3 Summary of the additional analyses undertaken by the ERG

The following analyses were undertaken using the company's model with ERG adjustments:

- ERG base-case: alternative transition probability matrices for burosumab, utilities from Lloyd et al., decline in quality of life 20 years after end of treatment, discounting costs and health outcomes at 3.5% and adverse event costs.
- ERG PSA: standard errors (instead of standard deviations) specified in utility distributions, unbound utilities with respect to next worse health state and approaches Dirichlet(1, 1, 1, 1) prior distributions for burosumab transition matrices.
- Additional scenario 1: changing the age where the decline in utilities is assumed.
- Additional scenario 2: using utilities from Table 31 in the CS.
- Additional scenario 3: rounding up the dose for burosumab.
- Additional scenario 4: running PSA with bounded utilities.

- Additional scenario 5: changing the prior distribution in transition matrices and run PSA.

6.4 Cost-consequence results produced by the ERG

6.4.1 Headline results produced by the ERG base-case analysis

The cost effectiveness results of the new ERG base-case are shown in Table 6.5. These are presented in 5 steps, showing the cumulative impact of each of the changes made by the ERG on the model results. It is clear that assuming a decline in utilities 20 years after treatment and considering a 3.5% discount rate resulted in a significant increase in the ICER. The other three changes had a minor/moderate impact on the ICER. In particular, the ERG preferred base-case analysis (Step 5 in Table 6.5) estimated that patients treated with burosumab accumulated 3.947 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When the discount rate was 1.5% (Step 4 in Table 6.5), as in the company's base-case, the estimated gain in QALYs was 5.773 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

Table 6.5: Comparison company base-case vs. ERG (step-by-step) base-case results

Scenario	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Difference (%) in ICER
	Burosumab	SoC	Burosumab	SoC				
Base-case (company)	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	
Step 1 – AEs costs	[redacted]	50,580	36.293	25.989	[redacted]	10.304	[redacted]	[redacted]
Step 2 – Transition matrices burosumab	[redacted]	50,580	36.301	25.989	[redacted]	10.312	[redacted]	[redacted]
Step 3 – Utilities from Lloyd et al.	[redacted]	50,580	34.232	26.007	[redacted]	8.225	[redacted]	[redacted]
Step 4 – Utilities decline 20 years after treatment	[redacted]	50,580	31.780	26.007	[redacted]	5.773	[redacted]	[redacted]
Step 5 – discount rate 3.5%	[redacted]	32,626	20.122	16.175	[redacted]	3.947	[redacted]	[redacted]

6.4.2 Probabilistic sensitivity analyses produced by the ERG

A PSA was conducted with the ERG preferred assumptions described in section 6.2.5. The average results (across 5,000 simulations) are shown in Table 6.6. The probabilistic ICER was [redacted]. This reflects the large uncertainty associated with the transition probability matrices for burosumab and the impact of choosing a prior distribution. This issue will be further discussed in section 6.4.3.5.

Table 6.6: ERG probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	16.271			
Burosumab	[redacted]	17.21	[redacted]	0.94	[redacted]
ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care					

The plot of the PSA outcomes in the cost effectiveness (CE) plane (Figure 6.1) shows that 88% of the simulations resulted in a gain in QALYs. The cost effectiveness acceptability curves in Figure 6.2 indicates that only at a high willingness to pay (approximately £500,000), the probability of burosumab being cost effective is not [redacted].

Figure 6.1: ERG PSA outcomes in the CE plane

Figure redacted - AIC

Figure 6.2: ERG-based cost effectiveness acceptability curves

Figure redacted - AIC

6.4.3 Exploratory sensitivity analyses produced by the ERG

6.4.3.1 Additional scenario 1: changing the age where the decline in utilities is assumed

In this series of scenarios, the ERG assessed the impact of assuming a different duration for the burosumab treatment effects on the cost effectiveness results. In the ERG base-case this was assumed to be 20 years after the end of treatment. Since this is unknown, the cost effectiveness results assuming a wide range of values for the burosumab treatment effect duration were calculated and summarised in Table 6.7. Note that in all these scenarios only the QALYs associated to burosumab change. Assuming five years for the duration of the burosumab treatment effects resulted in an ICER of [redacted], whilst assuming lifelong treatment effects resulted in an ICER of [redacted]. The difference between assuming 20 years duration of treatment effect (ERG) and lifelong treatment effects (company) was an ICER increased by approximately [redacted] under the ERG assumption.

Table 6.7: ERG cost effectiveness results for different durations of burosumab treatment effect

Years after treatment	Incremental costs (£)	Incremental QALYs	ICER (£)
5 years	[redacted]	3.001	[redacted]
10 years	[redacted]	3.375	[redacted]
15 years	[redacted]	3.688	[redacted]
20 years (ERG assumption)	[redacted]	3.947	[redacted]
30 years	[redacted]	4.336	[redacted]
40 years	[redacted]	4.594	[redacted]
50 years	[redacted]	4.759	[redacted]
No decline (company assumption)	[redacted]	4.906	[redacted]

6.4.3.2 Additional scenario 2: utilities from the company submission

In this scenario, the ERG explored the impact of using the utilities reported in Table 31 of the CS (Table 5.9) instead of the utility values as presented in the report about the vignette study by Lloyd et al. 2018.[63] As discussed in section 5.3.3.3, for each age group, the value for 'healed rickets' was higher in the CS than in Lloyd et al. whereas the value for 'severe rickets' was lower in the CS than in the Lloyd et al. report. The results from this scenario can be seen in Table 6.8. As expected, choosing the utilities from Table 31 in the CS, favoured the results burosumab, resulting in an ICER decreased by approximately [redacted] compared to the ERG base-case ICER.

Table 6.8: Results scenario using utilities from the company submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	16.121			
Burosumab	[redacted]	21.020	[redacted]	4.899	[redacted]
ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care					

6.4.3.3 Additional scenario 3: rounding up burosumab dose

The ERG explored in this scenario the impact on the model results of assuming that the exact dose for burosumab was given to patients. Since burosumab is available in vials of size 10 mg, 20 mg and 30 mg, it was assumed that when the calculated dose exceeded the dose of one vial, another complete vial would be needed and therefore the costs of these extra vial were added to the model's calculations. The impact of this assumption on the ICER was moderate, resulting in an ICER increased by approximately [redacted] compared to the ERG base-case ICER.

Table 6.9: Results scenario rounding up burosumab dose

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	16.175			
Burosumab	[redacted]	20.122	[redacted]	3.947	[redacted]
Abbreviations: ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care					

6.4.3.4 Additional scenario 4: running PSA with bounded utilities

In this scenario, the ERG tested the assumption made by the company in their base-case of bounding the utilities in such a way that the better health states were always assigned with a utility higher than or equal to the next worse health state. It should be noted that in the ERG base-case, standard errors instead of standard deviations were used to sample utilities. Therefore, the impact of this assumption was expected to be minor, as confirmed by the results shown in Table 6.10. The probabilistic ICER was [redacted]. Thus, the probabilistic ICER, the plot of the PSA outcomes in the CE plane and the cost effectiveness acceptability curves (not shown) obtained in this scenario were very similar to those obtained in the ERG PSA.

Table 6.10: Probabilistic sensitivity analysis results with bounded utilities

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	16.180			
Burosumab	[redacted]	17.190	[redacted]	1.01	[redacted]
Abbreviations: ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care					

6.4.3.5 Additional scenario 5: prior distributions in transition probability matrices for burosumab

As mentioned in the ERG critique to section 5.4.2, an arbitrary factor 0.05 was added to the random draw of the Gamma distributions to account for non-observed transitions in the PSA. However, the model results are highly sensitive to changes in that value, as suggested by the ERG PSA results shown in section 6.4.2. The ERG asked the company to perform sensitivity/scenario analyses on this factor but unfortunately the company did not address this question (see clarification letter response to Question B23[2]).

Uninformative prior distributions over the rows of transition probability matrices are recommended by Briggs et al. 2003.[84] In particular, a prior Dirichlet(1, 1, 1, 1), in case of four health states, is suggested and this was the choice made by the ERG in their base-case. This can be interpreted as a uniform prior distribution expressing the belief that each transition is equally likely (i.e. 0.25 probability to all transitions with a high level of uncertainty). However, since the number of observations from which the transition matrices for burosumab are estimated is quite small, the choice of this prior distribution has a major impact on the PSA results as shown below. Further details on the choice and the impact of choosing prior distributions for the burosumab transition probability matrices are given in Appendix 3 of this report.

When running the PSA with the values shown in Table 6.1 and Table 6.2 (ERG preferred deterministic base-case), which should not be done because it would ignore the aforementioned uncertainty, the probabilistic ICER was [redacted], which is in line with the deterministic ICER obtained by the ERG (see Step 5 in Table 6.5), and the probability that burosumab is cost effective at thresholds smaller than or equal to £300,000 was [redacted]. When the PSA was run assuming a prior Dirichlet(0.05, 0.05, 0.05, 0.05) for all possible transitions, which was the choice made by the company, the probabilistic ICER obtained was [redacted] but the probability that burosumab is cost effective at thresholds smaller than or equal to £300,000 was still [redacted].

As the prior distribution approaches a Dirichlet(1, 1, 1, 1) , it is expected that the probabilistic ICER increases. This is because most of the cells of the observed burosumab transition probability matrices show either a probability 0 or 1 at key transitions which favour burosumab (e.g. probability of becoming severe is always 0), as shown in Table 6.1 and Table 6.2. Thus, as the prior approaches a Dirichlet(1, 1, 1, 1) , the posterior matrix deviates more from the observed matrix. Since the impact of the originally assumed 0 or 1 probabilities fades out, this has a significant impact on the model results. Thus, assuming a prior Dirichlet(0.1, 0.1, 0.1, 0.1) resulted in an ICER of [redacted] and assuming a Dirichlet(0.5, 0.5, 0.5, 0.5) resulted in an ICER of [redacted]. Finally, assuming a prior Dirichlet(1, 1, 1, 1) for all possible transitions resulted in the ERG PSA ICER of [redacted] and a [redacted] probability that burosumab is cost effective at thresholds smaller than or equal to £300,000.

6.5 Discussion

The additional analyses performed by the ERG were presented in this chapter. The main changes made by the ERG to the company's model included the use of alternative transition probabilities for burosumab, sourcing utilities directly from Lloyd et al. 2018[63] and the operationalisation of the full recovery and the lifelong treatment effects of burosumab. Minor changes included discounting costs and health outcomes at 3.5%, although this was proven to have a major impact on the model results.

The results of the ERG base-case, before applying the 3.5% discount rate on costs and health outcomes, resulted in an ICER increased by [redacted] compared to the company's base-case ICER. After applying the 3.5% discount rate, the ICER increased by [redacted]. Although sourcing the utilities from Lloyd et al. had a substantial impact on the ICER (increased by [redacted]), most of the total increase in the ICER (before applying the 3.5% discount rate) was due to the assumption of waning of treatment effect, implemented by reducing the utilities of burosumab patients 20 years after the end of treatment. Since there is uncertainty on whether this value of 20 years will be observed in real life, the ERG assessed the impact of assuming a different duration for the burosumab treatment effects on the cost effectiveness results. The difference between assuming 20 years duration of treatment effect (ERG) and lifelong treatment effects (company) was an ICER increase by approximately [redacted] under the ERG assumption. Assuming smaller values for the duration of the burosumab treatment effect increased the ICER. In particular, when this was assumed to be five years the deterministic ICER was [redacted].

The ERG was concerned that the PSA results presented by the company were underestimating the uncertainty associated with the transition probabilities for burosumab. For that reason, a new PSA and additional scenarios exploring the impact of choosing prior distributions for the burosumab transition matrices were conducted by the ERG. The latter was proven to be crucial and in the several scenarios provided by the ERG, the probabilistic ICER ranged from [redacted] to [redacted]. The ERG has concerns regarding the appropriateness of the choice of prior distribution made by the company for their PSA since this seemed to be based on matching the observed matrix and not representing prior beliefs about these transitions. The prior distribution assumed by the ERG, resulted in a more conservative approach and a more appropriate representation of the uncertainty associated to the transition probability matrices for burosumab.

Other scenarios explored by the ERG like using the utilities reported in Table 31 of the CS, rounding up the burosumab dose or bounding the utilities in the PSA were shown to have a minor to moderate impact on the model results.

Based on the ERG results, it is expected though that, from the payer perspective, the decision uncertainty related to burosumab's value for money would be low, given that the ICER estimates from all ERG analyses are above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

7 COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

The CS includes a budget impact model to estimate the total costs to the NHS, for a period of five years, of adopting burosumab in England. [redacted].[8] This prevalence has been applied to the general population for England in children aged between one and 17 years to estimate the size of the population of [redacted] children with XLH eligible for treatment with burosumab (Table 2.1 of this report).[9] In the CS, it was reported that the number of patients eligible for burosumab [redacted] The company indicated that XLH is associated with skeletal deformations, pain and functional impairment; therefore, it is unlikely that there are undiagnosed children that would benefit from treatment with burosumab. Thus, the estimated prevalence based on primary care data is unlikely to be a significant underestimate.

In the CS, it was reported that the size of the patient population ([redacted]) is not expected to change over time as patients are only treated if they have growing skeletons i.e. each year there may be new patients but there will also be a likely similar number of patients ceasing treatment. In the CS, it was stated that XLH is not associated with an increased risk of death, compared to the standard population.[85] Therefore, the potential (and theoretical) population size is assumed to remain constant.

In the CS, based on clinical expert opinion, the yearly expected uptake rates of burosumab are calculated as follows: using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab.

Table 7.1: Market update of burosumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected uptake of burosumab	40%	65%	90%	90%	90%
Patients treated with burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 61 in the CS[1]
* The number in the CS reported here is 74; however, this should probably be 104.

[redacted]

[redacted]

The company stated that the weight, gender distribution and dosage of burosumab used to calculate treatment costs per age in the budget impact analysis is in line with the cost effectiveness model (CS Table 49).[1] The distribution of patients age was obtained from Study CL201 and CL205 (CS Table 36),[1] to estimate mean number of 10 mg, 20 mg, 30 mg vials required per patient, across the treated cohort.

[redacted] The company indicated that factoring in costs of monitoring and cost savings through displaced conventional therapy, will result in a net budget impact of [redacted] in Year 1, [redacted] in Year 2 and [redacted] per year thereafter (Table 7.2).

Table 7.2: Net budget impact of burosumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients treated with burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of continuing patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of burosumab (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offsets in drug costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 62 in the CS[1]

In addition, the company reported the following information regarding resource savings associated with the use of burosumab: oral phosphate and vitamin D analogues should be discontinued one week prior to initiation of treatment with burosumab.[50] The company stated that, if a patient is treated with burosumab, there will be savings in the costs of oral phosphate and vitamin D analogues. The costs of these treatments in children are £492.57 per year (CS Table 51).[1] It was indicated in the CS that there

are also savings with regards to fewer surgical interventions, as well as reduced and/or deferred need for physiotherapy to manage the long-term consequences attributed to XLH. In the CS, these have not been factored in the budget impact analysis given its short time horizon.

7.2 ERG critique of the company's budget impact analysis

The ERG considers the assumptions made in the budget impact analysis questionable. There are concerns about the theoretical population size and the expected uptake rate of burosumab in England. In the CS, it was reported that the size of the patient population [redacted] is not expected to change over time. This estimate is based on an assumption that the patients are only treated if they have growing skeletons. In the CS, it was stated that XLH is not associated with an increased risk of death, compared to the standard population.[85] The potential (and theoretical) population size is assumed to remain constant.

Since real-world data suggests there could be [redacted] XLH patients between one and 17 years of age in England (see response to clarification letter – Question A4),[2] using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to 77 children in year 1, 125 children in Year 2 and 174 children thereafter being treated with burosumab. The cost of burosumab at year 5 would then amount to [redacted]. The company indicated that burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by the company and will therefore not have any additional financial or resource impact on the NHS.

8 IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the CS

8.1.1 Nature of estimates presented

The CS did not include any estimates of costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab. The company indicated that at this stage this was not possible to quantify. However, the company expects significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab.

8.1.2 Societal costs

As mentioned above, it was not possible for the company to identify and quantify costs to other government bodies. The company expects that patients treated with burosumab may be able to work more or developed further in their careers through improved education not inhibited by XLH. The company also expects that life-long disability will be avoided in people with XLH treated with burosumab. This will result in patients who will be less dependent their caregivers or on disability and other welfare payments. In the short term, the company expects that parents might not have to take time off from work to care for their child suffering with XLH.

8.1.3 Costs borne by patients

Most children experience interruptions to their schooling to attend hospital and GP appointments. Family members or caregivers may be absent from work to attend those appointments. In addition, costs of travel may be borne. Due to the limited number of specialist centres, patients and parents (or caregivers) may have to travel considerably. The results of an online survey carried out in January 2018 showed that

[redacted]

The study conducted by Berndt et al. in 1996 assessed the clinical and psychosocial aspects of XLH in 23 adults in Germany using a standardised questionnaire on pain and psychosocial rehabilitation (schooling, vocational training, employment and marital status).[28] Responders indicated that they struggled due to a lack of schooling and vocational training resulting from a lifetime of managing disease-related complications. A summary of the main findings is given below:

- Thirteen out of 20 patients were able to attend school regularly and to finish school adequately. Seven patients reported to have missed school repeatedly because of multiple hospitalisations leading to class repetition and to an inappropriate school qualification in four of them.
- Twelve out of 20 patients finished vocational training, five did not start and three attended but did not complete vocational training.
- Eight patients were employed, four were unemployed, four women were housewives, two patients received a social insurance payment because of inability to work (two patients did not answer questions on vocational training and profession).

Many adults with XLH also require surgery to correct skeletal deformities. In the study CL001,[86] [redacted]

[redacted]. In a case-note review of 59 adults with XLH, attending a single inherited metabolic disease service in the UK from 1998, 42% had had an osteotomy.4 Having surgery requires time off work not only for the surgery but also for recovery. For example, for an osteotomy, patients are not able to return to work for between two weeks and four months, depending on the nature of the work they do. Furthermore, results from CL001 indicated that most adult patents require [redacted].[86]

8.1.4 Other carer costs

As mentioned above, it was not possible for the company to quantify costs associated to caregivers.

8.1.5 Discussion of wider societal (non-health) benefits

Several issues regarding the impact of burosumab beyond direct health benefits were discussed qualitatively in the submission. However, the company were not able to provide any estimates of costs associated to inability to work or attend school, or costs borne by patients of caregivers.

The ERG considers it as inadequate that the impact of XLH on costs (savings) or benefits incurred outside of the NHS and PSS associated with burosumab was not identified prior to the submission to NICE.

8.2 Staffing and infrastructure requirements associated with the use of the technology

It was stated in the CS that, according to the draft Summary of Product Characteristics for burosumab, treatment with burosumab should be initiated by a physician experienced in the management of patients with metabolic bone diseases. The company indicated that following discussions with NHS England it was suggested that treatment with burosumab would only be initiated and prescribed by specialist centres that are members of the European Reference Network on Rare Bone Disorders (ERN-BOND). Furthermore, it is planned that burosumab will be supplied via a homecare service (to be provided and funded by the company) after patients have been established on a maintenance dose. During the initial dose titration period burosumab will be supplied directly to designated hospitals. Blood tests required for monitoring can be carried out in line with local arrangements, without visiting the specialist centre. Therefore, according to the company, no other additional facilities, technologies or infrastructures are required for the implementation of burosumab.

9 DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

The studies included in the submission focus on the following populations and studies:

- Paediatric patients with XLH, five to 12 years old: Study CL201 (open-label RCT comparing different doses of burosumab biweekly or monthly administration of burosumab (doses 0.1 to 2.0 mg/kg))
- Paediatric patients with XLH, 1 to 4 years old: Study CL205 (open-label study to assess the safety, pharmacodynamics and efficacy of burosumab biweekly administration of burosumab at a target dose of 0.8 mg/kg))
- Paediatric Patients with XLH, 5 – 14 years old: Study CL002 (A retrospective longitudinal study of skeletal outcomes in children with XLH. No burosumab administered; however, study inclusion required the use of conventional therapy (oral phosphate/active vitamin D))

Results from CL201 show that burosumab significantly improves rickets at week 40 and week 64, compared to baseline. The primary endpoint, the rickets severity score (RSS) was reduced from baseline by 61% at week 40 ($p<0.0001$) by 58% at week 64 ($p < 0.0001$) with biweekly burosumab. Burosumab treatment also resulted in healing of rickets as assessed by RGI-C scores. The RGI-C score at Week 64 was +1.62. At Week 64, [redacted]% of children treated with biweekly burosumab had healing of rickets (RGI-C global scores ≥ 1.0). Furthermore, [redacted] of children treated with burosumab had substantial healing of rickets (RGI-C global scores ≥ 2.0). Growth velocity increased by [redacted]) in children treated with burosumab every two weeks, with a corresponding least-squared (LS) mean change in standing height z-score of [redacted]). Biweekly burosumab also resulted in improved functional assessments and patient-reported outcomes in CL201. Walking ability, as assessed by LS mean distance walked in the six-minute walk test (6MWT), increased from baseline by [redacted] at week 64 ([redacted]). Functional disability was assessed using the Pediatric Orthopedic Society of North America - Pediatric Outcomes Data Collection Instrument (POSNA-PODCI). Biweekly burosumab treatment increased scores for Sports/Physical Functioning and Pain/Comfort into the normal range seen in healthy children; LS mean scores showed improvements of [redacted] and [redacted] at week 64, respectively.

Results from CL002 show that RSS was reduced by [redacted] (over a median period of 102 weeks) after long-term conventional therapy. The RGI-C score was [redacted] with conventional therapy in Study CL002 (median [redacted] weeks). Furthermore, [redacted] of children treated with conventional therapy in Study CL002 had substantial healing of rickets (RGI-C global scores ≥ 2.0). After long-term treatment with conventional therapy in Study CL002, [redacted].

In study CL205 (13 children with XLH aged 1-4 years), burosumab treatment for 40 weeks significantly reduced RSS total score at week 40 by 59% (LS mean change of -1.73, $p < 0.0001$, ANCOVA model).

No patient died or discontinued from CL201 or CL205 for any reason; all patients continued treatment on study as of the data cut-off dates.

The most common adverse drug reaction reported in paediatric patients up to 64 weeks treatment with burosumab was injection site reactions (57%), headache (54%), pain in extremity (42%), vitamin D decreased (28%), rash (23%), toothache (19%), tooth abscess (14%), myalgia (14%), and dizziness (11%). Approximately 57% of the patients had an injection site reaction. The injection site reactions were generally mild in severity, occurred within one day of medicinal product administration, lasted approximately one to three days, required no treatment, and resolved in almost all instances.

In study CL201, one patient experienced serious TEAEs, and [redacted]. The most frequent TEAEs (>30% incidence) in study CL201 were [redacted].

The most frequent TEAEs (> 30% incidence [four or more of 13 patients]) in study CL205 were [redacted]

Adverse events of treatment with conventional therapy have not been reported. Therefore, it is not possible to assess the relative safety and toxicity in relation to the comparator.

9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis

9.2.1 Cost-consequence analysis

The company conducted a systematic review of cost effectiveness studies of burosumab and other studies including costs, resource use and any HRQoL measure associated with XLH. A total of eight full-text studies were assessed for eligibility which were included in the final evaluation of evidence. However, none of these studies were deemed relevant to the economic evaluation of burosumab.

The company's deterministic analysis estimated that patients treated with burosumab accumulated 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discount was applied, the estimated gain in QALYs was 17.008 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

The ERG identified several issues in the company's analyses. The ERG main concerns were related to the method used by the company to estimate the transition probability matrices for burosumab, the source of utilities used by the company, and the assumption of lifelong treatment effects of burosumab. The latter was expected to have a major impact on the model results. The choice of the discount rate was also challenged by the ERG. Furthermore, given the limited evidence in this submission, the ERG highlighted the extra importance of the probabilistic results. In light of these issues, the ERG performed a new base-case analysis and a number of additional scenarios.

The results of the deterministic ERG base-case resulted in an ICER increased by [redacted] compared to the company's base-case ICER. Most of the total increase in the ICER (despite the effect of applying the 3.5% discount rate) was due to assuming a treatment effect duration for burosumab of 20 years. The ERG also conducted a new PSA and additional scenario analyses exploring the impact of choosing prior distributions for the burosumab transition matrices. The latter was proven to be crucial and in the several scenarios provided by the ERG, the probabilistic ICER ranged from [redacted] to [redacted]. Other scenarios explored by the ERG like using the utilities reported in Table 31 of the CS, rounding up the burosumab dose or bounding the utilities in the PSA were shown to have a minor to moderate impact on the model results.

Based on the ERG results, it is expected that, from the payer perspective, the decision uncertainty related to burosumab value for money would be low, given that the ICER estimates from all ERG analyses are above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

9.2.2 Cost to the NHS and PSS

A budget impact model to estimate the costs to the NHS for a period of five years of adopting burosumab in England is also included in the CS. The results presented by the company suggested that the net budget impact of implementing burosumab (with an estimated prevalence of [redacted] patients) will be [redacted] in the first year and will rise to [redacted] in the fifth year. The cost of burosumab at year 5 amounts to [redacted]. The estimated total number of patients eligible for burosumab treatment after five years is [redacted] and the uptake of burosumab rises from 40% in year 1 to 90% in year 5. When a prevalence of [redacted] is considered by the ERG (with the same uptake rates), the estimated total number of patients eligible for burosumab treatment after five years reaches to [redacted]. The cost of burosumab at year 5 would then amount to [redacted].

9.2.3 Non-health benefits

The CS did not include any estimates of costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab. The company indicated that at this stage this was not possible to quantify. However, the company expects significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab.

The ERG considers it as inadequate that the impact of XLH on costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab was not identified prior to the submission to NICE.

9.3 Strengths and limitations

9.3.1 Strengths of the CS

The ERG is confident that all relevant studies (published and unpublished) of burosumab were included in the CS, including data from ongoing studies. The same applies to the historical control patients. A control study in UK patients was mentioned in the CS without any results being report in the CS. However, results were provided as part of the response to the clarification letter. The reporting of outcomes from included studies also seems complete.

A range of relevant economic information was incorporated in the CS, including a QALY-based cost effectiveness model and an assessment of the expected costs to the NHS and PSS in England.

9.3.2 Weaknesses of the CS

The main limitation of the efficacy data reported in the CS is the study design of the included studies. Due to the absence of a control group in most studies it is not possible to make any direct comparisons between burosumab and conventional therapy. As stated by the company, the "burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).[1]

For children between one to four years old, only one study is presented in which all children received burosumab (CL205, N=13). A comparison with "established clinical management without burosumab" is not possible in this group of patients.

For children between five to 12 years old, the CS presents a study in which all children received burosumab (CL201). In addition, the CS presents a control study (CL002) in which children aged between five to 14 years received conventional therapy (i.e. oral phosphate/active vitamin D). Results of these two studies are mainly presented as a naïve comparison, simply reporting individual results from each study side by side. In addition, the company presents comparisons of 'rickets healing' with conventional therapy (Study CL002) versus burosumab (Study CL201) using propensity analysis matching.

In the CS, the company uses the term 'healing' and 'substantial healing of rickets'. This is defined using RGI-C global scores, where scores ≥ +1.0 indicate 'healing of rickets' and scores ≥ +2.0 'substantial healing of rickets'. The company does explain that "Healing in this context indicates improvement in the radiographic abnormalities and does not imply that complete healing was observed" (CS, page 100).[1] However, throughout the report the term 'healing of rickets' is used without any explanation of the degree of healing (minimal, substantial or complete). Moreover, RGI-C global scores and RSS scores do not capture all clinical aspects of XLH. That is of particular importance in the context of the economic model, which only considers RSS score alone as a clinical outcome measure. The diverse physiological impacts of hypophosphataemia, which may be independent of rickets, are therefore not captured as outcomes in the economic model.

In the response to the clarification letter the company described the vignettes for the various health states that informed the economic model in detail (Clarification Letter Response Question B7, Table 10). However, each health state was defined in such a way that there appears to be a perfect association between the RSS score and other clinical descriptors of the health state. For example, as the RSS score decreases so does the risk of fracture and the presence of deformity. However, this does not appear to be realistic in that it seems likely that there might be some resolution of the bone disorder such that the RSS score decreases, but that this resolution only occurs after incurring deformity, which cannot be completely resolved and with some continued increased risk of fracture.

In addition, the model currently assumed that the effect of burosumab, although stopped at age 16 (women) or 17 (men) lasts for the rest of their lives. This also seems unrealistic, the effects of burosumab on stature, bowing of the legs, joint deformity etc. are likely to persist fairly long but may wane as osteomalacia itself and the resulting fractures may lead to associated problems in later life. Effects on bone strength will wane quicker, therefore repeated fractures and badly healing fractures after 10 or 20 years are likely to occur. Effects of burosumab on symptoms caused by hypophosphatemia itself will disappear as soon as therapy is stopped. Therefore, we have assumed in the ERG base-case that patients will experience a decline in quality of life 20 years after the end of treatment, which was operationalised by moving to the utility value of the next worse health state (see section 6.2.3 in this report).

Regarding the evidence synthesis, the naïve comparison is unreliable because there are important differences between the inclusion criteria in both studies. Inclusion criteria for patients in studies CL201 and CL002 are similar in that patients in both studies were diagnosed with XLH and were of similar age. However, children in study CL201 also had: biochemical findings associated with XLH, standing height < 50th percentile for age and gender and radiographic evidence of active bone disease including rickets in the wrists and/or knees, and/or femoral/tibial bowing, or, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read. In other words, study CL002 included all children with XLH, while study CL201 included children with more severe symptoms of XLH. This is also reflected in the relatively [redacted] standing height and [redacted] rickets severity score for children in study CL201 when compared to children in study CL002.

The adjusted comparison, using propensity analysis matching, is unreliable because of the limitations associated with these methods, in that the matching can only include those variables measured in both studies. Randomisation in a clinical trial creates balanced group for both measured and unmeasured variables. In observational studies, the most important factors which are predictive of the outcome may not have been measured and any treatment comparisons using observational study data may be biased. In the CS the company only included three variables in the PSM: age, gender and RSS total score at baseline. The rationale for variable selection was not provided other than whether they seemed similar or not between the two study populations. No details were provided of how this similarity was judged. The ERG found no statistically significant differences in age and gender between the two groups and considered that only including three variables in the creation of the propensity scores may have been too few.

Given the aforementioned limitations regarding the evidence presented by the company, the model results are highly uncertain and sensitive to key assumptions. Furthermore, the CS lacks an analysis of the wider societal (non-health) benefits associated with burosumab.

9.4 Uncertainties

The main uncertainty regarding the effectiveness evidence is the comparability of results from treated patients and historical control patients. Most of the evidence is presented as single arm studies including either treated patients (two studies, both with extensions that are still ongoing) or historical control patients (one study, with patients from one single centre, Radiographic analysis set ([redacted])). The historical control study (CL002) included patients aged from five to 14 years and can therefore only serve as a control group for study CL201 (children aged five to 12 years).

For patients with XLH aged one to four years old, the CS only presents a single arm burosumab study (CL205), no control data for this age group were provided. Only 13 children were enrolled in study CL205; therefore, results in this age group are very uncertain.

A randomised controlled study comparing burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) is currently ongoing. [redacted]. Results from this study will considerably reduce the uncertainty surrounding the clinical effectiveness of burosumab relative to conventional therapy in children with XLH aged between one and 12 years.

There is substantial uncertainty about the long-term effects of burosumab. The company conducted their analysis upon the assumption that these effects would be lifelong, despite treatment being stopped at the age of 16 in females and 17 in males, but there is no evidence to support that assumption. This assumption was proven to be crucial and one of the main drivers of the cost effectiveness results.

Additional uncertainty is generated when translating the clinical outcomes to QALYs since the evidence on HRQoL was based on a vignette study describing the health states of the economic model that were valued by (only six) clinical experts. Having HRQoL assessed by patients or caregivers, given that most of the patients are children, would reduce this uncertainty.

Since there is no direct or indirect evidence comparing burosumab to SoC, the assumed treatment effect of burosumab, as reflected by the transition probability matrices, is also very uncertain.

The ERG considers that the uncertainty around the reported ICERs is likely to be larger than suggested by the PSAs presented in this report. Given that PSA only addresses parameter uncertainty, other sources of uncertainty, like the ones mentioned above, could not be included in the PSA.

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Appendix 1: ERG search strategies

The following searches were run to investigate additional population terms identified by the ERG and to identify the number of records retrieved. The ERG feels the number of references retrieved was a manageable number for the company to screen in order to identify potentially relevant clinical and cost-effectiveness studies without the use of study design filters.

MEDLINE (Ovid): 1946 to March Week 3 2018

1 exp Familial Hypophosphatemic Rickets/ (449)

2 ((familial or hereditary or genetic) adj2 (hypophosphataemi$ or hypophosphatemi$ or hypophosphatami$)).ti,ab. (269)

3 ("x linked" adj2 (hypophosphataemi$ or hypophosphatemi$ or hypophosphatami$)).ti,ab. (701)

4 (rickets adj3 (hypophosphataemi$ or hypophosphatemi$ or hypophosphatami$ or familial or hereditary or genetic or "D resistant" or "x linked")).ti,ab. (1554)

5 (XLH or HHRH or HPDR or ADHR).ti,ab. (389)

6 1 or 2 or 3 or 4 or 5 (1961)

7 limit 6 to yr="1945 - 2017" (1961)

[Records retrieved by Company searches: clinical effectiveness – 149; cost effectiveness – 10]

Embase (Ovid): 1974 to 2018 March 23

1 exp Familial Hypophosphatemic Rickets/ (742)

2 ((familial or hereditary or genetic) adj2 (hypophosphataemi$ or hypophosphatemi$ or hypophosphatami$)).ti,ab. (327)

3 ("x linked" adj2 (hypophosphataemi$ or hypophosphatemi$ or hypophosphatami$)).ti,ab. (998)

4 (rickets adj3 (hypophosphataemi$ or hypophosphatemi$ or hypophosphatami$ or familial or hereditary or genetic or "D resistant" or "x linked")).ti,ab. (2051)

5 (XLH or HHRH or HPDR or ADHR).ti,ab. (638)

6 1 or 2 or 3 or 4 or 5 (2725)

7 limit 6 to yr="1945 - 2017" (2707)

[Records retrieved by Company searches: clinical effectiveness – 200 (assuming error in reporting); cost effectiveness – 23]

CENTRAL Register of Controlled Trials (The Cochrane Library)

#1 MeSH descriptor: [Familial Hypophosphatemic Rickets] explode all trees 5

#2 (familial or hereditary or genetic) near/2 (hypophosphataemi* or hypophosphatemi* or hypophosphatami*) 15

#3 ('x linked' or 'x-linked') near/2 (hypophosphataemi* or hypophosphatemi* or hypophosphatami*) 32

#4 rickets near/3 (hypophosphataemi* or hypophosphatemi* or hypophosphatami* or familial or hereditary or genetic or 'D resistant' or 'D-resistant' or 'x linked' or 'x-linked') 43

#5 XLH or HHRH or HPDR or ADHR 23

#6 #1 or #2 or #3 or #4 or #5 in Trials 40

[Records retrieved by Company searches: clinical effectiveness – 9]

Clinical effectiveness – minor issues

- It is not clear which records in the PRISMA flow diagram were identified from database searches. The ERG assumes that flow diagram includes results from both database searches and hand-searching, as the numbers do not reflect the database searches alone.
- There appears to be an error in the documentation of the search results from Embase. In the CS, Table 2 - #24 gives the number of records retrieved as 20, but this is an unlikely reduction from the 208 records found before the date limit 1945-2017 was applied. Test searches run by the ERG suggest that this is a reporting error.
- MEDLINE In Process search strategies are not supplied separately. The ERG assumes that MEDLINE In Process is included in the MEDLINE searches, although this is not specified.

Cost effectiveness – minor issues

- It is not clear which records in the PRISMA flow diagram were identified from database searches. The ERG assumes that flow diagram includes results from both database searches and hand-searching, as the numbers do not reflect the database searches alone.
- The Embase strategy contains MEDLINE (MeSH) indexing terms (CS, Table 8 - #4)
- There are redundant lines in the MEDLINE (Table 7 - #36) and Embase (CS, Table 8 - #9, #62) strategies
- The MEDLINE strategy appears to contain unused searches (CS, Table 7 - #13, #27) on the epidemiology of XLH.

Appendix 2: Estimation of transition probability matrices

A Markov model with M health states can be characterised by the transition probability matrix P:

$$P = \begin{pmatrix} p_{1,1} & \cdots & p_{1,M} \\ \vdots & \ddots & \vdots \\ p_{M,1} & \cdots & p_{M,M} \end{pmatrix}$$

where $p_{i,j}$ denotes the transition probability from health state i to health state j (at time T) for $i, j = 1, \ldots, M$. The maximum likelihood estimate (MLE) of P, denoted by $\hat{P}$, can be obtained from the transition count matrix N

$$N = \begin{pmatrix} n_{1,1} & \cdots & n_{1,M} \\ \vdots & \ddots & \vdots \\ n_{M,1} & \cdots & n_{M,M} \end{pmatrix}$$

where $n_{i,j}$ denotes the number of event occurrences between health state i to health state j (at time T) for $i, j = 1, \ldots, M$. Then, $\hat{P}$ is the row proportions of N, so that

$$\hat{p}_{i,j} = \frac{n_{i,j}}{\sum_{m=1}^{M} n_{i,m}}$$

The company presented three transition count matrices with different observation periods (40 weeks, 64 weeks and 104 weeks). The problem at hand is to estimate the three corresponding transition probability matrices for a different time scale (52 weeks = 1 year). In general, this can be done as explained below.

Suppose the number of occurrences is obtained at time t_0, then the MLE of the transition probability matrix can be denoted by $\hat{P}_{t_0}$. If t denotes the desired time scale, then the MLE of the transition probability matrix associated with a cycle length t can be calculated as

$$\widehat{P_t} = P_{t_0}^{\left(t/t_0\right)}$$

For example, to obtain a one-year transition probability matrix from a one-month transition probability matrix, raise the one-month transition probability matrix to the twelfth power. Note that this approach works well when t is a multiple of t_0, i.e. when t/t_0 is a positive integer (as it occurs with a monthly to yearly conversion). When this is not the case, the spectral decomposition of P (eigenvalues and eigenvectors) needs to be calculated. Therefore, if we are interested in calculating $\hat{P}_t$, where t is not necessarily an integer multiple of the original scale, then $\widehat{P_t} = VD^tV^{-1}$, where

$$D^t = \begin{pmatrix} \lambda_1^t & 0 & 0 \\ 0 & \lambda_2^t & 0 \\ \vdots & \ddots & \vdots \\ 0 & 0 & \lambda_M^t \end{pmatrix}$$

and λ_i is the i^{th} eigenvalue of $\hat{P}_t$ and V is the matrix of eigenvectors (i^{th} column of V). Thus, in D^t the eigenvalues are raised to the power t but the eigenvectors do not change.

In practice, these calculations can be performed in *R* as shown below.

Transition probability matrix for burosumab age 1-4

The 40-week observation matrix for burosumab age 1-4 (denoted by N_40w) is the following:

```
N_40w <- matrix(c(1, 0, 0, 0, 2, 2, 0, 0, 4, 4, 0, 0, 0, 0, 0, 1), byrow = T, ncol
= 4)

rownames(N_40w) <- c("Mild","Moderate","Severe","Healed")
colnames(N_40w) <- rownames(N_40w)


N_40w

##          Mild Moderate Severe Healed
## Mild        1        0      0      0
## Moderate    2        2      0      0
## Severe      4        4      0      0
## Healed      0        0      0      1

P_40w <- matrix(nrow = 4, ncol = 4, 0)
colnames(P_40w)<-rownames(P_40w)<-colnames(N_40w)
```

The corresponding 40-week transition probabilities (denoted by P_40w) are then given below:

```
for (i in 1:4) P_40w[i, ] <- N_40w[i, ] / sum(N_40w[i, ])
P_40w

##          Mild Moderate Severe Healed
## Mild      1.0      0.0      0      0
## Moderate  0.5      0.5      0      0
## Severe    0.5      0.5      0      0
## Healed    0.0      0.0      0      1
```

Since the model's time horizon is one year (i.e. 52 weeks) the time scale of the transition matrix has to be changed. This can be done as explained above, i.e. by calculating eigenvalues and eigenvectors of the original transition matrix.

```
eig_40w <- eigen(P_40w)
eig_40w

## eigen() decomposition
## $values
## [1] 1.0 1.0 0.5 0.0
##
## $vectors
##           [,1] [,2]      [,3] [,4]
## [1,] 0.5773503    0 0.0000000    0
## [2,] 0.5773503    0 0.7071068    0
## [3,] 0.5773503    0 0.7071068    1
## [4,] 0.0000000    1 0.0000000    0

D_40w <- diag(eig_40w$values)
D_40w

##      [,1] [,2] [,3] [,4]
## [1,]    1    0  0.0    0
## [2,]    0    1  0.0    0
## [3,]    0    0  0.5    0
## [4,]    0    0  0.0    0
```

```
V_40w <- eig_40w$vectors
V_40w
```

```
##           [,1] [,2]      [,3] [,4]
## [1,] 0.5773503    0 0.0000000    0
## [2,] 0.5773503    0 0.7071068    0
## [3,] 0.5773503    0 0.7071068    1
## [4,] 0.0000000    1 0.0000000    0
```

Note that the command below should calculate the initial transition matrix (P_40w) as it occurs here.

```
V_40w %*% D_40w %*% solve(V_40w)
```

```
##      [,1] [,2] [,3] [,4]
## [1,]  1.0  0.0    0    0
## [2,]  0.5  0.5    0    0
## [3,]  0.5  0.5    0    0
## [4,]  0.0  0.0    0    1
```

We calculate first a weekly factor, since we want to obtain a transition probability matrix for one week. Then with this one-week matrix we can easily calculate the 52-week transition matrix by multiplying the one-week matrix 52 times. Note that other approaches than calculating the one-week matrix are possible but, in this case, it worked well as we will see below.

```
d_40w <- D_40w^(1/40)
d_40w
```

```
##      [,1] [,2]      [,3] [,4]
## [1,]    1    0 0.0000000    0
## [2,]    0    1 0.0000000    0
## [3,]    0    0 0.9828206    0
## [4,]    0    0 0.0000000    0
```

Thus, the one-week transition matrix is the following (P1_40w):

```
P1_40w <- V_40w %*% d_40w %*% solve(V_40w)
P1_40w
```

```
##           [,1]      [,2] [,3] [,4]
## [1,] 1.0000000 0.0000000    0    0
## [2,] 0.0171794 0.9828206    0    0
## [3,] 0.0171794 0.9828206    0    0
## [4,] 0.0000000 0.0000000    0    1
```

Note that, although it was possible to estimate the one-week transition matrix (P1_40w), some of the estimated values seem implausible, especially those regarding transitions from the severe health state (third row in P1_40w) as these values imply essentially instantaneous transition from the severe health state to either the mild or moderate health state.

As mentioned above, to obtain a one-year transition matrix we need to take the power 52 of the one-week matrix.

```
library(expm)

P1_40w %^% 52
```

```
##           [,1]      [,2] [,3] [,4]
## [1,] 1.0000000 0.0000000    0    0
## [2,] 0.5938738 0.4061262    0    0
```

```
## [3,] 0.5938738 0.4061262    0    0
## [4,] 0.0000000 0.0000000    0    1
```

As a validation step, note that by taking the power 40 of the one-week transition matrix we should obtain the original transition matrix, which is indeed happening as shown below.

```
P1_40w %^% 40

##      [,1] [,2] [,3] [,4]
## [1,]  1.0  0.0    0    0
## [2,]  0.5  0.5    0    0
## [3,]  0.5  0.5    0    0
## [4,]  0.0  0.0    0    1
```

Transition probability matrix for burosumab age 5+

The 64-week observation matrix for burosumab age 5+ (denoted by N_64w) is the following:

```
N_64w <- matrix(c(4, 0, 0, 4, 3, 3, 0, 1, 6, 3, 0, 1, 0, 0, 0, 1), byrow = T, ncol
= 4)
rownames(N_64w) <- c("Mild","Moderate","Severe","Healed")
colnames(N_64w) <- rownames(N_64w)
N_64w

##          Mild Moderate Severe Healed
## Mild        4        0      0      4
## Moderate    3        3      0      1
## Severe      6        3      0      1
## Healed      0        0      0      1

P_64w <- matrix(nrow = 4, ncol = 4, 0)
colnames(P_64w)<-rownames(P_64w)<-colnames(N_64w)
```

The corresponding 64-week transition probability matrix is then given by P_64w. We should repeat the same steps as in the 40-week case in order to obtain a one-week transition probability matrix. This is described in the `R` code below.

```
for (i in 1:4) P_64w[i, ] <- N_64w[i, ] / sum(N_64w[i, ])
round(P_64w,2)

##          Mild Moderate Severe Healed
## Mild     0.50     0.00      0   0.50
## Moderate 0.43     0.43      0   0.14
## Severe   0.60     0.30      0   0.10
## Healed   0.00     0.00      0   1.00

eig_64w <- eigen(P_64w)
eig_64w

## eigen() decomposition
## $values
## [1] 1.0000000 0.5000000 0.4285714 0.0000000
##
## $vectors
##      [,1]      [,2]      [,3] [,4]
## [1,]  0.5 0.1290564 0.0000000    0
## [2,]  0.5 0.7743386 0.8192319    0
```

```
## [3,]  0.5 0.6194709 0.5734623    1
## [4,]  0.5 0.0000000 0.0000000    0

D_64w <- diag(eig_64w$values)
D_64w

##      [,1] [,2]      [,3] [,4]
## [1,]    1  0.0 0.0000000    0
## [2,]    0  0.5 0.0000000    0
## [3,]    0  0.0 0.4285714    0
## [4,]    0  0.0 0.0000000    0

V_64w <- eig_64w$vectors
V_64w

##      [,1]      [,2]      [,3] [,4]
## [1,]  0.5 0.1290564 0.0000000    0
## [2,]  0.5 0.7743386 0.8192319    0
## [3,]  0.5 0.6194709 0.5734623    1
## [4,]  0.5 0.0000000 0.0000000    0

### This should be P
round(V_64w %*% D_64w %*% solve(V_64w),2)

##      [,1] [,2] [,3] [,4]
## [1,] 0.50 0.00    0 0.50
## [2,] 0.43 0.43    0 0.14
## [3,] 0.60 0.30    0 0.10
## [4,] 0.00 0.00    0 1.00

### Weekly factor
d_64w <- D_64w^(1/64)
d_64w

##      [,1]      [,2]      [,3] [,4]
## [1,]    1 0.000000 0.000000    0
## [2,]    0 0.989228 0.000000    0
## [3,]    0 0.000000 0.986482    0
## [4,]    0 0.000000 0.000000    0
```

However, in this case the one-week transition matrix is non-stochastic since one of its elements is negative, although the one-year transition matrix is actually stochastic, as shown below.

```
### One week transition matrix
P1_64w <- V_64w %*% d_64w %*% solve(V_64w)
round(P1_64w,2)

##      [,1] [,2] [,3]  [,4]
## [1,] 0.99 0.00    0  0.01
## [2,] 0.01 0.99    0  0.00
## [3,] 0.60 0.69    0 -0.29
## [4,] 0.00 0.00    0  1.00

### One-year transition matrix

round(P1_64w %^% 52,2)

##      [,1] [,2] [,3] [,4]
## [1,] 0.57 0.00    0 0.43
## [2,] 0.40 0.50    0 0.10
```

```
## [3,] 0.62 0.35    0 0.03
## [4,] 0.00 0.00    0 1.00
```

Furthermore, the original matrix could also be replicated.

```
round(P1_64w %^% 64,2)

##      [,1] [,2] [,3] [,4]
## [1,] 0.50 0.00    0 0.50
## [2,] 0.43 0.43    0 0.14
## [3,] 0.60 0.30    0 0.10
## [4,] 0.00 0.00    0 1.00
```

Alternatively, to overcome the issue of non-stochasticity, we propose using the approximation method described in Chhatwal et al. 2016.[75] Their algorithm is available online:

http://www.mgh-ita.org/ita-tools/online-modeling-tools.html

Using this approximation algorithm, based on the original 64-week observed matrix, the estimated stochastic four-week (note four weeks were chosen because calculating the one-week matrix was time consuming and it seemed unstable; note also that 4 is the greatest common divisor of 64 and 52, so both matrices could be estimated with the four-week matrix) matrix is the following:

```
round(matrix(c(0.963702, 0.00020038, 0., 0.036098, 0.0538478, 0.946152, 0., 0., 0.
0945621, 0.113132, 0.792306, 0., 0., 0., 0., 1.),byrow=T,nrow=4)
```

The estimated one-year matrix would be then the four-week matrix multiplied 13-times.

```
round(matrix(c(0.963702, 0.00020038, 0., 0.036098, 0.0538478, 0.946152, 0., 0., 0.
0945621, 0.113132, 0.792306, 0., 0., 0., 0., 1.),byrow=T,nrow=4)%^%13,2)

##      [,1] [,2] [,3] [,4]
## [1,] 0.62 0.00 0.00 0.38
## [2,] 0.40 0.49 0.00 0.11
## [3,] 0.48 0.32 0.05 0.15
## [4,] 0.00 0.00 0.00 1.00
```

Likewise, the 64-week matrix would be the four-week matrix multiplied 16-times, which is not the same as the observed one

```
round(matrix(c(0.963702, 0.00020038, 0., 0.036098, 0.0538478, 0.946152, 0., 0., 0.
0945621, 0.113132, 0.792306, 0., 0., 0., 0., 1.),byrow=T,nrow=4)%^%16,2)

##      [,1] [,2] [,3] [,4]
## [1,] 0.55 0.00 0.00 0.44
## [2,] 0.43 0.41 0.00 0.15
## [3,] 0.49 0.29 0.02 0.20
## [4,] 0.00 0.00 0.00 1.00
```

Appendix 3: Choice of prior distributions for transition probability matrices

Estimating reliable transition probability matrices for burosumab is challenging due to the overall low number of observed counts and the substantial number of zeroes in the matrices. *Uninformative* prior distributions over the rows of transition probability matrices are recommended by Briggs et al. 2003 to overcome this issue.[84] In particular, a prior Dirichlet(1, 1, 1, 1), in case of transition matrices having four health states, is suggested. This was the rationale for the choice made by the ERG in their base-case. Note that a Dirichlet(1, 1, 1, 1) can be interpreted as a uniform prior distribution expressing the *prior belief* that each transition is equally likely (in this case 1/4 = 0.25) but with a high level of uncertainty (since these prior estimation is only based on four counts). This prior distribution can be then be combined with the actual observed data, for example with the first row of Table A3.1 to give a *posterior* distribution Dirichlet(1+1, 1+0, 1+0, 1+0) = Dirichlet(2, 1, 1, 1), which assigns an average probability of transitioning from mild to (mild, moderate, severe, healed) equal to (2/5, 1/5, 1/5, 1/5) = (0.4, 0.2, 0.2, 0.2). Thus, the prior uninformative beliefs have been updated with the observed data and the result is a posterior probability that gives more *weight* to one transition over the others depending on the observed transitions. It is clear that, when more observed data become available, the estimated transition probabilities also become more reliable (i.e. the bias and the uncertainty in the point estimates are reduced) and the choice of the prior distribution becomes less relevant. However, since the number of observations from which the transition matrices for burosumab are estimated (in the example above just 1), the choice of this prior distribution has a major impact on the PSA results as shown in section 6.4.3.5.

An example with the transition matrix for burosumab patients aged one to four years is given below, although the same applies to the transition matrix for patients aged five to 12 years. The transition probability matrix for burosumab patients aged one to four years was estimated based on only 14 observations, which were distributed per health state as indicated in Table A3.1, although the last element of the matrix (healed, healed) was added for completeness but it was not observed in the trial (there were no healed patients).

Table A3.1. Predicted number of observations per health state at year 1 (52 weeks) for burosumab patients (one to four years old)

	Mild	Moderate	Severe	Healed	Total
Mild	1.00	0.00	0.00	0.00	1
Moderate	2.36	1.64	0.00	0.00	4
Severe	4.72	3.28	0.00	0.00	8
Healed	0.00	0.00	0.00	1.00	1
Note that non-integer observations are due to transforming the originally observed transition probability matrix from 40 weeks to 1 year (52 weeks).					

From the counts in Table A3.1, the transition probability matrix can be calculated simply by taking the proportions per row as shown in Table A3.2.

Table A3.2. ERG transition probability matrix for burosumab patients (1 to 4 years old)

	Mild	Moderate	Severe	Healed
Mild	1.00	0.00	0.00	0.00
Moderate	0.59	0.41	0.00	0.00
Severe	0.59	0.41	0.00	0.00
Healed	0.00	0.00	0.00	1.00

However, as mentioned above, due to the low number of observations, there is great uncertainty around the values shown in this transition matrix. For example, most of the cells of the matrix show either a probability 0 or 1, which have a significant impact on the model results. This issue can be overcome (or at least partially) by assuming an uninformative prior Dirichlet(1, 1, 1, 1) for all transitions. The resulting posterior distribution of the number of observations per health state at year 1 is shown in Table A3.3.

Table A3.3. Posterior distribution of the number of observations per health state at year 1 (52 weeks) for burosumab patients (one to four years old) – ERG estimate

	Mild	Moderate	Severe	Healed	Total
Mild	2.00	1.00	1.00	1.00	5
Moderate	3.36	2.64	1.00	1.00	8
Severe	5.72	4.28	1.00	1.00	12
Healed	1.00	1.00	1.00	2.00	5

The next step is then to re-estimate the transition probability matrix but now based on the 30 "observations" from Table A3.3. The resulting posterior transition probability matrix is given in Table A3.4. Note that there are significant differences between Table A3.2 and Table A3.4. Notably, Table A3.4 has no cells with a probability 0 or 1. It should be emphasised that even though the number of observations was increased from 14 to 30, the transition matrix in Table A3.4 is still surrounded by great uncertainty. This matrix was used by the ERG in their PSA.

Table A3.4. ERG transition probability matrix for burosumab patients (one to four years old) as used in the PSA

	Mild	Moderate	Severe	Healed
Mild	0.40	0.20	0.20	0.20
Moderate	0.42	0.33	0.13	0.13
Severe	0.48	0.36	0.08	0.08
Healed	0.20	0.20	0.20	0.40

It is clear that, in this case, changing the prior distribution will have a significant impact on the posterior distribution because the number of observations is very low. This is illustrated in Table A3.5 and Table A3.6, where the posterior matrices, as estimated by the company, are shown.

Note that the company chose as prior distribution a Dirichlet(0.05, 0.05, 0.05, 0.05), which can also be interpreted as a uniform prior distribution expressing the prior belief that each transition is equally likely (0.05/0.2 = 0.25) but with a very high level of uncertainty (since these prior estimation is only based on 0.2 "counts"). However, with this prior distribution, the posterior matrix in A3.6 is more similar to the original matrix in Table A3.2 than the ERG matrix in Table A3.4. Since the company indicated that the choice of this prior was arbitrary, the ERG was concerned regarding the appropriateness of this choice since it seems to be based on matching the observed matrix (which very much favours burosumab given the high number of cells with either 0 or 1) and not representing prior beliefs about these transitions.

Table A3.5. Posterior distribution of the number of observations per health state at year 1 (52 weeks) for burosumab patients (one to four years old) – company estimate

	Mild	Moderate	Severe	Healed	Total
Mild	1.05	0.05	0.05	0.05	1.2
Moderate	2.41	1.69	0.05	0.05	4.2
Severe	4.77	3.33	0.05	0.05	8.2
Healed	0.05	0.05	0.05	1.05	1.2

Table A3.6. Transition probability matrix for burosumab patients (one to four years old) as used in the company PSA

	Mild	Moderate	Severe	Healed
Mild	0.88	0.04	0.04	0.04
Moderate	0.57	0.40	0.01	0.01
Severe	0.58	0.41	0.01	0.01
Healed	0.04	0.04	0.04	0.88

In conclusion, it seems clear that running the analyses with the ERG or the company posterior transition probability matrices is expected to have a major impact on the model results. This was shown by the ERG in section 6.4.3.5. When the PSA was run with the posterior transition probability matrices estimated by the company (i.e. based on a prior Dirichlet(0.05, 0.05, 0.05, 0.05) for all possible transitions), the ICER obtained was [redacted]. As the prior distribution approached a Dirichlet(1, 1, 1, 1), the ICER increased. In particular, assuming a prior Dirichlet(1, 1, 1, 1) for all possible transitions, resulted in the ERG PSA ICER of [redacted].

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Burosumab for treating X-linked hypophosphataemia [ID1151]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Friday 4 May 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Clinical expert opinion sought by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has only sought clinical expert opinion from Professor Peter Selby, who specialises in adults with metabolic bone disease.	Consultation of a specialist in paediatric bone disease should be conducted.	Burosumab is indicated for use in children only, and therefore, it may have been appropriate to consult a specialist in paediatric bone disease.	Not a factual error.

Issue 2 Typographical errors and confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4 (page 11) states "At Week 64, [redacted]% of children treated with biweekly burosumab had healing of rickets (RGI-C global scores ≥ 1.0)". The figure [redacted]% is incorrect. The correct figure is [redacted] and should be marked academic in confidence (AIC).	At Week 64, [redacted] of children treated with biweekly burosumab had healing of rickets (RGI-C global scores ≥ 1.0)	Correction of a typographical error and confidential marking.	Not a factual error. Please see p.13 of the CS in the section: Impact of the new technology
Section 1.4 (page 11) "Furthermore, [redacted] of children treated with burosumab had substantial healing of rickets (RGI-C global scores ≥ 2.0). Growth velocity increased by [redacted]) in children treated with burosumab every two weeks, with a corresponding least-squared (LS) mean change in standing height z-	Furthermore, [redacted] of children treated with burosumab had substantial healing of rickets (RGI-C global scores ≥ 2.0). Growth velocity increased by [redacted]) in children treated with burosumab every two weeks, with a corresponding least-squared (LS) mean change in standing height z-score of +[redacted]."	Correction of confidential marking.	Not a factual error.

score of + [redacted]).”The figures should be marked AIC.			
Section 1.4 (page 11) “The RGI-C score was [redacted] with conventional therapy in Study CL002 (median 102 weeks). Furthermore, [redacted] of children treated with conventional therapy in Study CL002 had substantial healing of rickets (RGI-C global scores ≥ 2.0).” The figures should be marked AIC.	The RGI-C score was [redacted] with conventional therapy in Study CL002 (median 102 weeks). Furthermore, [redacted] of children treated with conventional therapy in Study CL002 had substantial healing of rickets (RGI-C global scores ≥ 2.0).	Correction of confidential marking.	Not a factual error.
Section 1.4 (page 12) “All 52 patients (100%) experienced at least one TEAE during the study.” This should not be marked AIC	All 52 patients (100%) experienced at least one TEAE during the study.	Correction of confidential marking.	Not a factual error.
Section 1.6 (page 14) states that when discounting was not applied the company’s analysis, the estimated gain in QALYs was 17.008 at an additional cost of [redacted]. The same text is repeated in section 5.4.1 (page 102), section 5.3 (page 112) and section 9.2.1 (page 129).	The estimated gain in QALYs was 16.891 at an additional cost of [redacted]	Correction of a typographical error.	The company is correct. Correction made.
Section 1.9 (page 15): The ERG explores a scenario in which the number of prevalent patients is 193 rather than 174. Based on this, the acquisition cost of burosumab is quoted as [redacted].	The acquisition cost of burosumab at list price in this scenario would be [redacted].	Correction of a typographical error.	The company is correct. Correction made.

Section 1.9 (page 15) “Since real-world data suggest that there could be [redacted] XLH patients between one and 17 years of age in England, using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab.” Figures should be marked AIC.	Since real-world data suggest that there could be [redacted] XLH patients between one and 17 years of age in England, using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab.	Correction of confidential marking.	Not a factual error.
Section 2.2.2.1 (page 20) “[redacted] of these [redacted] patients appear to be currently treated in ERN-BOND centres.” Figures should be marked AIC.	[redacted] of these [redacted] patients appear to be currently treated in ERN-BOND centres.	Correction of confidential marking.	Not a factual error.
Section 2.2.2.1 (page 20) “…but have identified an average of [redacted] new patients per year based on a real-world confirmed patient dataset” Figure should be marked AIC.	…but have identified an average of [redacted] new patients per year based on a real-world confirmed patient dataset.	Correction of confidential marking.	Not a factual error.
Section 2.2.8.1 (page 25) “In the interim analysis of [redacted] in the UK, it is not clear how many children are being analysed” Figure should be marked AIC.	In the interim analysis of [redacted] in the UK, it is not clear how many children are being analysed	Correction of confidential marking.	Not a factual error.
Section 2.5 (page 27) “Burosumab is expected to be used in line with the	Burosumab is expected to be used in line with the anticipated marketing	Wording correction.	Not a factual error.

anticipated marketing authorisation in children and adolescents with XLH from the age of one year old who have radiographic evidence of bone disease." Please use the exact indication wording.	authorisation, for treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.		
Section 4.2.1 (page 37) and Table 4.6. "All [redacted] patients who contributed the radiographs for RSS and RGI-C analyses were enrolled at a single US site, Shriners Hospital in St. Louis, Missouri." The number (n=[redacted]) should be marked AIC throughout (has also been corrected in marking of main submission)	All [redacted] patients who contributed the radiographs for RSS and RGI-C analyses were enrolled at a single US site, Shriners Hospital in St. Louis, Missouri.	Correction of confidential marking.	Not a factual error.
Section 4.2.4.1 (page 51) states "The Q2W regimen is [redacted] and are the only results presented here." This is no longer confidential and will be corrected in marking of the main submission.	The Q2W regimen is the expected licensed dosing frequency and are the only results presented here.	Correction of confidential marking.	Not a factual error.
Section 4.2.4.1 (page 53) states "In the Q2W group (N = 26), RSS total scores were reduced by 61% at week 40 (LS mean (SE) change: [redacted]), p < 0.0001) and by 58% at week 64 (-[redacted]), p < 0.0001)."	In the Q2W group (N = 26), RSS total scores were reduced by 61% at week 40 (LS mean (SE) change: [redacted]), p < 0.0001) and by 58% at week 64 (-[redacted]), p < 0.0001).	Correction of confidential marking.	Not a factual error.

Some of these figures should be marked AIC.			
Section 4.2.4.1 (page 53) states “In the Q2W-treated higher RSS subgroup (baseline RSS total score ≥ 1.5; N = 17), RSS total score was reduced by 71% at week 40 (LS mean [SE] change: -[redacted]], p < 0.0001) and by 62% at week 64 [redacted]], p < 0.0001).” Some of these figures should be marked AIC.	In the Q2W-treated higher RSS subgroup (baseline RSS total score ≥ 1.5; N = 17), RSS total score was reduced by 71% at week 40 (LS mean [SE] change: -[redacted]], p < 0.0001) and by 62% at week 64 [redacted]], p < 0.0001).	Correction of confidential marking.	Not a factual error.
In Table 4.7, the RSS total scores (baseline and mean change) and should be marked AIC. RGI-C total scores should be marked AIC.	Baseline:[redacted], Mean change Week 40: [redacted] and Mean change Week 64: [redacted]. Mean Week 40: +[redacted], Mean Week 40: [redacted]	Correction of confidential marking.	Not a factual error.
Section 4.2.4.1 (page 53) states “Similarly, RSS wrist scores and knee scores were reduced at week 40 by [redacted]), respectively.” Some of these figures should be marked AIC.	Similarly, RSS wrist scores and knee scores were reduced at week 40 by [redacted]), respectively.	Correction of confidential marking.	Not a factual error.
Section 4.2.4.1 (page 57) states. “Observational data corresponding to the [redacted] paired baseline radiographs showed that many patients in this study had decreased height for age	Observational data corresponding to the [redacted] paired baseline radiographs showed that many patients in this study had decreased height for age	Correction of confidential marking.	Not a factual error.

(mean [SD] standing height z-score of [redacted].” The height z-score should be marked AIC (has also been corrected in marking of main submission)	(mean [SD] standing height z-score of [redacted]		
Section 4.3.1 (page 62) states “For baseline age the mean was [redacted] for CL201 and [redacted] for CL002 giving a mean difference of [redacted] and for gender there were [redacted] in CL201 and [redacted] males in CL002 with a p-value [redacted] chi-squared test). However, the baseline total RSS score was significantly higher in CL201 (mean difference[redacted])” The baseline characteristics for studies CL201 and CL002 used in the Propensity Score Matching are AIC.	For baseline age the mean was [redacted] for CL201 and [redacted] for CL002 giving a mean difference of [redacted] and for gender there were [redacted] in CL201 and [redacted] males in CL002 with a p-value [redacted] chi-squared test). However, the baseline total RSS score was significantly higher in CL201 (mean difference[redacted])	Correction of confidential marking.	Not a factual error.
Section 4.5 (page 65) states “Additional work on clinical effectiveness undertaken by the ERG has been included in section 4.2.4 of this report.” It is unclear what additional work the ERG completed in Section 4.2.4.	Suggest amending or deleting this sentence.	Correction of a typographical error.	Changed to: “Additional work on clinical effectiveness undertaken by the ERG has been included in section 4.3.2 of this report.”
Section 8.1.3 (page 126) states “In a case-note review of 59 adults with XLH, attending a single inherited metabolic disease service in the UK	In a case-note review of 59 adults with XLH, attending a single inherited metabolic disease service in the UK	Correction of confidential marking.	Not a factual error.

from 1998, 42% had had an osteotomy" This study is published so this is no longer confidential.	from 1998, 42% had had an osteotomy.		
Section 9.1 (page 128) states "At Week 64, [redacted] of children treated with biweekly burosumab had healing of rickets (RGI-C global scores ≥ 1.0)". The figure [redacted] is incorrect. The correct figure is [redacted] and should be marked AIC.	At Week 64, [redacted] of children treated with biweekly burosumab had healing of rickets (RGI-C global scores ≥ 1.0).	Correction of a typographical error and confidential marking.	Not a factual error. Please see p.13 of the CS in the section: Impact of the new technology
Section 9.1 (page 128) states "Furthermore, [redacted] of children treated with burosumab had substantial healing of rickets (RGI-C global scores ≥ 2.0). Growth velocity increased by [redacted]) in children treated with burosumab every two weeks, with a corresponding least-squared (LS) mean change in standing height z-score of +[redacted])." The figures should be marked AIC.	Furthermore, [redacted] of children treated with burosumab had substantial healing of rickets (RGI-C global scores ≥ 2.0). Growth velocity increased by [redacted]) in children treated with burosumab every two weeks, with a corresponding least-squared (LS) mean change in standing height z-score of +[redacted]).	Correction of confidential marking.	Not a factual error.
Section 9.1 (page 128) states "The RGI-C score was [redacted] with conventional therapy in Study CL002 (median [redacted]weeks). Furthermore, [redacted] of children treated with conventional therapy in Study CL002 had substantial healing of rickets (RGI-C global scores ≥ 2.0)."	The RGI-C score was [redacted] with conventional therapy in Study CL002 (median [redacted]weeks). Furthermore, [redacted] of children treated with conventional therapy in Study CL002 had substantial healing of rickets (RGI-C global scores ≥ 2.0).	Correction of confidential marking.	Not a factual error.

The figures should be marked AIC.			
Table 5.3 (page 80): cross-referencing error in the second row of the table.	Correct cross-referencing.	Correction of a typographical error.	Not a factual error.
Section 5.3.3 (page 81): cross-referencing error in the text	Correct cross-referencing.	Correction of a typographical error.	Not a factual error.
Section 5.3.3.4 (page 95) ERG comment includes the statement: "These revisions have been included in the revised base-case."	Suggest delete this statement.	The text prior to this statement does not make reference to any revisions.	Agree. Text deleted.
Many sections of the report make reference to fractures (for example on page 34), but these are most likely to be non-traumatic pseudofractures.	Please check whether appropriate wording is fractures or pseudofractures.	Correction of type of fracture referred to throughout report.	Not a factual error.

Issue 3 Healing of rickets

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state several times "In the CS, the company uses the terms 'healing' and 'substantial healing of rickets'. These are defined using RGI-C global scores, where scores ≥+1.0 indicate 'healing of rickets' and scores ≥+2.0 'substantial healing of rickets'. The company does explain that "Healing in this context indicates improvement in the radiographic abnormalities and does not imply that	Please delete.	The relationship between RGI-C scores and the terms, healing and substantial healing is clearly described in the CS, and the RGI-C scores are clearly presented. Therefore, we feel this statement is misleading. The duration of the studies is relatively short and so the company was unable to show that patients had fully healed rickets, hence the use of	Not a factual error.

complete healing was observed" (CS, page 100). However, throughout the report the term 'healing of rickets' is used without any explanation of the degree of healing (minimal, substantial or complete)." As stated above and described in the CS, RGI-C scores ≥+1.0 indicate 'healing of rickets' and scores ≥+2.0 'substantial healing of rickets'. Therefore, where it states in the CS that patients had healing of rickets, this would equate to RGI-C global scores ≥ 1.0. In the CS RGI-C scores are presented alongside the description of the degree of healing, therefore this statement is misleading.		the term 'healing rickets' to show that there was on-going improvement. Given that bone metabolism is a complex process and that in children it is not just a case of healing existing bone, but also laying down new bone, this is likely to take longer than the 64-week study period of CL201.	

Issue 4 Dose titration based on residual gene activity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.5, page 23. The ERG state "Some patients with a PHEX mutation who are diagnosed with XLH retain residual gene activity.[17] In practical terms, this may mean that further dose-titrations are necessary that take into consideration not just weight but also residual gene activity. It is unclear if there is a validated test available to determine PHEX activity."	This statement should be removed.	The statement is incorrect. According to the Summary of Product Characteristics for burosumab, dose titration should be based on serum phosphate levels (not residual gene activity).	Agree. This statement has been removed.

In the clinical trials for burosumab, dose was adjusted based on fasting serum phosphate levels. In clinical practice, dose adjustments will also be made based on fasting serum phosphate levels, as outlined in the Summary of Product Characteristics.			

Issue 5 Burosumab mechanism of action

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.4.1, page 27. "Since the aetiology and pathophysiological mechanisms behind XLH remain largely unknown, the mechanism-of-action of burosumab must be considered as ameliorating the symptoms rather than treating the underlying cause."	Delete this statement.	The pathophysiology of XLH is reasonably well characterised by Feng et al (2013)[1]. Burosumab is the only treatment for children with XLH that addresses the underlying pathophysiology. As detailed in section 6.1 of the CS, the defect in PHEX leads to an erroneous signal in the phosphate sensing control system that leads to inappropriate excess levels of FGF23 (Jonsson et al., 2003; Yamazaki et al., 2002). Excess FGF23 drives the pathophysiology of XLH leading to impaired conservation of phosphate by the kidney and consequent hypophosphatemia (Jonsson et al., 2003; Yamazaki et al., 2002). FGF23 also suppresses 1,25(OH)2D production (Perwad et al., 2005), resulting in decreased intestinal absorption of calcium and phosphate, further impairing the body's phosphorus supply (Sabbagh et al., 2008). Burosumab is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the activity of FGF23, which	Agree. This statement has been removed.

[1] Feng JQ, Clinkenbeard EL, Yuan B, White KE, and Drezner MK. Osteocyte regulation of phosphate homeostasis and bone mineralization underlies the pathophysiology of the heritable disorders of rickets and osteomalacia Bone. 2013 June ; 54(2): 213–221. doi:10.1016/j.bone.2013.01.046

		increases tubular reabsorption of phosphate from the kidney and increases the production of serum concentration of 1, 25 dihydroxy-Vitamin D that enhances intestinal absorption of calcium and phosphate (Carpenter et al., 2014; Summary of Product Characteristics (Crysvita), 2017). By directly inhibiting excess FGF23, improving phosphate homeostasis, and healing rickets, burosumab has the potential to significantly alter the natural history of the disease. In Study 201, renal phosphate reabsorption (TmP/GFR) increased in all subjects to levels close to, or into, the normal range, showing clear evidence of an effect on the main pathophysiologic problem in XLH.	

Issue 6 Skeletal normalisation and associated long-term benefits

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The scientific plausibility that correcting a patient's skeleton during growth will lead to the avoidance the lifelong impacts in adulthood, has been questioned. Section 1.10 (page 16) states: the company conducted their analysis upon the assumption that these effects would be lifelong, despite	Rather than stating that there is no evidence to support the assumption of lifelong effects, the wording should be corrected to state that this assumption is based on scientific reasoning that correcting skeletal deformities during growth will normalise the skeleton, and that this normalisation is expected to result in	It is important for the ERG and committee to understand that burosumab normalises development of the skeleton. The company does not assume that burosumab has a lifelong treatment effect, but rather that a normalised skeleton at the end of growth will result in lifelong changes.	Not a factual error. In the absence of evidence as to the treatment effect of burosumab on the various manifestations of the condition and consequent quality of life over the entire lifetime it is necessary to make assumptions. Such

treatment being stopped at the age of 16 in females and 17 in males, but there is no evidence to support that assumption. This assumption was proven to be crucial and one of the main drivers of the cost effectiveness results. Section 4.6.2 (page 69) states: In addition, the model currently assumed that the effect of burosumab, although stopped at age 16 (women) or 17 (men) lasts for the rest of their lives. This also seems unrealistic, the effects of burosumab on stature, bowing of the legs, joint deformity etc. are likely to persist fairly long but may wane as osteomalacia itself and the resulting fractures may lead to associated problems in later life. Effects on bone strength will wane quicker, therefore repeated fractures and badly healing fractures after 10 or 20 years are likely to occur. Effects of burosumab on symptoms caused by hypophosphatemia itself will disappear as soon as therapy is stopped. Therefore, we have assumed in the ERG base-case that patients will experience a decline in quality of life 20 years after the end of treatment, which was operationalised by moving to the utility value of the next worse health state.	lifelong avoidance and reduction of manifestations in adulthood. Furthermore, all scenarios explored in relation to a decline in quality of life should be corrected, such that the decline is applied equally in both arms. The current analysis is biased against burosumab, as the decrement is only applied in the burosumab arm and not in the SoC arm. Correcting for this bias increases the ERGs estimated discounted QALY gain from 3.9 to 4.4 and reduces the ICER from [redacted] to [redacted].	XLH is a highly complex multi-system disorder with interdependent elements which are beyond the ability to model given the currently available data sets. For this reason, it was not possible to specifically model the likely long-term impacts of a misaligned skeleton for untreated patients who develop deformities during growth. Therefore, patients were conservatively assumed to remain in their health state from the age of 18. Age-dependant utility multipliers were applied to attempt to account for declining health-related quality of life over time. The assumption is conservative since any decline in health status as a result of symptoms in adulthood would likely be greater in the SoC arm than the burosumab arm. Furthermore, the significant costs incurred in adulthood are likely to be underestimated in the SoC arm as only dental abnormality costs, hip arthroplasty costs and knee arthroplasty costs were considered, which do not reflect the lifelong financial impact of a misaligned skeleton, hyperparathyroidism and renal disease. As is mentioned in the ERG report, rickets, the hallmark of XLH in children, is associated with substantial skeletal deformities and that these children will go on to suffer lifelong disability and pain as these deformities become irreversible when growth ceases. Once	assumptions are a matter of judgement and therefore a disagreement with those assumptions does not constitute a factual error. The company have assumed that all patients whilst taking burosumab will have their rickets healed and thus be restored to full health and that this will continue until death. Unlike with SoC, there is no possibility of any deterioration. This is not a conservative assumption and therefore the ERG have explored a means by which the duration of the treatment effect might be reduced.

		growth is completed, although osteomalacia may be present, skeletal deformities will not develop, therefore in patients in whom skeletal deformities have been avoided or corrected and normal or improved height has been achieved, these benefits can be expected to be lifelong: • The long-term consequences of unresolved skeletal disease in childhood include bowing deformities of the legs, short stature, and/or inward twisting of the tibiae (in-toeing). Correcting the skeletal geometry in childhood would avoid these deformities throughout adulthood. • Nearly half of adults require some form of corrective surgery of skeletal abnormalities that originated during skeletal growth (Chesher et al., 2018). It is expected that this type of surgery will be greatly reduced or will no longer be required if the patient received burosumab in childhood. • In adults, skeletal abnormalities that originated during skeletal growth contribute to early osteoarthritis, stiffness and enthesopathy that cause pain and continue to limit physical	

		function. In patients in whom skeletal deformities have been avoided or corrected, this will result in reduced osteoarthritis, stiffness and enthesopathy, reduced pain and improved mobility throughout their lifetime. The ability to engage in increased levels of activity can be expected to be bone protective even in the absence of additional pharmacotherapy. There is however no data set which would allow this effect to be accounted for in the model and so whilst it would be reasonable to expect, an additional benefit in favour of patients treated with burosumab has been omitted. Bone remodelling continues throughout life. In patients with XLH this means that new bone being laid down may not be fully mineralised, leading to a reduction in bone quality. The clinical effects of this gradual reduction of bone quality in adult life will not become apparent until it reaches a clinically meaningful threshold. Adults who have had no previous disease-modifying treatment can be expected to start at or reach any such threshold earlier than patients who have had such treatment. So, in a cohort of adults managed with SoC it would be expected that, relative to those treated with burosumab, they would start adulthood with much lower	

		bone quality, in addition to any skeletal deformities present from childhood. Following cessation of burosumab treatment, adults may receive conventional therapy to treat the symptoms of osteomalacia. Skeletal abnormalities can only be prevented in childhood - surgery can be used to attempt to correct deformities at the end of growth but patients often require ongoing surgery that fails to completely correct the abnormality or restore physical function. For these reasons, the ERGs base case analysis which assumes a significant quality of life decrement for adults aged 38 and over treated with burosumab is inappropriate: • Firstly, the ERGs analysis is only applied to the burosumab arm and fails to apply the same assumptions to the SoC arm, which biases the analysis against burosumab. • Secondly, the magnitude of the decrement is very significant and is assumed to apply to all patients. The expectation is that any symptoms that do develop (e.g. osteomalacia) can be treated with conventional therapy, would not occur in 100% of patients, and would	

		not be associated with the modelled utility change of 0.1 or 0.14. The phosphate needs of adults are lower than in patients with a growing skeleton, thus conventional therapy is likely to be more effective. • Lastly, the age at which this has been assumed to apply is entirely arbitrary and does not seem to be scientifically justified. There is no rationale for rapidly developing osteomalacia in patients that are mobile and have an aligned skeleton. It is unrealistic to develop osteomalacia before the age of 40 in patients with healthy skeletons at the end of growth.	

Issue 7 Prevalence calculation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.2.1 (page 19) states: it remains unclear how this prevalence value has been calculated (e.g. the denominator, how the 522 test cases were originally identified etc.).	Appendix 1 of the company response to clarification questions clearly provided the details, and each of the records that made up the denominator of 522 patients that were selected as not XLH, possibly, probably or definitely XLH. The details of each of	The company has sought very detailed information from the authors and on the prevalence calculation and has provided the ERG with far more detail than would normally be provided on prevalence calculations. The ERG has not requested any further clarification	Not a factual error, The denominator here refers to the total number of male and female patients aged 1-16 or 1-17, respectively, whose anonymised records are present in the CPRD database and who should have therefore been captured in the

	the 522 patient records is provided in this Appendix.	and appears to have overlooked the detailed information provided in response to clarification questions.	analysis i.e. segregated into 'not XLH, possibly, probably or definitely XLH' categories. Detailed information was provided by the company on the clinical records for the 522 patients included in the analysis. However, it was not clear which patients the authors considered to fall into the 'not XLH, possibly, probably or definitely XLH' categories, and therefore it was not possible for the ERG to further assess the proposed prevalence values based on this data. Ultimately, the question of XLH prevalence will only be addressed with any certainty with respect to this specific (currently unpublished) dataset after "[redacted]

Issue 8 Equity weighting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 5.1 (page 75) states that an additional weighting can be applied for incremental QALYs above 10 years, but that the company submission included no additional equity weighting applied to QALY gains.	Remove this row from the table.	Whilst we appreciate that the ERG is referencing the new value for money guidelines used within the HST process from April 2017, this was not explicitly included within the company submission as the company felt that was relevant only to decision making and was not something that needed to be presented within the submission.	Agree. This has been removed from the table.

Issue 9 Description of company assumptions for transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3.1 (page 83) states: Since the company assumed that the treatment effect of burosumab on RSS was not the same in both trials, in the model each trial result was applied to those patients that better matched the trial population.	Delete the first part of this sentence, leaving only: In the model each trial result was applied to those patients that better matched the trial population.	Section 5.3.2, point 2 states "when this issue was brought up in the clarification letter, the company reiterated that transition probabilities are age dependent for burosumab but according to the ERG this answer lacked a proper justification." We apologise that this was not a detailed enough response and would have been happy to provide further clarification if it had been sought. Later in Section 5.3.2, the ERG states "It seems that this assumption was	Not a factual error. By using the data from each separate trial for each specific age group, rather than pooling the data and using it for patients 1-12, the company implicitly assumed that the treatment effect for burosumab was different between age groups (but no formal statistical test was conducted). The ERG has only

		made only based on the available data (CL205 for patients aged one to four and CL201 for patients aged five to 12)". This is correct, as stated in the clarification response. This should therefore be reflected in Section 5.3.3.1, as it is factually inaccurate to state that a specific assumption around treatment effects in the two population was made by the company.	made this implicit assumption explicit for the committee.

Issue 10 Derivation of utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3.3 (page 87) states: the utility values that the company presents in Table 31 of the CS (Table 5.9) do not match all the utility values as presented in the report about the vignette study by Lloyd et al. 2018. No explanation for this discrepancy was provided. The report then states: In addition, it is not clear to the ERG how the standard deviations were derived that are presented in Table 5.9 for the non-moderate health states. For the three moderate health states it is unclear whether these values represent the SDs as observed from the vignette study, or the standard	The text should be updated as follows: The utility values that the company presents in Table 31 of the CS (Table 5.9) do not match all the utility values as presented in the report about the vignette study by Lloyd et al. 2018. The company adjusted the utilities to account for missing estimates for some of the healed and severe health states. The moderate health state was used as an anchor and the values for other health states were calculated based on differences to the moderate state.	As stated on page 143 of the company submission, the moderate health state was used as an anchor and the values for other health states were calculated based on differences to the moderate state. This is the justification for using different utilities to those in the main report (Lloyd et al). The report presented the mean of the utilities for each health state and did not account for some respondents not providing estimates for the healed or severe health states. A spreadsheet provided alongside this response shows the exact calculation. This spreadsheet also details the calculation of the standard deviations.	Not a factual error. The company did not provide any explanation to the ERG regarding the adjustments made on the utilities. The idea that the ERG should have asked for this in the clarification letter is illogical, given that we only received the report by Lloyd in response to the clarification letter, so the ERG was not aware of a discrepancy until that time. In addition, the ERG asked in their clarification letter for *all* the details of the vignette study, so

errors (SEs), representing the uncertainty of the mean estimate. In the electronic model, these values have been used as if they represent SEs.		We agree with the ERG that it would have been more appropriate to use standard errors rather than standard deviations. The values that were reported in the submission are standard deviations. If a clarification question had been provided around this issue, the company could have provided a response rather than responding as a factual error.	information regarding any adjustment should have been provided at that time. It is important to emphasise that the ERG does not consider the method used by the company (using the moderate health state as anchor) incorrect but understands that using health state utilities or the difference with respect to the moderate health state should lead to the same base case values. The latter did not occur and the ERG could not understand why that was the case. For that reason, the ERG decided to use the utilities provided in the report by Lloyd in their base case. Unfortunately, the ERG is not aware of any spreadsheet where the exact calculation is shown. Finally, we are happy that the company has now confirmed that they made an error when using the SDs as if they were SEs in the PSA.
Section 3.3.4 (page 33) states the vignettes for the various health states do not appear to be realistic in that it seems likely that there might be some resolution of the bone disorder such that the RSS score decreases, but		These health state descriptors were generated from clinical experts in XLH. It is factually inaccurate for the ERG to state that the vignettes are not realistic when they have been	Not a factual error. As the company states the descriptors were based on clinical expert opinion and

that this resolution only occurs after incurring deformity, which cannot be completely resolved and with some continued increased risk of fracture.		described by clinicians treating patients with XLH.	therefore it is perfectly legitimate to question this opinion.

Issue 11 Discounting of costs and health effects

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.2 (page 79) states that NICE Technology Appraisal Methods Guide specifies that a rate of 1.5% could be considered by the Appraisal Committee but that it is not specified that a rate of 1.5% should be applied in the base-case analysis. For this reason, the ERG has considered a discount rate of 3.5% in their base case.	A discount rate of 1.5% should be used on the basis that burosumab meets the following criteria: • Treatment restores people who would otherwise have a very severely impaired life to near full health • This is effect is sustained for more than 30 years • Whilst there is uncertainty regarding the probability of developing complications such as osteomalacia in adulthood, the probability following burosumab treatment in childhood (and the associated corrections to skeletal geometry) is expected to be less, and certainly no more than, with conventional	The Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes[2] provides a discussion of NICE guidelines regarding discounting that apply to the HST programme. In particular, the guide states: "In line with the Guide to the Methods of Technology Appraisal, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Evaluation	Not a factual error. The ERG leaves it up to the committee to decide if all criteria will be fulfilled for this case.

[2] https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf

	treatment. Therefore, it is highly likely that the long-term health benefits are likely to be achieved. • The treatment does not commit the NHS to significant irrecoverable costs	Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved." On this basis, it is inaccurate for the ERG to not consider using the 1.5% discount rate in the base case analysis. Given that burosumab is expected to result in a lifelong benefit with most patients remaining in the healed state, the 1.5% discount rate appears to be the most appropriate. Even in the extreme scenario presented by the ERG, in which there is a significant utility decline at 38 years, this would suggest an effect of over 30 years which further supports the use of the 1.5% discount rate. During the recent HST appraisal of Strimvelis[3], the committee considered that it was likely that the alternative 1.5% discounting rate was intended to cover situations when costs are incurred up-front but benefits are accrued over a longer period. This is comparable to burosumab, in which the costs are incurred in childhood resulting in lifelong benefits. Furthermore, the HM Treasury Green Book[4] has recently been updated and	

[3] https://www.nice.org.uk/guidance/hst7/resources/strimvelis-for-treating-adenosine-deaminase-deficiencysevere-combined-immunodeficiency-pdf-1394905926085
[4] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/685903/The_Green_Book.pdf

		specifically states that QALYs should be discounted at a rate of 1.5%.	

Issue 12 Model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.2 (page 78) states: It is likely that RSS can improve and indeed rickets appear to be healed, but for there to be residual deformity and increased fracture risk. Since deformity and fracture risk would likely be negatively associated with utility, defining health states only by RSS is likely to overestimate any improvement due to burosumab in moving to states with a lower RSS.	Delete statement that the definition of health states will be overestimating the improvement with burosumab.	Any residual deformity would exist in both arms i.e. burosumab and conventional therapy. Given burosumab is expected to correct skeletal deformity, there is likely to be less residual deformity compared to conventional therapy. Therefore, it is factually inaccurate to state that defining health states only by RSS is likely to overestimate any improvement due to burosumab.	As stated for Issue 6 this is a matter of judgement.

Issue 13 Outcomes reporting the physiological impacts of hypophosphataemia

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 2.2.1 (page 19), the ERG states that “the diverse physiological impacts of hypophosphataemia are not	Delete this statement.	The CS does describe the impact of disease, and the treatment benefits on functional ability and pain and also on mobility as measured by the 6MWT. RSS was selected for the	Not a factual error.

captured at all in this submission". This is factually inaccurate.		model as x-ray assessments for rickets are generally considered the gold standard for assessing rickets and radiological evidence for disease is required in the licence for burosumab. In addition, previous HSTs have used 6MWT as a functional measure against which the health economic analyses have been calculated and these have been subject to considerable criticism from both the ERG and the NICE committee.	

Issue 14 Utilities in PSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.4.2.3 (page 109) states that for patients aged 13 years and older the 95% confidence intervals for the utilities are: Healed (0.018,0.364) Mild (-0.085,0.277) Moderate (0.417,0.727) Severe (-0.378,0.152) There confidence intervals are inconsistent with the ERGs statement that standard errors should be used rather than standard deviations.	Correct the 95% confidence intervals to: Healed (0.098, 0.283) Mild (0.015, 0.178) Moderate (0.505, 0.644) Severe (-0.254, 0.028)	The ERG has appropriately highlighted that the standard error should be used, rather than the standard deviation, in sampling utilities. Therefore, the confidence intervals should be based on standard errors rather than standard deviations. Based on these 95% CIs, the ERGs concern regarding the bounding of utilities in the PSA should be reduced by using standard errors rather than standard deviations, as the bounding will only impact the severe utility which crosses zero. In the PSA, this 95% CI for the severe health state	The company is correct in that the CIs referred to in this issue are based on SDs and not SEs, and therefore they are incorrect. This was done on purpose to show the way the company included uncertainty into the model (even though it was mentioned that this is incorrect). The ERG would like to emphasise that in the revised model the CI's are based on SEs.

Page 110 states that, according to the ERG, the combination of using standard deviations (instead of standard errors) and the bounding condition introduced by the company implies that the model samples very large utility values for the mild and especially the healed health state, and very low for the severe health state. The ERG is of the opinion that the current PSA results, as presented by the company, are biased in favour of burosumab		would effectively be bounded to (0.254, 0). None of the other sampled values for this age group would be affected. Consequently, as only the severe utility would be impacted by bounding, then the PSA results would in fact be biased against burosumab, rather than in favour of burosumab.	In the ERG base case, the utilities are unbounded and therefore the bias is no longer an issue. The following text has been added to indicate that what it is shown in the ERG report relates to the implications of the approach taken by the company: "Note that this CI (and the ones shown below) are based on the standard deviation instead of the standard error and therefore it is incorrect. These CIs are used to illustrate the way the company included the uncertainty into the model."
In their estimation of standard errors rather than standard deviation in the model, the ERG has assumed a sample size of 4 (healed, severe states) and 6 (mild, moderate). The correct number of respondents is 5 and 7, respectively.	If timelines permit, reproduce PSA results with these corrected sample sizes.	The ERG had used incorrect sample sizes within the calculation of standard errors in the updated model.	Not a factual error. The information in Lloyd et al. was unclear in this respect and the ERG had to make an assumption. Given the current timelines, it is infeasible to re-run the PSA. In any case, this is expected to have a minor impact on the model results.

Issue 15 Transition probabilities in the PSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.4.2.3 (page 110) includes a paragraph discussing the use of prior distributions when sampling transition probabilities. The report describes the 0.05 prior used by the company as "a sort of prior distribution". The report then introduces uninformative prior distributions (as if they have not be considered by the company) and states "that this can be achieved for example by employing a minimally informative prior distribution like a Dirichlet(1, 1, 1, 1), which can be interpreted as a uniform prior distribution expressing the belief that each transition is equally likely (i.e. this prior distribution assumes a 0.25 probability to all transitions with a high level of uncertainty). Given the low number of observations in the burosumab arm, using uninformative prior distributions for the transition matrices seems appropriate to the ERG and will be assumed in the ERG preferred base-case analysis in section 6." The company analysis had already used an uninformative prior distribution with a probability of 0.05 rather than 0.5 used by the ERG. A	Amend the text as follows: "As a first step for the calculation of the transition probabilities in the PSA, the model calculates "Cumulative Gamma functions" (see e.g. "Transition probabilities" sheet, cell Q9) where a factor 0.05 was added to the random draw of the Gamma distributions to account for non-observed transitions (empty cells in matrix) in the PSA (e.g. from Severe to Severe). The use of such a uniform prior distribution is an appropriate approach. The choice of a prior distribution for transition matrices is discussed in the paper by Briggs et al. 2003,[84] where an uninformative prior distribution over the rows of transition probability matrices is recommended to overcome the potential problem of zero observed counts in some of the cells of the matrices. This can be achieved for example by employing a minimally informative prior distribution like a Dirichlet(1, 1, 1, 1), which can be interpreted as a uniform prior distribution expressing the belief that each transition is equally likely (i.e. this prior distribution assumes a 0.25	The ERG report currently implies that the company has not used a uniform prior distribution, but it has. Dirichlet(0.05, 0.05, 0.05, 0.05) is a uniform prior distribution. A non-uniform prior distribution would be Dirichlet(0, 0, 0.05, 0.05). We agree the model in sensitive to the choice of prior distribution. There are no definitive indicators for what value should be used as this is the definition of an *assumed* prior distribution. However, given the small number of observations in some transitions, the use of 0.5 or 1 (as per the ERG, rather than 0.05) effectively assumes a high likelihood that a patient will transition from the healed to severe health states in one cycle. Given the transition probabilities relate to the skeleton, such dramatic variances between cycles is clinically unlikely. Therefore, it is more appropriate to use a lower prior value such that the actual observed values carry more weight. Using a lower value is still using a uniformed prior, but one that is more clinically	Not a factual error. The first issue raised by the company is simply a matter of terminology. The notion of prior distribution (or any Bayesian concept) was not introduced by the company in the report or in the response of the clarification letter even though the ERG asked specifically about why the factor 0.05 was used in the PSA. The important issue is that both prior distributions are 'non-informative' in the sense that they both give equal weight to the 4 health states. However, the prior distribution used by the company implies that this prior is relatively unimportant compared to the data whereas the ERG is of the opinion that the data are lacking so much, that they provide hardly any information. For example, for children aged 1 to 4 years, there are only 13 patients to inform probabilities to

Dirichlet(0.5, 0.5, 0.5, 0.5) applies the same beliefs as a Dirichlet(0.05, 0.05, 0.05, 0.05), which can both be interpreted as a uniform prior distribution expressing the belief that each transition is equally likely (i.e. this prior distribution assumes a 0.25 probability). Furthermore, Appendix 3 of the ERG report implies that the value chosen for the prior was 1 but the model indicates it was 0.5.	probability to all transitions with a high level of uncertainty). The model results are sensitive to changes in the prior value chosen. The ERG is of the opinion that the arbitrary value used should be 0.5, rather than the company's choice of 0.05. Given the low number of observations in the burosumab arm, using a value of 0.5 in the uninformative prior distributions for the transition matrices seems appropriate to the ERG and will be assumed in the ERG preferred base-case analysis in section 6. Furthermore, the ERG noted that when UK chart data were chosen for the comparator arm, this adjustment was not needed because all possible transitions were observed. The company corrected this in the model." In addition, please provide clarity on whether the chosen value was 0.5 or 1.	plausible and will not produce unfeasibly extreme results.	4 health states. These 13 patients are not providing much information (many unobserved transitions), and it is likely that what was observed could be pure chance. Thus, the ERG considers that it is worrying that, knowing that the choice of the prior distribution has a large impact on the PSA outcomes, and having pointed this out explicitly in the clarification letter, the company opted to choose a rather extreme prior with the most positive impact for burosumab and not provide any further sensitivity analysis on this issue. Finally, the ERG would like to clarify that the model shows 0.5 because it is the last scenario run by the ERG and it was simply not reset to 1. The ERG PSA base case uses a 1.

Issue 16 Calculation of transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Appendix 2 provides detailed explanations of the derivation of transition probabilities. Some of the outputs are not accurately described in the text, for example, that some of the predicted transition probabilities are negative, which is implausible. The transition probabilities for patients aged 5 and older receiving burosumab have been calculated from a negative probability, which may invalidate the transitions used by the ERG. To overcome this negative probability, the ERG has also explored an alternative approach, but a clear description of the source of values has not been provided. Specifically, the values used in the following command: round(matrix(c(0.963702, 0.00020038, 0., 0.036098, 0.0538478, 0.946152, 0., 0., 0.0945621, 0.113132, 0.792306, 0., 0., 0., 0., 1.),byrow=T,nrow=4) In addition, the ERG has only applied their approach to the burosumab transition probabilities and not the SoC transition probabilities.	Please provide a more balanced view of the method and outputs of the proposed approach to adjusting transitions for time. In particular, an acknowledgement of the limitations of the approach including the estimation of negative probabilities (non-stochasticity). Please provide clarification on the values used in the alternative approach based on Chhatwal et al. 2016. Please also provide the same analysis for the SoC transition probabilities.	The method used to adjust the transition probabilities from 40 or 64 weeks to 1-year results in slightly different transition probabilities and therefore impacts the QALY gain and ICER associated with burosumab. The method used by the company is a standard approach that is associated will some limited uncertainty (as demonstrated in the response to clarification questions where the error was small). The alternative approach used by the ERG is much less transparent and more complex, and importantly, is also associated with limitations because it results in some (implausible) negative probabilities. In order for the committee to consider which may be suitable for decision-making, a balanced view of the two approaches should be provided by the ERG.	Not a factual error. The ERG agrees with the company in that the method used by the ERG is not perfect and it is associated with limitations. However, it is theoretically correct and the limitations have been explained in Appendix 2, including the issue of the negative probabilities which is indeed implausible. Negative probabilities were also obtained by the company in their model using their method and it was mentioned that an additional adjustment was made to correct it. The method used by the company is incorrect when there are competing risks. We have raised this issue several times but the company decided to stick to their method, which is only standard (and correct) when there are no competing risks.

			The ERG does not agree with the company in that the method used is much less transparent. The ERG has provided several papers describing the methods and an appendix including the R code. Furthermore, the ERG has provided a link to the algorithm provided by Chhatwal et al. The ERG cannot think of anything more transparent than that. The values used in the command: round(matrix(c(0.963702, 0.00020038, 0., 0.036098, 0.0538478, 0.946152, 0., 0., 0.0945621, 0.113132, 0.792306, 0., 0., 0., 0., 1.),byrow=T,nrow=4) were obtained after applying the algorithm by Chhatwal et al. A link to the tool used to get those values is provided in Appendix 2. The ERG has not applied their method to the SoC transition matrix because as far as it was understood, the UK chart review data was already for one year and therefore no

			change in the time scale was needed. Finally, the ERG would like to emphasise that, despite this being a rather technical and complex issue, its impact on the ICER is rather modest, as it was shown by the ERG with their additional scenario analyses.

Issue 17 PSA results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.4.2 (page 118) reports PSA results with incremental QALYs of 0.94. When re-running the ERGs PSA in the model received with the ERG report, the incremental QALYs appear to be greater.	Please clarify if the PSA results reported in the report and based on the model received.	The PSA results may have been misreported.	Not a factual error. Please run the PSA using a Dirichlet(1,1,1,1) as prior distribution.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Burosumab for treating X-linked hypophosphataemia

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check. The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
14, 102, 112, 129, 130	Correction of typographical error: [redacted]
15, 125, 130	Correction of typographical error: [redacted]
23	Text deleted: Clinical heterogeneity, which the CS highlights has been frequently reported for XLH patients, is a core issue that may impact burosumab treatment. Some patients with a PHEX mutation who are diagnosed with XLH retain residual gene activity. In practical terms, this may mean that further dose-titrations are necessary that take into consideration not just weight but also residual gene activity. It is unclear if there is a validated test available to determine PHEX activity.
27	Text deleted: Since the aetiology and pathophysiological mechanisms behind XLH remain largely unknown, the mechanism-of-action of burosumab must be considered as ameliorating the symptoms rather than treating the underlying cause.
65	Text changed to: Additional work on clinical effectiveness undertaken by the ERG has been included in section 4.3.2 of this report.
74,75	Section Equity weighting removed from Table 5.1.
95	Text deleted: These revisions have been included in the revised base-case.
109	Text added: Note that this CI (and the ones shown below) is based on the standard deviation instead of the standard error and therefore it is incorrect. These CI's are used to illustrate the way the company included the uncertainty into the model.

Multiple sources of evidence were used to inform the parameters of the economic model. The proportion of males/females at baseline, the initial distribution of patients per disease severity stratified by age and the transition probabilities for burosumab were derived from the clinical studies CL201 and CL205. Transition probabilities for the SoC arm were derived from a UK chart review in the base-case analysis and from the study CL002 in a scenario analysis. General population weight data (UK growth charts) were used for the weight distribution. Mortality rates were obtained from the national life tables for England, for the period 2014 to 2016, as published by the Office of National Statistics. Utility values for the health states of the model were derived from a vignette study conducted by the company. Additionally, age specific multipliers were used based on the general population.

The price of burosumab was provided by the company. Burosumab is available in 10 mg, 20 mg and 30 mg vials. In the CS, it was stated that the Summary of Product Characteristics (SmPC) recommends dose rounding to the nearest 10 mg. Based on this assumption, annual patient costs by age and weight were estimated in the base-case analysis. Resource use for burosumab monitoring was based on expert opinion, while unit costs were taken from NHS reference costs. Standard of care treatment costs were estimated based on the dose recommended in clinical guidelines and the summary of product characteristics. Unit costs were taken from the British National Formulary (BNF). Resource use for surveillance costs was based on expert opinion and unit costs were taken from NHS reference costs. Physiotherapy resource use was based on published literature and complemented by expert opinion. Unit costs taken from PSSRU. A number of different sources were used for the estimation of orthopaedic intervention costs. Resource use was based on the prevalence observed in CL201, published literature and expert opinion. Unit costs were mostly sourced from the NHS reference costs, except the unit costs for osteotomy, which were based on published literature. A deterministic one-way sensitivity analysis was conducted for key clinical and economic parameters in the model. A probabilistic sensitivity analysis was also conducted. A number of scenario analyses were also performed to assess the robustness of the model results to changes in structural assumptions made by the company.

The company's analysis estimated that patients treated with burosumab gained 10.304 more discounted quality adjusted life years (QALYs) compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When discounting was not applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

1.7 Summary of the ERG's critique of the value for money evidence submitted

The CS states that a systematic review search was undertaken for economic, cost and resource use and HRQoL evidence using a combined search for all of these areas. The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. Of main concern to the ERG was the narrow search conducted, which included few XLH synonyms and an unnecessarily restrictive use of study design filters.

The ERG identified several issues in the company's analyses. The ERG main concerns were related to the method used by the company to estimate the transition probability matrices for burosumab, the source of utilities used by the company and the assumption of lifelong treatment effects of burosumab. The choice of the discount rate was also challenged by the ERG.

The results of the ERG base-case resulted in an ICER increased by [redacted] compared to the company's base-case ICER. Most of the total increase in the ICER (despite the effect of applying the 3.5% discount rate) was due to assuming a treatment effect duration for burosumab of 20 years instead of lifelong as

assumed by the company. The ERG also conducted a new probabilistic sensitivity analysis (PSA) and additional scenario analyses exploring the impact of choosing prior distributions for the burosumab transition matrices. The latter was proven to be crucial and in the several scenarios provided by the ERG, the ICER ranged from [redacted] to [redacted].

Based on the ERG results, it is expected that, from the payer perspective, the decision uncertainty related to burosumab value for money would be low, given that the ICER estimates from all ERG analyses are above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

A budget impact model to estimate the costs to the NHS for a period of five years of adopting burosumab in England was also included in the CS. The results presented by the company suggested that the net budget impact of implementing burosumab (with an estimated prevalence of [redacted] patients) will be [redacted] in the first year and will rise to [redacted] in the fifth year. The cost of burosumab at year 5 amounts to [redacted]. The estimated total number of patients eligible for burosumab treatment after five years is [redacted] and the uptake of burosumab rises from 40% in year 1 to 90% in year 5.

The CS did not include any estimates of costs (savings) or benefits incurred outside of the NHS and PSS associated with of burosumab. The company indicated that at this stage this was not possible to quantify. However, the company expects significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health related benefits

The ERG considers the assumptions made in the budget impact analysis questionable. There are concerns about the theoretical population size and the expected uptake rate of burosumab in England. In the CS, it was reported that the size of the patient population [redacted] is not expected to change over time. This estimate is based on an assumption that the patients are only treated if they have growing skeletons. In the CS, it was stated that XLH is not associated with an increased risk of death, compared to the standard population. The potential (and theoretical) population size is assumed to remain constant.

Since real-world data suggest that there could be [redacted] XLH patients between one and 17 years of age in England, using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab. The cost of burosumab at year 5 would then amount to [redacted]. The company indicated that burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by the company and will therefore not have any additional financial or resource impact on the NHS.

The ERG considers it inadequate that the impact of XLH on costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab was not identified prior to the submission to NICE.

presumed from this value that the remaining 60-75% of patients with well-controlled XLH achieve normal growth rates with conventional therapy. Other research has indicated that height velocity commonly increases during the first year of conventional therapy, and after two years of successful treatment, can be restored to its maximal potential in the majority of patients, although adult height usually remains compromised.[3, 23]

Dental disease in XLH patients is highlighted in the CS with a study by Anderson 2012 that assesses 53 patients with hypophosphataemic rickets.[21] Sixteen out of 53 patients were <18 years of age and therefore represent the population of interest for the burosumab indication described in the CS. Of these 16 patients, the mean number of endodontically affected teeth was 0.3 (standard deviation (SD) 0.9), while the median number was 0 (first and third quartile: 0.0 and 0.0). No comparisons were provided either in the referenced study, in the CS[1] or in the company's response to clarification letter (question A17[2]) for the number of endodontically affected teeth that would be expected in a healthy age-matched population. Based on the current information, the need for endodontic treatment among paediatric HR patients cannot be considered comprehensive, although it appears clear that dental issues are prevalent in adult XLH patients.

2.2.6 Diagnosis

Diagnosis of XLH is typically based on clinical findings, radiographic findings, biochemical testing and family history. Family history remains critically important to the early recognition of inherited forms. Although, genetic testing is increasingly used to confirm the diagnosis of XLH, radiographs have been the gold standard for the diagnosis and evaluation of rickets for several decades.[18, 40-42] The radiographic characteristics of rickets include lucency in the metaphyses, physeal widening, fraying and cupping.[6, 42] These diagnostic radiographic features of rickets typically reflect the impaired mineralisation and ossification affecting the growth plate. Bone manifestations are best seen in the metaphyses of rapidly growing bones, including the distal radius and ulna, distal femur, proximal and distal tibia and proximal humerus.[6, 42]

Paediatric patients with XLH are managed by paediatric endocrinologists and paediatric nephrologists. There are a limited number of expert clinicians with the necessary training and experience in rare metabolic bone diseases to appropriately manage children with XLH. It is anticipated that treatment would be initiated and monitored by specialist centres and clinicians.

2.2.7 Prognosis

As an update from the CS, which stated that no empirical evidence documenting the impact of XLH on mortality has been identified and that XLH is not thought to have an impact on the life expectancy of patients, a new analysis provided in the company's response to clarification letter stated that [redacted].[2]

ERG comment: The original statement (that XLH had no impact on life expectancy) was unlikely to be accurate given the extensive pathological manifestations associated with the disease. The updated

phosphate). Normalising phosphate levels is reported to ameliorate the bone-related symptoms (e.g. rickets) associated with XLH.

2.5 Current usage in the NHS

Burosumab is not currently in use in the NHS. The MHRA granted burosumab a 'Promising Innovative Medicine' (PIM) designation on 31 January 2017, and the EMA awarded burosumab conditional marketing authorisation on 23 February 2018. Burosumab is expected to be used in line with the anticipated marketing authorisation in children and adolescents with XLH from the age of one year old who have radiographic evidence of bone disease.
Burosumab is a monotherapy, meaning oral phosphate and vitamin D analogue therapy should be discontinued one week prior to initiation of treatment. Concurrent use of oral phosphate and vitamin D analogues is contraindicated with burosumab. Burosumab is administered every two weeks by subcutaneous injection.

Clinical expert opinion has suggested that patients responding well to burosumab treatment are likely to have a diminishing frequency of consultant visits over the longer term. In addition, burosumab will either prevent or improve skeletal abnormalities, and reduce the need for corrective surgery. Routine treatment with burosumab should also remove the need for additional supplementation with growth hormone in a small subset of patients where this is required.

The following ongoing monitoring is recommended with burosumab (Summary of Product Characteristics (Crysvita), 2017):[50]

- Monitoring for signs and symptoms of nephrocalcinosis, e.g. by renal ultrasonography, is recommended at the start of treatment and every six months for the first 12 months of treatment, and annually thereafter.

- Monitoring of plasma alkaline phosphatases, calcium, PTH and creatinine is recommended every six months (every three months for children 1- 2 years) or as indicated. Monitoring of urine calcium and phosphate is suggested every three months. Patient's fasting serum phosphate level should be monitored due to the risk of hyperphosphataemia. To decrease the risk for ectopic mineralisation, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age. Dose interruption and/or dose reduction may be required.

- Increases in serum parathyroid hormone have been observed in some XLH patients during treatment with burosumab. Periodic measurement of serum parathyroid hormone is advised.

The high burden of frequent monitoring when the drug is first introduced will tail off once the patient is on a stable dose, and the overall burden of monitoring is expected to be reduced compared with that required for conventional therapy.

ERG comment: Kyowa Kirin aim to treat a paediatric and adolescent population of XLH patients from 1-17 years of age who have radiographic evidence of bone disease. After the age of approximately 17, when growth plates fuse, it is indicated that burosumab will be discontinued as it will no longer be required to stabilise rickets symptoms. Based on the therapeutic target of burosumab (FGF23) and the largely unknown pathological mechanisms of XLH, there is no evidence presented that burosumab therapy in childhood has long-term therapeutic consequences in adulthood following treatment cessation. Bone metabolism is an ongoing and dynamic process that will continue to be subject to the pathological consequences of hypophosphataemia. Thus, the ERG considers it unlikely that the diverse pathologic and phenotypic consequences of XLH will be ameliorated without therapeutic intervention

ERG comment: As there was no direct or indirect evidence available to compare burosumab with conventional therapy using evidence from RCTs, the evidence in the CS is based on a comparison of data from two single arm studies. Although the burosumab evidence is from a phase 2 trial, there was no control group and the randomisation was between different regimens of burosumab. The data for conventional therapy was obtained from a historical cohort study, which was different to the burosumab trial in terms of inclusion criteria and patient population. In order to try and adjust for differences between these two studies the company performed additional analyses which matched the two groups using propensity score matching. However, these analysis methods have major limitations, in that the matching can only include those variables measured in both studies. Randomisation in a clinical trial creates balanced group for both measured and unmeasured variables. In observational studies, the most important factors which are predictive of the outcome may not have been measured and any treatment comparisons using observational study data may be biased.[58]
The company only included three variables in the PSM, age, gender and RSS total score at baseline. The rationale for variable selection was not provided other than whether they seemed similar or not between the two study populations. No details were provided of how this similarity was judged. The ERG found no statistically significant differences in age and gender between the two groups and considered that only including three variables in the creation of the propensity scores may have been too few. Although the PSM groups were closer at baseline for these three variables compared to the original data, the results of the PSM analyses were very similar to those from a naïve comparison between the two study populations.

The company provided the statistical analysis programs used for the PSM analyses in the response to the clarification letter but not the data. Therefore, the ERG could not check the PSM analyses to establish that they could reproduce the results. Three different PSM methods were used and although they provided similar results it is not clear which PSM result should be considered the most reliable. The PSM analyses were only performed for rickets and not for any other relevant clinical or safety outcomes.

Due to the lack of a direct comparison between burosumab and conventional therapy and the limitations of using propensity score matching with data from two different observational studies the results of the rickets analyses presented by the company should be considered with caution. The results from CL301, a randomised controlled trial comparing the efficacy and safety of burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) are expected [redacted]. These will provide more reliable estimates for the clinical effectiveness and safety of burosumab compared to conventional therapy and should be given greater consideration than the naïve and adjusted analyses presented in the company submission.

4.4 Summary of evidence presented in other submissions

No other scientific evidence was submitted by other consultees.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work on clinical effectiveness undertaken by the ERG has been included in section 4.3.2 of this report. In addition, we will discuss the longitudinal review of patient records from three expert UK centres to provide additional data (n=43) commissioned by Kyowa Kirin as a UK alternative to CL002 which was a US study. The company provided a synopsis with details on the rationale, methodology and results of this UK study as part of the response to the clarification letter.[2]

of systematic oral phosphate supplements and active vitamin D analogues in the form of alfacalcidol A, or oral or injectable calcitriol.

The economic evaluation was conducted from the perspective of the NHS and PSS in England. The model estimates cost and health consequences over a lifetime time horizon for a cohort of patients with XLH aged one to 12 years at the beginning of the simulation. The cycle length of the model is one year. The outcomes of the model are the estimated incremental QALYs, the incremental costs and the incremental cost effectiveness ratio (ICER) associated with burosumab vs. SoC for treating XLH. Cost and health outcomes are discounted at a rate of 1.5%.

ERG comment: The scope of the economic evaluation is generally in line with the scope developed by NICE. Deviations in the company's decision problem were discussed in section 3.3 of this report. The adherence of the scope of the economic evaluation to the NICE reference case was also assessed by the ERG, and it is shown in Table 5.1 below.

Table 5.1: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE	The scope of the economic evaluation is generally in line with the scope developed by NICE. Deviations were discussed in Section 3.3 of this report.
Comparator	Therapies routinely used in the NHS, including technologies regarded as the current best practice	Standard of care (SoC) is the only comparator considered. It is the established clinical management without burosumab (systematic oral phosphate supplements and active vitamin D analogues in the form of alfacalcidol A, or oral or injectable calcitriol).
Perspective on costs	NHS and PSS	NHS perspective was adopted.
Perspective on outcomes	All health effects on individuals.	Patient health benefits were included in the model. Benefits to other afflicted individuals (e.g. caregivers) were not included in the model but discussed qualitatively in the company's submission (CS Chapter 14).
Type of economic evaluation	Cost-effectiveness analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Based on a systematic review	Meta-analysis was not used, as there is no direct or indirect evidence of the effectiveness of burosumab vs. SoC available. Effectiveness data was

Element of economic analysis	Reference case	ERG comment
		obtained from single-arm studies.
Measure of health effects	QALYs and life years	Health benefits are valued in terms of life years and QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	No, the utility values associated with the model's health states were derived from a vignette study conducted with 6 UK XLH clinical experts. The valuation was based on EQ-5D, which is the NICE standard.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects.	No, costs and outcomes were discounted at 1.5%.

5.3.2 Model structure

An Excel-based Markov model was developed by the company to perform the economic evaluation of burosumab for treating XLH patients in the UK. The model simulates the disease progression of XLH by using the Rickets Severity Score (RSS) as a surrogate for disease severity, which defines the different health states of the model, in patients treated with either burosumab or SoC. The impact of the disease is translated to lifetime costs and QALYs in the submitted cost effectiveness model. The model consists of four (mutually exclusive) health states representing different rickets severity levels (healed, mild, moderate, and severe) and a death state. The severity levels are defined based on the RSS, a radiographic scoring method developed to assess the severity of nutritional rickets. It scores abnormalities in the wrists and knees and is defined on a scale between 0 and 10. Healed rickets correspond to an RSS equal to 0, mild rickets correspond to an RSS between 0.5 and 1.0, moderate rickets correspond to an RSS between 1.5 and 2.0, and severe rickets correspond to an RSS larger or equal than 2.5. Transitions from every alive health state to any other alive health state are allowed in the model. Additionally, patients can move from any of the alive health states to the death state. The relation between the RSS and HRQoL and the choice of cut-offs on the RSS to define meaningful health states was based on a consensus from clinical experts. Figure 5.2 provides the graphical representation of the conceptual model as presented by the company.

Adverse event costs
No costs associated with AEs were used in the base-case analysis. In the sensitivity analysis, the impact of including costs associated with AEs (lower limit £0 and upper limit £5) were explored, using an incidence rate of 28.2% for injection site reactions based on Study CL201 and Study CL205.

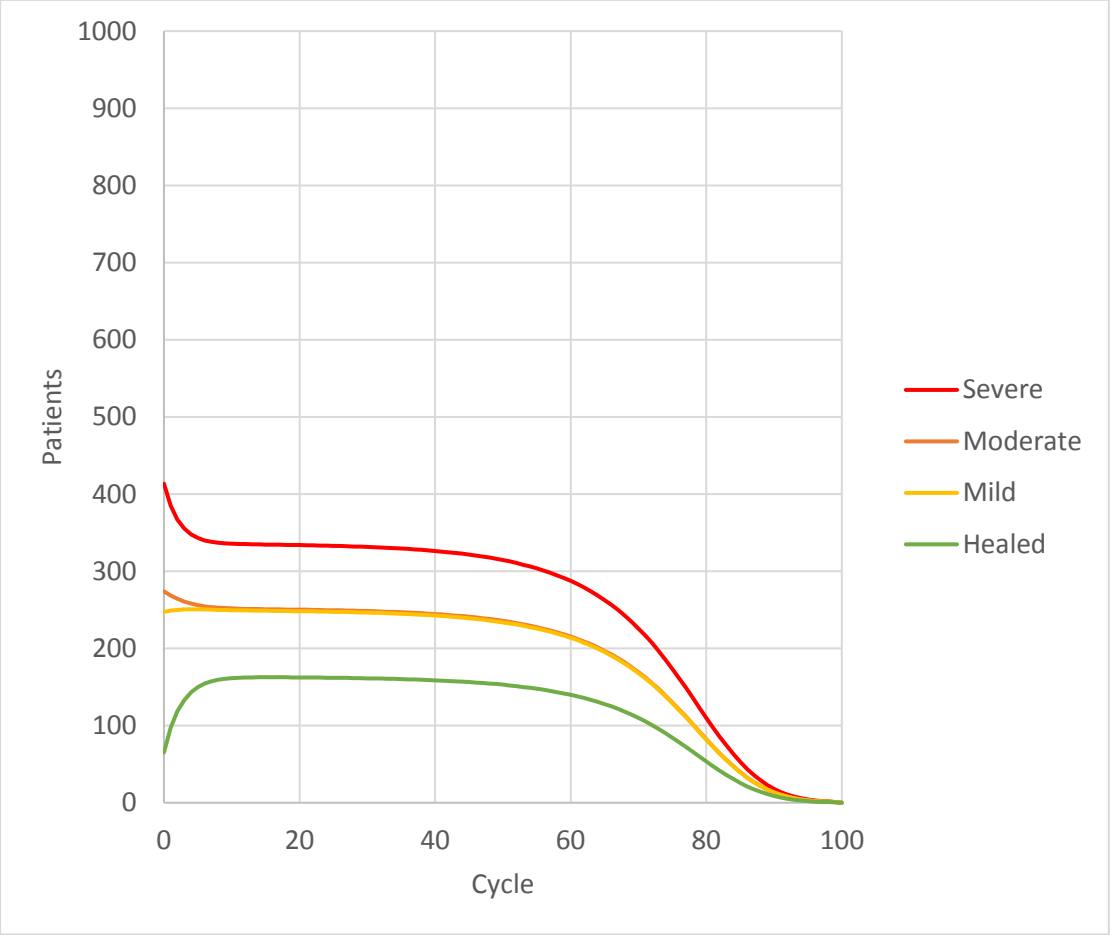
ERG comment: The company indicated that all known costs and resources have been considered. The ERG requested clarification of the orthopaedic intervention costs which are only considered to occur in patients with a rickets score of 1.5 or higher, but no evidence was provided for the relevant cut-off. In the CL, it was indicated that orthopaedic interventions are only required in patients that have a need for such intervention, who are mostly likely to have more severe rickets. The assumption (confirmed by clinical experts) states that if a patient has healed or mild rickets, then it is unlikely that they would require orthopaedic interventions. The ERG also indicated that the monitoring costs are applied only in the first year of treatment (for dose adjustments). Patients up to the age of 17 are expected to see a specialist every three months, regardless of whether they receive SoC or burosumab. This is incorporated into the surveillance costs which are incurred by all patients. These consultations with clinical specialists are to monitor the disease and treatment. The company indicated that after the first three months, burosumab is not expected to require any additional monitoring over that already conducted with SoC. The ERG indicated that treatment costs of the comparator are not age specific, but an average treatment cost for all patients age one to 17 is used in the model. Given that the comparator consists of two treatments, only one of which has a cost that is age-related (alfacalcidol) and the cost of alfacalcidol is not a driver of costs, the simplification of an average cost (instead of age specific) is acceptable. The revised model sent after the clarification phase comprised updated costs that reflect the same year (2016/17). Overall, the applied changes did not have an impact on the results. Surveillance costs are applicable to all patients and orthopaedic intervention costs are not drivers of the results.

In addition, the ERG had two priority questions in the CL about dosing and vial sharing of burosumab. The company indicated that vial sharing is not applied to burosumab. According to the company, if patients received their exact dose as per their weight, which could be a proxy scenario for vial sharing, the ICER would become [redacted]. Based on the SPC, if a patients' weight indicates a dose of 7.5 mg, then this will be rounded up to 10 mg. It was further stated that when patients are five years old, the calculated dose is 14.8 mg but the recommended dose to be administered is 10 mg. The recommended starting dose regimen in children, according to the CS, is based on experience in Study CL201 and Study CL205. Rounding to the nearest 10 mg was used during dose titration in Study CL201. The company indicated that when pharmacokinetic (PK) modelled dose levels were rounded to the nearest 10 mg a difference in dose of <5 mg is not expected to affect response. The maximum dose of 90 mg is recommended based on PK simulations and the practical limitation of a tolerable injection volume. It was stated that this information was presented to the EMA.

5.3.3.5 Demographic parameters included in the model

A number of demographic characteristics were considered in the model as input parameters. These included the initial distribution of patients per health state stratified by age (see Table 35 and Table 36 in the CS[1]) and the percentage of males (50.77%) at baseline. These parameters were obtained by combining the data from CL201 (all doses) and CL205. Weight by age and

Figure 5.1: Base-case: SoC Markov trace



Source: Electronic model (after clarification).[2]

5.4.1 Headline total QALYs and total costs for burosumab versus standard care

Table 5.14 presents the results of the cost effectiveness analysis of burosumab versus SoC for the base-case scenario.

Table 5.2: Summary results of the company's base-case scenario

	Costs	QALYs	ICER	Costs	QALYs	ICER
	Discounted			Undiscounted		
SoC	[redacted]	25.989	--	[redacted]	41.786	--
Burosumab	[redacted]	36.293	[redacted]	[redacted]	58.677	[redacted]

Source: Electronic model (after clarification).[2]
Abbreviations: ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care

The company's analysis estimated that patients treated with burosumab gained 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discounting was applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

Tables 5.15 and 5.16 below present a breakdown of discounted QALYs and costs for burosumab and SoC. The company's analysis suggests that under burosumab patients accrue more than 95% of the total QALYs in the "Healed rickets" health state (least severe state),

Figure 5.2: Cost effectiveness acceptability curves

Figure redacted - CIC

Source: Figure 10 in response to clarification letter.[2]

ERG comment: The PSA analyses were well-performed in general and the ERG agrees with most of the choices regarding probability distributions made by the company.

After clarification, the ERG detected an error in the model, which was using the standard deviation instead of the standard error when sampling random values for the utilities. The company used the following approach to obtain random utilities for the PSA: first a utility for the moderate health state is randomly drawn from a Beta distribution, with parameters estimated from the mean and standard deviation values obtained in the vignette study. That utility value for the moderate health state is then used as reference and the utilities for the other health states are calculated by randomly drawing the difference in utility compared to the moderate health state from a Normal distribution, with mean and standard deviation also obtained in the vignette study. For example, for patients aged 13 years and older (note that these utilities are applied in the model until patients die, thus for a large number of model cycles) the estimated mean utility in the moderate health state is 0.575 and 95% confidence interval (CI) is (0.417,0.727). Note that this CI (and the ones shown below) is based on the standard deviation instead of the standard error and therefore it is incorrect. These CI's are used to illustrate the way the company included the uncertainty into the model. In order to calculate utilities for the mild health state, a random value is drawn from a Normal distribution with mean 0.096 (the estimated mean difference in utility in the mild health state compared to the moderate health state) and standard deviation 0.11. With these parameters, a 95% confidence interval for the difference in utility in the mild health state compared to the moderate health state is (-0.085,0.277). Likewise, a 95% CI for the difference in utility in the healed and severe health states compared to the moderate health state is (0.018,0.364) and (-0.378,0.152), respectively. However, the company made a further assumption when modelling the utilities which was bounding the sampled utilities so that the health states with less severe rickets get always a higher or equal utility value compared to the next more severe health state (i.e. healed ≥ mild ≥ moderate ≥ severe). The ERG does not agree with this assumption as will be explained below. This assumption results in practice in

provided, it was not mentioned for example what kind of internal validation tests were conducted. A detailed discussion on the face validity of the results was missing in the CS and the response to the clarification letter. Given the lack of cost effectiveness studies on XLH, the ERG feels that additional attention on the face validity of the results would have been helpful in this case. The ERG also asked the company to include in the response to the clarification letter the results of the ongoing external validation indicated on page 167 of the CS but these were not reported.

5.5 Discussion of available evidence relating to value for money for the NHS and PSS

Chapter 5 of this report focused on the economic evidence for burosumab submitted to NICE by the company. The company presented a QALY-based cost effectiveness model-based analysis comparing burosumab with SoC. The company's analysis estimated that patients treated with burosumab accumulated 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discount was applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

The ERG identified several issues in the company's analyses. The most important concerns were related to the operationalisation of "full recovery" in the healed rickets health state and lifelong burosumab treatment effect and the choice of the utilities for the base-case. These seemed to bias the results in favour of burosumab. The choice of the discount rate also had a significant impact on the model's results, as shown by the company in one of the scenarios they conducted. The ERG was also concerned about some of the assumptions made by the company in their PSA since these also seemed to bias the results in favour of burosumab.

Other issues discussed by the ERG were the difference of the effects of burosumab on patients younger than age five and patients older than age five, the method used by the company to estimate transition probability matrices, the choice of baseline weight, age and disease severity distribution, and the lack of any treatment/disease related adverse events. However, all these were proven to have a minor impact on the model's results.

Some of the problems identified within the critical appraisal of the economic analyses were addressed by the ERG in the next chapter of this report. Thus, the next chapter outlines the additional analyses conducted by the ERG, which includes the development of a new base-case analysis (including a PSA) and several additional scenarios.

for physiotherapy to manage the long-term consequences attributed to XLH. In the CS, these have not been factored in the budget impact analysis given its short time horizon.

7.2 ERG critique of the company's budget impact analysis

The ERG considers the assumptions made in the budget impact analysis questionable. There are concerns about the theoretical population size and the expected uptake rate of burosumab in England. In the CS, it was reported that the size of the patient population [redacted] is not expected to change over time. This estimate is based on an assumption that the patients are only treated if they have growing skeletons. In the CS, it was stated that XLH is not associated with an increased risk of death, compared to the standard population.[85] The potential (and theoretical) population size is assumed to remain constant.

Since real-world data suggests there could be [redacted] XLH patients between one and 17 years of age in England (see response to clarification letter – Question A4),[2] using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab. The cost of burosumab at year 5 would then amount to [redacted]. The company indicated that burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by the company and will therefore not have any additional financial or resource impact on the NHS.

In study CL201, one patient experienced serious TEAEs, and [redacted]). All 52 patients (100%) experienced at least one TEAE during the study. The most frequent TEAEs (>30% incidence) in study CL201 were [redacted].

The most frequent TEAEs (> 30% incidence [four or more of 13 patients]) in study CL205 were [redacted]

Adverse events of treatment with conventional therapy have not been reported. Therefore, it is not possible to assess the relative safety and toxicity in relation to the comparator.

9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis

9.2.1 Cost-consequence analysis

The company conducted a systematic review of cost effectiveness studies of burosumab and other studies including costs, resource use and any HRQoL measure associated with XLH. A total of eight full-text studies were assessed for eligibility which were included in the final evaluation of evidence. However, none of these studies were deemed relevant to the economic evaluation of burosumab.

The company's deterministic analysis estimated that patients treated with burosumab accumulated 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discount was applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

The ERG identified several issues in the company's analyses. The ERG main concerns were related to the method used by the company to estimate the transition probability matrices for burosumab, the source of utilities used by the company, and the assumption of lifelong treatment effects of burosumab. The latter was expected to have a major impact on the model results. The choice of the discount rate was also challenged by the ERG. Furthermore, given the limited evidence in this submission, the ERG highlighted the extra importance of the probabilistic results. In light of these issues, the ERG performed a new base-case analysis and a number of additional scenarios.

The results of the deterministic ERG base-case resulted in an ICER increased by [redacted] compared to the company's base-case ICER. Most of the total increase in the ICER (despite the effect of applying the 3.5% discount rate) was due to assuming a treatment effect duration for burosumab of 20 years. The ERG also conducted a new PSA and additional scenario analyses exploring the impact of choosing prior distributions for the burosumab transition matrices. The latter was proven to be crucial and in the several scenarios provided by the ERG, the probabilistic ICER ranged from [redacted] to [redacted]. Other scenarios explored by the ERG like using the utilities reported in Table 31 of the CS, rounding up the burosumab dose or bounding the utilities in the PSA were shown to have a minor to moderate impact on the model results.

Based on the ERG results, it is expected that, from the payer perspective, the decision uncertainty related to burosumab value for money would be low, given that the ICER estimates from all ERG analyses are

above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

9.2.2 Cost to the NHS and PSS

A budget impact model to estimate the costs to the NHS for a period of five years of adopting burosumab in England is also included in the CS. The results presented by the company suggested that the net budget impact of implementing burosumab (with an estimated prevalence of [redacted] patients) will be [redacted] in the first year and will rise to [redacted] in the fifth year. The cost of burosumab at year 5 amounts to [redacted]. The estimated total number of patients eligible for burosumab treatment after five years is [redacted] and the uptake of burosumab rises from 40% in year 1 to 90% in year 5. When a prevalence of [redacted] is considered by the ERG (with the same uptake rates), the estimated total number of patients eligible for burosumab treatment after five years reaches to [redacted]. The cost of burosumab at year 5 would then amount to [redacted].

9.2.3 Non-health benefits

The CS did not include any estimates of costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab. The company indicated that at this stage this was not possible to quantify. However, the company expects significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab.

The ERG considers it as inadequate that the impact of XLH on costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab was not identified prior to the submission to NICE.

9.3 Strengths and limitations

9.3.1 Strengths of the CS

The ERG is confident that all relevant studies (published and unpublished) of burosumab were included in the CS, including data from ongoing studies. The same applies to the historical control patients. A control study in UK patients was mentioned in the CS without any results being report in the CS. However, results were provided as part of the response to the clarification letter. The reporting of outcomes from included studies also seems complete.

A range of relevant economic information was incorporated in the CS, including a QALY-based cost effectiveness model and an assessment of the expected costs to the NHS and PSS in England.

9.3.2 Weaknesses of the CS

The main limitation of the efficacy data reported in the CS is the study design of the included studies. Due to the absence of a control group in most studies it is not possible to make any direct comparisons between burosumab and conventional therapy. As stated by the company, the "burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).[1]

For children between one to four years old, only one study is presented in which all children received burosumab (CL205, N=13). A comparison with "established clinical management without burosumab" is not possible in this group of patients.

For children between five to 12 years old, the CS presents a study in which all children received burosumab (CL201). In addition, the CS presents a control study (CL002) in which children aged