Lead team presentation

Burosumab for treating X-linked hypophosphataemia

1st Evaluation Committee Meeting
Highly Specialised Technology, 23 May 2018

Lead team: Stuart Davies, Jeremy Manuel, Glenda Sobey

Company: Kyowa Kirin

Chair: Peter Jackson

Evidence review group: Kleijnen Systematic Reviews

NICE team: Thomas Paling, Ian Watson, Sheela Upadhyaya

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?

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 → erroneous signal in phosphate sensing → increased levels of fibroblast growth factor 23 (FGF23)
- Excess FGF23 → impaired phosphate conservation + excess excretion → supressed vitamin-D production, decreased 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]

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

Symptoms and complications

- **Rickets** is associated with substantial skeletal deformities which limit physical function and lead to life long disability and pain
  - Children often have difficulties with motor activities – e.g. walking, running and playing
  - Psychosocial consequences from impairment of growth and short stature

- **XLH can manifest with other skeletal effects**: bone/joint pain, calcification of tendons and ligaments, dental problems
- Some patients experience **hearing loss** (predominately sensorineural)
- Low serum phosphorous may also cause **further physiological effects**: muscle weakness, reduced physical functioning, and fatigue

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

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 phosphate and vitamin D (alfacalcidol) commonly used
  - Often has poor adherence because of complex regimen (4–6 times a day) and unpleasant taste and side effects
- Early treatment can result in improved outcomes
- Aims:
  - In children: alleviate bone or joint pain, prevent skeletal deformities caused by rickets and improve growth
  - In adults: reduce pain, reduce osteomalacia, improve fracture healing and surgical recovery
- Corrective surgery of skeletal deformities is often required
- XLH can cause dental disease: root canals and tooth extractions are often performed

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 (conventional therapy)	• Surgery for lower limb deformity
Side effects of phosphate and vitamin D	
• Nausea • Calcification in the kidneys • Hyperparathyroidism	• Diarrhoea • Abdominal pain
Without treatment	
• Normal height not achieved	• Deformity is likely

Burosumab (Crysvita, Kyowa Kirin)

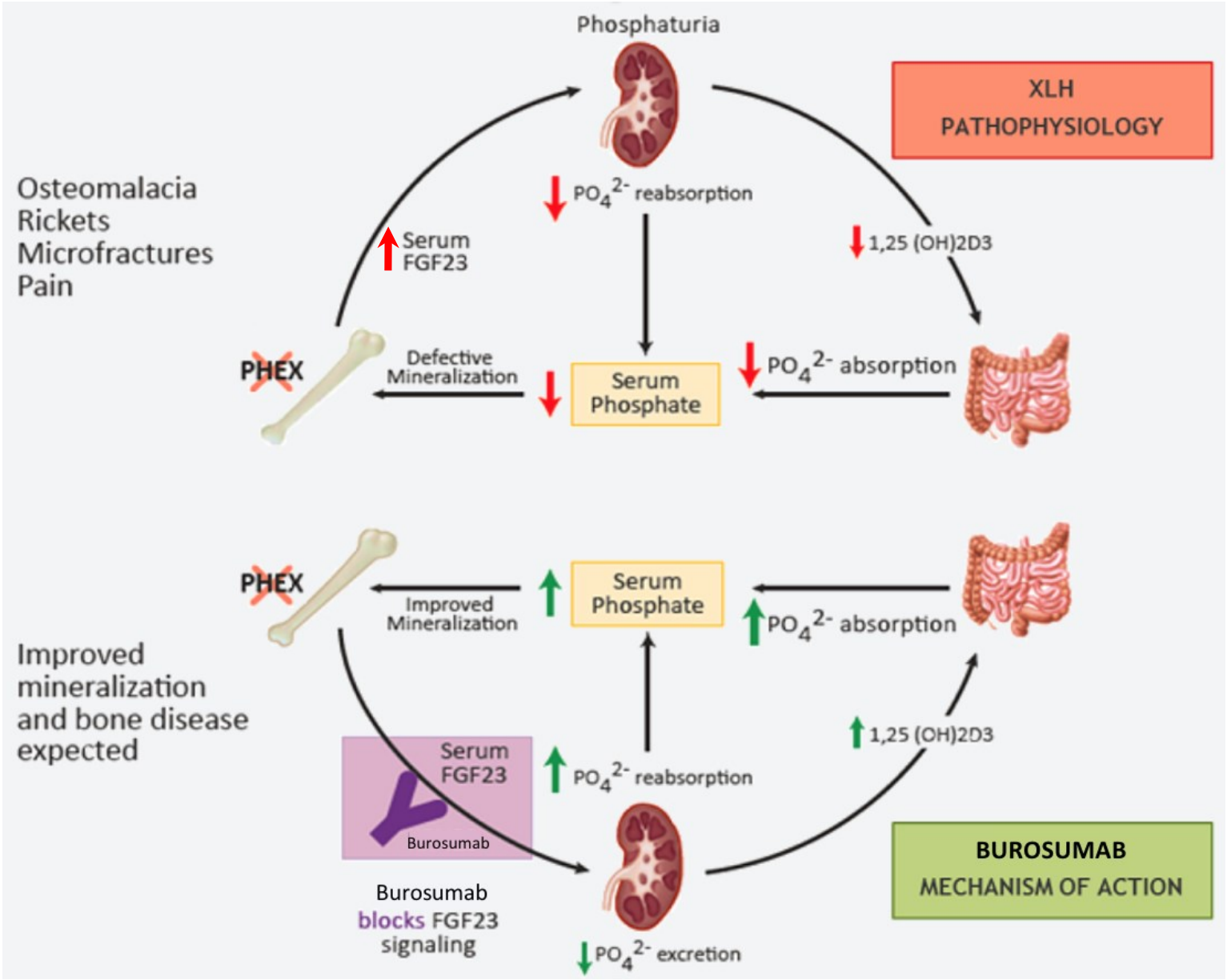
Marketing authorisation	"for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons"
Mechanism of action	Monoclonal antibody that binds to and inhibits the activity of FGF23
Administration & dose	Subcutaneous injection, once every 2 weeks. Starting dose: 0.4 mg/kg, maintenance dose 0.8 mg/kg, maximum 2mg/kg, 90mg
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

Mechanism of action and pathophysiology

XLH manifestations

Burosumab impact



Clinical experts: *Burosumab*

Innovation	
• Targets pathophysiology of XLH • No advances in 35 years	• Innovative administration compared to complex dosing of current treatments
Benefits	
• 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	

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

Clinical effectiveness evidence

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)

Clinical evidence summary
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 phosphate
CL201	randomised, multicentre, open-label, dose-finding Phase 2 study	• 9 centres (incl 3 UK) • 40 week primary efficacy analysis, 64 week extended • N=52, aged 5 -12 years	Change from baseline rickets severity score (RSS)

Burosumab 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*

Baseline characteristics

	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]
Weight (kg), mean (SD)	12.92 (1.81)	31.87 (7.92)	[redacted]
Height: **Percentile, mean (SD)** **Z-score, mean (SD)**	[redacted] -1.38 (1.19)	[redacted] -1.72 (1.03)	[redacted]
Prior conventional therapy **Number (%) who received** **Duration (yrs), mean (SD)** **Age (yrs) when started, mean (SD)**	13 (100%) 1.39 (1.20) [redacted]	24 (92.3%) 7.02 (2.14) [redacted]	[redacted]
Rickets severity **RSS Total score, mean (SD)**	2.92 (1.37)	1.92 (1.17)	[redacted]

Source: adapted from table 13 company submission

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
  - Phase III study (CL301) will reduce the uncertainty in the effectiveness of burosumab compared to conventional therapy
- CL201 has more restrictive inclusion criteria than CL002, including people with more severe XLH
- The historical control study CL002 does not include patients under 5 years old, therefore only provides comparison with CL201, not CL205
  - 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

⊙ ***Does the clinical evidence provide a suitable basis to establish the effectiveness of burosumab compared to conventional therapy?***

Summary of effectiveness analyses

Outcomes

- Rickets: Rickets severity score (RSS) and Radiographic Global Impression of Change (RGI-C)
- Growth, walking ability (6MWT), functional disability and pain (POSNA-PODCI), phosphate homeostasis and bone metabolism

Comparison methods

- Baseline vs post-baseline assessments
- Naïve comparison (CL201 v CL002) – no comparison in children aged 1-4 years
- Matched comparison (accounts for imbalances in baseline characteristics)

ERG comments

- Due to differences in inclusion criteria, naïve comparison is unreliable - people in CL201 had more severe disease ([redacted] baseline RSS) than CL002
- Matched comparison is unreliable due to limitations with the methods
  - Subjects can only be matched on measured variables
  - Selection of matching variables not fully explained (age, gender, and RSS)
  - Possibly insufficient number of variables (3)

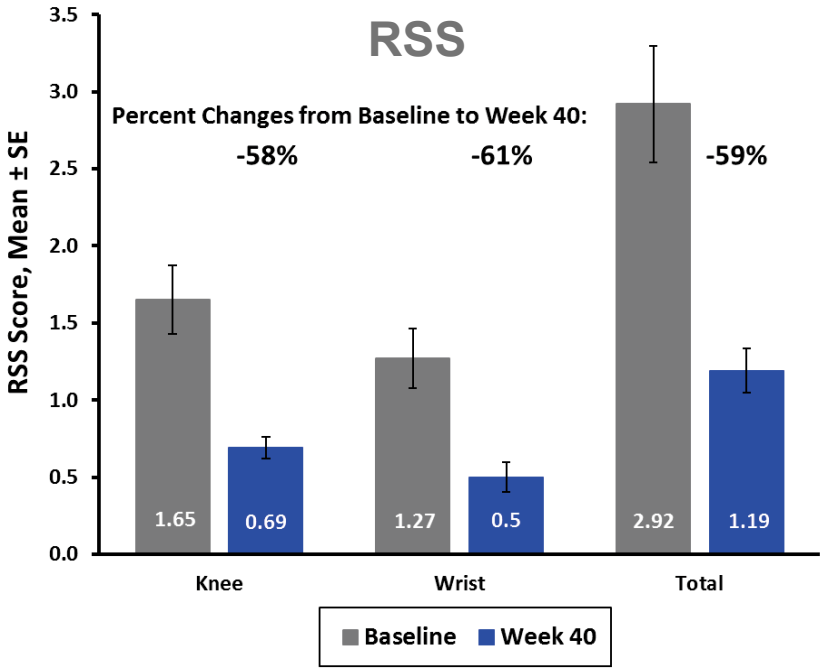
⊙ ***Is the evidence suitable to establish the effectiveness of burosumab vs conventional therapy?***

⊙ ***Do RSS and RGI-C capture important aspects of XLH?***

Clinical effectiveness – results

Effectiveness in children aged 1 to 4 years

CL205



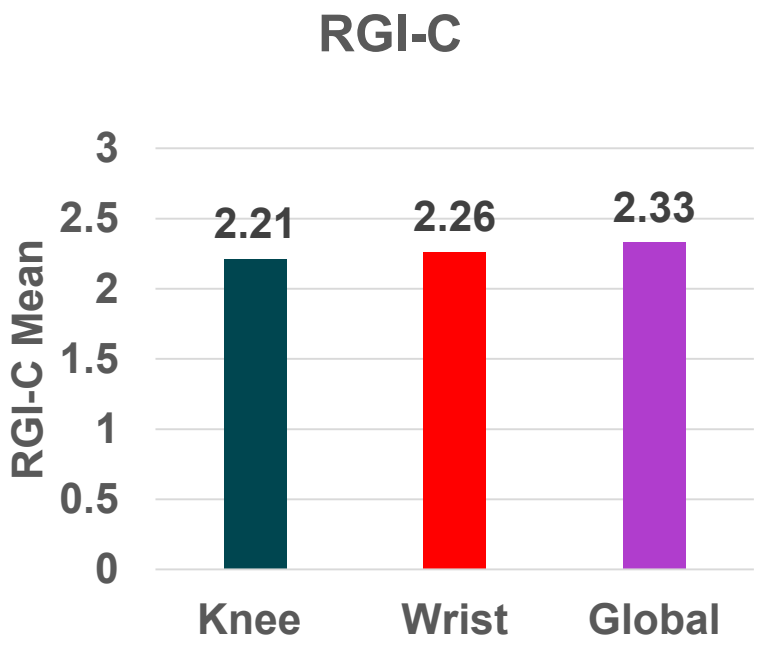


Figure redacted AIC

Change from baseline height	[redacted]
Change in z-score	[redacted]

Source: figure 15 , table 25 and p114 company submission

Effectiveness in children aged 5 to 12 years:
Naïve comparison (CL201 v CL002): rickets healing

- 58% reduction in RSS on burosumab, compared to [redacted] with long-term conventional therapy

Figure redacted - AIC

- [redacted] on burosumab after 64 weeks than conventional therapy after 102 weeks

Figure redacted - AIC

Source: figure 17 and 18 company submission

Effectiveness in children aged 5–12 years

Matched comparison (CL201 v CL002): rickets healing

Figure redacted - AIC

The company presented analysis using 3 methods (IPTW, PSM with or without replacement); for brevity only IPTW is presented, other methods provided consistent findings

Effectiveness in children aged 5–12 years

CL201 v CL002: Other outcomes

	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]

Source: adapted from table 17 company submission

Subgroups: low vs high RSS

CL201 v CL002: RSS total score

Figure redacted - AIC

Figure redacted - AIC

Source: adapted from figure 7 and p106 company submission

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))

RGI-C scores show consistent findings

Adverse events (AEs)

CL201 (N=52)
Ages 5 to 12 years

- No significant safety concerns
- [redacted]
- [redacted]

Frequent TEAEs

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

CL205 (N=13)
Ages 1 to 4 years

- No significant safety concerns, 100% experienced at least 1 TEAE
- 1 SAE [redacted], unlikely related to burosumab
- 5 treatment-related AEs related to administration

Frequent TEAEs

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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

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Key issues for consideration (1)

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?

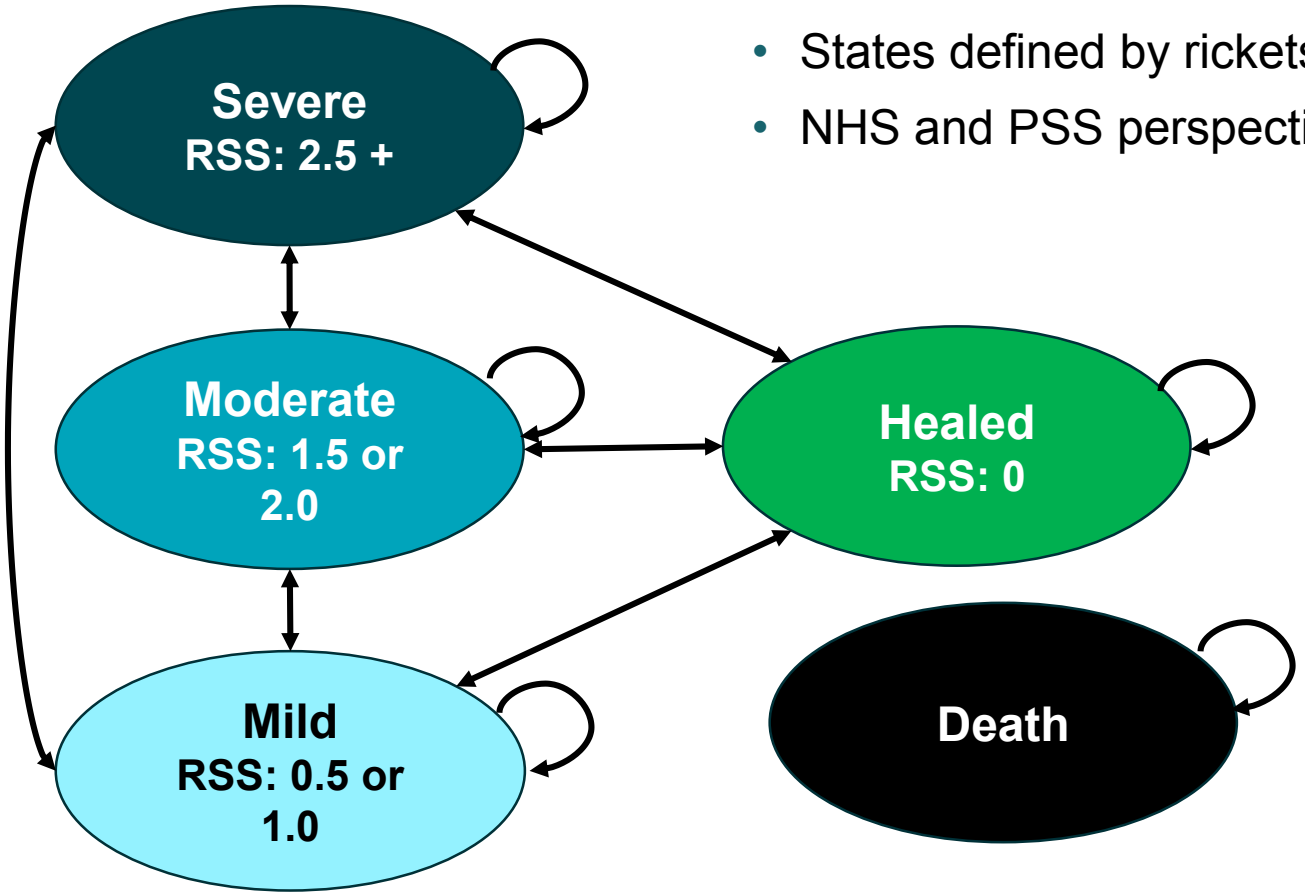
Key issues for consideration (2)

Cost-effectiveness

- 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?

Economic model

Structure: Markov model



Source: model diagram adapted from CS figure 24

- States defined by rickets severity score (RSS)
- NHS and PSS perspective
  - 1 year cycle length with half cycle correction
  - 1.5% discount rate
  - Stop treatment when bone growing ceases (16 in girls, 17 in boys)
  - Population: people with XLH with radiographic evidence of bone disease
  - Comparator: standard care

⊙ ***Is the structure of the economic model suitable for decision making?***

Cost effectiveness analysis
Clinical evidence applied in the model

CL205 and CL201:

- Transition probabilities for burosumab
- Baseline age and disease severity (starting health state distribution)

UK Chart review:

- Review of patient records from 3 expert UK centres (38 patients)
  - Wider age range (up to 18 yrs) than CL002, but not as well matched to CL201
- Used to estimate the transition probabilities for standard care

Lloyd et al: Vignette utility study used to inform health state utilities

ONS life tables: Background mortality

UK growth charts: Distribution of baseline weights

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 without reference to previous measures → may result in inconsistent scores between time points (could affect transition probabilities)
- RGI-C does capture changes over time, but does not indicate health status so cannot be considered as an alternative proxy

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, so defining health states by RSS may overestimate burosumab benefits

⊙***Do the health states (based on RSS) appropriately map the course of XLH?***

Baseline age, disease severity and weight

Age and disease severity	Matched to the baseline distribution of patients in CL205 and CL201

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

Weight	Weight by age and gender taken from UK growth charts • Base case: 50th percentile • Sensitivity analysis: 25th percentile (patients have short stature)

ERG comment:

- Rationale for the choice of data source is unclear
- Data available from the UK chart review dataset (representative cohort of UK XLH patients) but not used

⊙***Is the starting distribution of age, weight and disease severity appropriate?***

Transition probabilities (1)
Based on RSS data

- For burosumab:
  - Ages 1-4 years old: CL205, up to week 40
  - Ages 5 +: in CL201 (week 0 to week 64,Q2W only)
  - Transitions for 13-17 year olds extrapolated from for 5-12 year olds
- For standard care:
  - Based on data from UK patient chart review
- 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

ERG comment:
- Health effects of burosumab are assumed to be age-dependent
  - Unclear whether the distinction between age 1–4 and age 5–12 is due to different manifestation of disease or different treatment effect

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%

ERG comment:

- Adjusted transition probabilities to address flaw in the company's method
- ERG changes have a minimal impact

Source: tables 5.4, 5.7 and 5.8 ERG report

Utility values
Company

- 6 physicians experienced in treating XLH acted as a proxy to estimate HRQoL using 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 +).
- Small sample of experts means significant variation around the mean – affects probabilistic analysis
  - To ensure values were plausible, moderate health state used as an anchor

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

Age multipliers applied from age 18+
No adverse event disutility
Source: table 31 CS

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

Utility values
ERG comment

- 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

⊙***Which utility values are most appropriate? Lloyd et al, or adjusted***

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**

Source: table 6.3 ERG report

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

Utility values
Continued treatment benefit

- After age 17 (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 – overly optimistic
- The ERG assumed 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

⊙ ***Is it appropriate to assume QoL will decrease 20 years after treatment?***

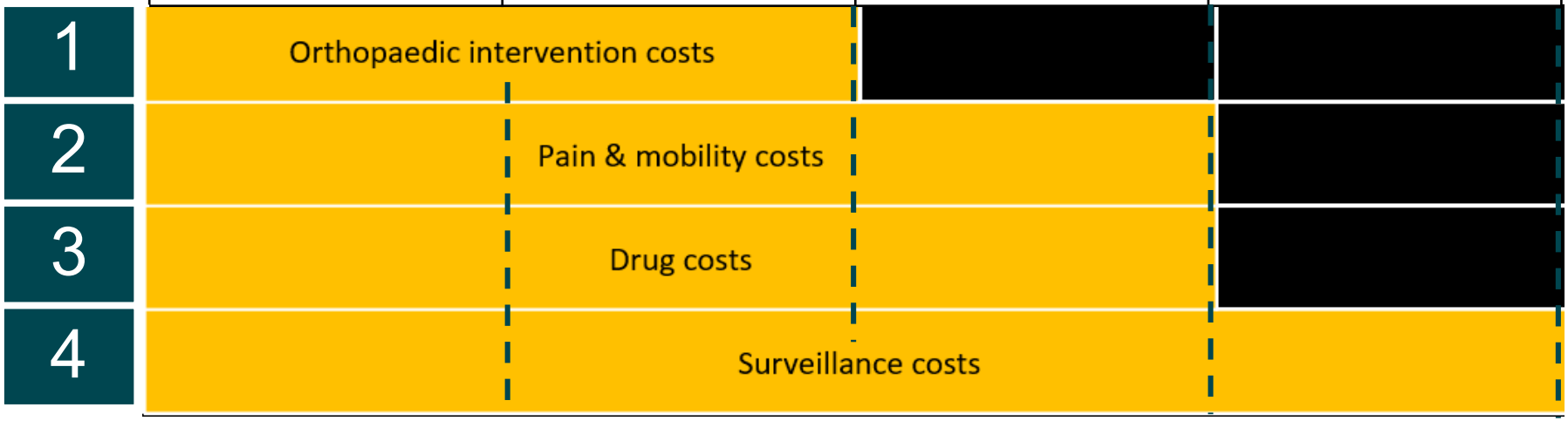
Treatment cost

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			£126.55
Conventional therapy acquisition cost			
Annual cost of alfacalcidol and oral phosphate			£492.57

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

Health state costs

	Total health state costs (per year)			
	Severe	**Moderate**	**Mild**	**Healed**
Children	£1,266.23	£1,266.23	£1,195.13	£1,142.93
Adults	£1,128.68	£1,128.68	£939.86	£235.90



Source: figure 26 CS

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 (5 tablets) 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

Company base case results

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

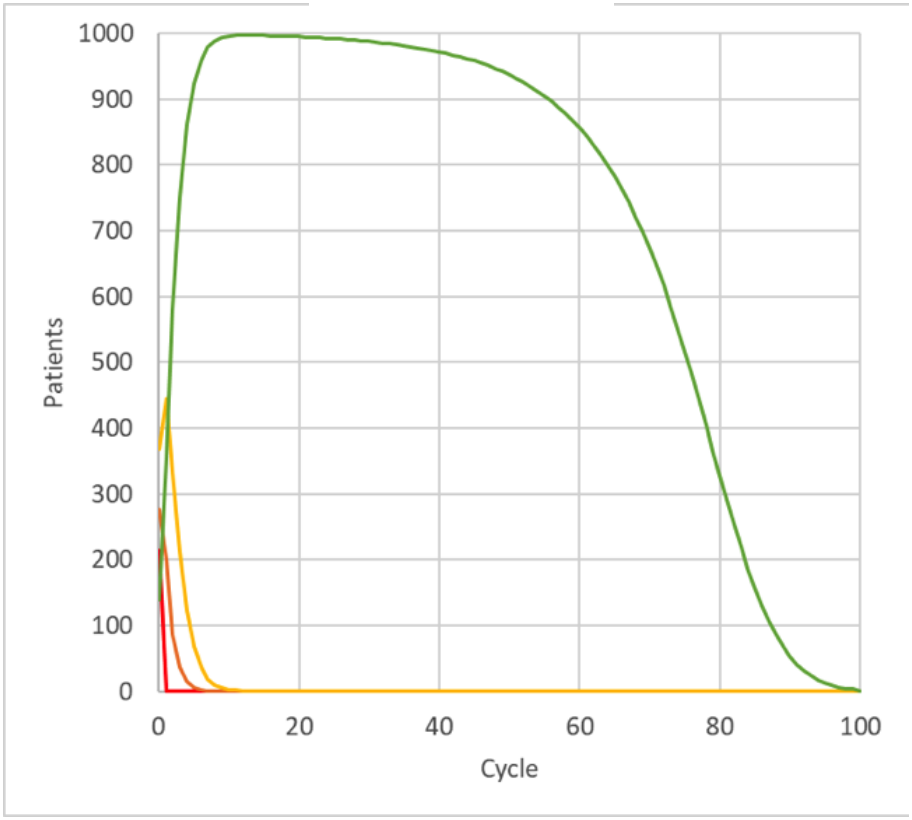
Source: economic model post clarification

Markov traces

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

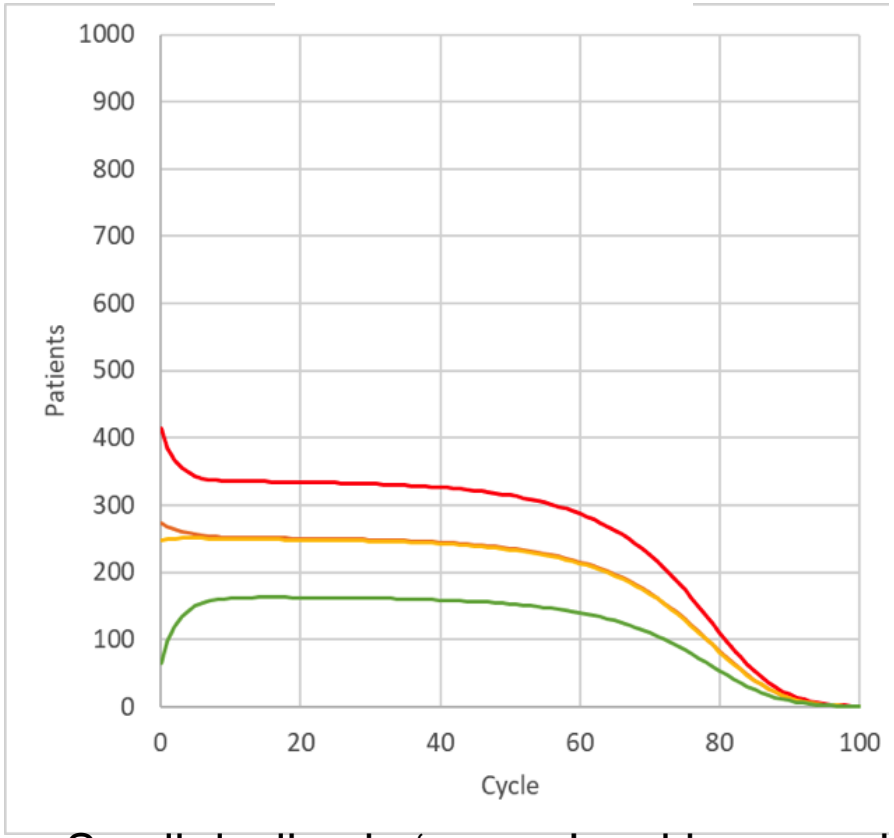
Severe Moderate Mild Healed

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

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]

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)

Company sensitivity analysis

Deterministic

Figure and text redacted - CIC

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

Source: figure 31 CS

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)
     - ERG: treatment/disease-related AEs were not included in the cost or utility calculations; likely to have a modest effect
  2. Corrected burosumab transition probabilities to account for completing risks between modelled health states (see slide 9)
  3. Applied utilities from Lloyd et al 2018 (see slide 12)
  4. Decline in QoL 20 years after the end of treatment (see slide 13)
  5. Discounting at 3.5%
     - ERG: 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	[redacted]	16.175			

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]

⊙***Which assumptions are the most appropriate?***

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]

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 - CIC

⊙***Is it appropriate to assume lifetime disease stabilisation at the end of treatment?***

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

Probabilistic analyses
ERG comments

Transition probabilities

- Uncertainty in transitions captured using a uniform '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: starting state distribution, gender, weight

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]

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%)***

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]

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]

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

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
- Administration is less burdensome that conventional therapy, this allows for a more normal life for patients and families
- Burosumab is well tolerated and avoids complications that are associated with conventional therapies

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

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

Managed access agreement

[redacted]

- [redacted]
- [redacted]

Key issues for consideration (1)

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?

Key issues for consideration (2)

Cost-effectiveness

- 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?

Lead team presentation

Burosumab for treating X-linked hypophosphataemia

1st Evaluation Committee Meeting
Highly Specialised Technologies, 23 May 2018

Lead team: Stuart Davies, Jeremy Manuel, Glenda Sobey

Company: Kyowa Kirin

Chair: Peter Jackson

Evidence review group: Kleijnen Systematic Reviews

NICE team: Thomas Paling, Ian Watson, Sheela Upadhyaya

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."*

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:
  - People with XLH have a physical difference which can be noticed
  - 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 cannot rely on other family members" who are also suffering*

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 alfacalcidol 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"*

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

- *"Phosphate and alfcalcidol has caused all members of my family ... varying degrees of diarrhoea including stomach pain which is very unpleasant to deal with"*
- *"This obviously has an impact on your school and work, to frequently be excused to take toilet breaks"*
- *"Phosphate is extremely bitter/sour so very unpleasant and difficult to administer to young children in particular"*
- *[Administering 6 times a day] "is very difficult to do when you're trying to go about everyday life"*

Patient perspectives: *Burosumab*

Innovation

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

Benefits

- 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

- 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

Patient perspectives: *Need for new treatment*

- 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 new 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

**Adult population is outside the marketing authorisation*