Public observer slides – [redacted]

NICE National Institute for Health and Care Excellence

Burosumab for treating X-linked hypophosphataemia

Chair's presentation

2nd Evaluation committee meeting

Highly Specialised Technologies, 25 July 2018

Lead team: Stuart Davies, Jeremy Manuel, Glenda Sobey

ERG: Kleijnen Systematic Reviews

NICE technical team: Thomas Paling, Ian Watson, Sheela Upadhyaya

Chair: Peter Jackson

Company: Kyowa Kirin

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
Source: Company submission	

[redacted]

Recap: The nature of the condition

X-Linked hypophosphataemia (XLH)

- XLH is caused by mutations in the PHEX gene which leads to increased levels of fibroblast growth factor 23 (FGF23)

Excess FGF23 → impaired phosphate conservation + excess excretion → supressed vitamin-D production, decreased calcium and phosphate absorption

- Symptoms include: bone defects, pain, functional impairment, muscle weakness and fatigue, dental problems and, in some people, hearing loss
- The symptoms of XLH usually start in childhood and continue into adulthood
- Bone defects will become permanent if the condition is untreated while the skeleton is growing; there also can be progressive bone disease in adults
- Low phosphate also associated with non-skeletal physiological effects (e.g. fatigue, muscle dysfunction) – affects both children and adults
- Clinical expression of XLH is widely variable, partly due to genetic differences
  - Males are more severely affected than females

Recap: Clinical effectiveness evidence

Studies: *single arm*

- Study CL205 (1-4 years) – burosumab
  - Multicentre, open-label, single-arm, Phase 2 study
- Study CL201 (5-12 years) - burosumab
  - Randomised, multicentre, open-label, dose-finding Phase 2 study
- Study CL002 (5-12 years) – conventional therapy
  - Evaluates long-term safety and efficacy (reference study to CL201)
- UK chart review:
  - Longitudinal review of patient records (n=43) from 3 expert centres

Comparison: *not randomised*

- Baseline vs post-baseline assessments
- Naïve and matched comparison (CL201 v CL002)

Results: *burosumab improves bone defects* [redacted]

- RSS: Burosumab 58% reduction vs [redacted] reduction on conventional therapy (ages 5-12 years)
- RGI-C: 1.62 for burosumab vs 0.79 for conventional therapy (*ages 5-12 years)*

[redacted]

Recap: Economic evidence

- Health states in the economic model are defined by rickets severity score (RSS)
- Transition probabilities:
  - CL205 and CL201 data used to calculate burosumab transitions
  - UK chart review used to calculate transitions for standard care
- Transitions between health states stop after treatment (growth) stops:
  - Treatment stopping age: 16 years in girls and 17 years in boys
- Lloyd et al:
  - Vignette utility study used to inform health state utilities
- Results:
  - Company base case: ICER [redacted]; incremental QALYs 17.31 (undiscounted)
  - ERG preferred analysis: ICER [redacted], incremental QALYS 8.29 (undiscounted)

[redacted]

ECD preliminary recommendation

*Burosumab is **not recommended**, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children aged 1 year and over, and in young people with growing skeletons.*

Recap of ECD considerations

Nature of the condition

XLH has a substantial impact patients and families

- XLH is a rare, chronically debilitating and deforming condition
- XLH impacts children's ability to participate in social and sporting activities, which affects the child and their family emotionally
- Skeletal and metabolic effects of XLH continue into adulthood
  - Not possible to determine the relative importance of established and ongoing damage in adults

There is an unmet need for an effective and practical treatment

- Conventional therapy has an impractical dosing regimen, and an unpleasant taste and side effects, which leads to poor adherence
- Conventional therapy is ineffective in healing bone deformities meaning multiple corrective surgeries are often needed

Recap of ECD considerations

Clinical

Significant uncertainties in the assessment of relative effectiveness

- Lack of head-to-head RCT data substantially reduced the robustness of the clinical-effectiveness comparison
- Differences in baseline characteristics between CL201 (burosumab) and CL002 (conventional therapy) limited the robustness of the comparison of the single arm studies

Limited clinical effectiveness evidence for age groups covered by the MA

- No comparative evidence for children aged 1-4 (only burosumab)
- No data for young people aged 13-17

Burosumab is effective in the short-term, long-term effects are uncertain

- Burosumab improves bone deformities more than conventional therapy
  - Correcting defects in childhood can lead to a long-term benefit
- Growth, mobility, physical function and pain were all improved by treatment
- Burosumab does not have a long-term effect on XLH (continued progression of bone disease or metabolic aspects)

[redacted]

Recap of ECD considerations

Value for money

Issue	Conclusion
Discount rate	Insufficient justification for deviation from 3.5%
Transition probabilities	Transition probabilities based on trials were appropriate, although based on small populations - uncertain but acceptable for decision-making
Disease stabilisation	Assuming disease stabilises when bones mature (growth stops) is unrealistic. Continued progression of bone deformities and other manifestations of XLH should be accounted for in the analysis.
	Committee queried the plausibility that all people treated with burosumab would stabilise in the healed health state.
	Continued disease progression was illustrated by the ERG using a utility decline (for burosumab) 20 years after treatment is stopped. This approach was uncertain but illustrated the impact on the ICER.
Adverse events	The committee accepted the ERGs inclusion of a cost for adverse events.

[redacted]

Recap of ECD considerations

Value for money

Issue	Conclusion
Utility values	The company amended the utility values reported in the study because not all experts provided estimates for all health states. The ERG used the utility values from the published report in their preferred analysis.
	The committee concluded that, on balance, using unadjusted utility values from the vignette study was more appropriate.
Results	Based on committee's preferred assumptions: • ICERs ranged from [redacted] to [redacted] per QALY gained • QALY weighting is met (1–1.36) (committee preferred assumptions)
Managed access agreement	A MAA would be unlikely to resolve the key uncertainties in the evidence base (the long term effectiveness of burosumab)
Beyond direct health benefits	Recognised that the full impact was not quantified
Other factors	• The population contains children • Impact of treatment on the need for surgery was not captured

[redacted]

ECD consultation responses

- Consultee comments from:
  - Kyowa Kirin
- Clinical and patient experts and professional organisations:
  - Metabolic Support UK
  - XLH UK
  - British Paediatric & Adolescent Group and Birmingham Women's & Children's NHS Foundation Trust
- Web comments from (n=51):
  - Patients, carers and the public
  - NHS professionals
  - Charity and research groups
- No comment response from:
  - The Department of Health and Social Care
  - NHS England

[redacted]

ECD consultation comments

Clinical expert and professional groups

Burosumab is an effective treatment

- Trial data suggests burosumab is effective in healing bone deformity, improving muscle function and increasing growth in people with XLH
- Burosumab is superior to conventional therapy in healing bone deformities

Burosumab is more tolerable and convenient than current treatment options

- Burosumab is safe with minimal side effects
- Improvements in quality of life of children with XLH, which results from a kinder dosing schedule, have not been fully considered

Burosumab is expensive but some cost savings are possible

- The cost of burosumab is high
- The development of a multi-dose delivery device could reduce the risk of wastage of a very expensive technology
- Cost savings from a reduced need for orthopaedic surgery and a reduction in the development of dental abscesses has not been captured

[redacted]

ECD consultation comments

Patient experts: Metabolic Support UK and XLH UK

Burosumab gives people the chance of having a normal skeleton (an improved starting point)

- Burosumab is the first treatment to target the cause of XLH
- Early intervention and improved bone mineralisation reduces the need for surgical intervention (in children and later in life) and reduces dental abscesses prevalence
  - Some fear surgery because of the risk of suffering from compound fractures
- Improving the skeletal architecture of children has a bigger impact on quality of life than ongoing metabolic manifestations of XLH

Burosumab is an improvement on current treatment options

- Burosumab is a more tolerable and effective alternative to current treatments
- Parents note improvements in: adherence; physical function; mobility; bone deformity; bone quality; pain; social functioning; and quality of life

The full impact of XLH needs to be considered

- Pain and fatigue experienced by people with XLH needs further consideration
- Social and psychological benefits observed in the trial will reduce the long-term burden of care. Burosumab allows children and families to live a more normal life.

[redacted]

ECD consultation comments

Patient, parent, and public comments (1): Impact of XLH

XLH causes pain and fatigue which impacts schooling and work

- "I wake up exhausted and go to bed exhausted. There is never any relief."
- Severe pain in bones and mouth abscesses is common
- Productivity loss is significant and needs to be accounted for in the analysis
- XLH delays development

There is a psychological impact of XLH on children, adults and families

- Children are self-conscious of their short stature and other differences from a young age
- XLH is a cruel conditional which affects relationships
- The genetic nature of XLH makes reproductive choices emotionally challenging
- Children can get PTSD due to the trauma of having multiple surgeries and constant pain

ECD consultation comments

Patient, parent, and public comments (2): Current treatments

Conventional therapy is impractical, unpleasant and ineffective

- Dosing interrupts sleep for the entire family
- “Phosphate causes extreme and painful abdominal cramping and diarrhoea”
- Conventional therapy options supress appetite
- Current treatment can lead to incontinence, which can be embarrassing
- Phosphate causes a burning when urinating
- Patients treated with conventional therapy never fully heal bone deformity
- The use of conventional therapy in adults is controversial due to serious side effects (kidney stones, hypercalcaemia)

Corrective surgical intervention has a broad impact

- Surgery is distressing for the child and parents
- Education can be disrupted when major surgeries take place
- Having multiple corrective surgeries can lead to anaesthetic allergies
- Surgical intervention is very costly

[redacted]

ECD consultation comments

Patient, parent, and public comments (3): Burosumab

Burosumab is more effective than current treatment options

- Burosumab improves bone strength and stops deformities, reducing the need for surgery
- Burosumab reduces pain and improves sleep, improving activity levels and quality of life
  - "I've gone from severe depression and being on the verge of being unable to work to working full time happily and actually enjoying life. "
  - Since being on treatment children can be more involved in sporting activities
- Growth is improved in those treated with burosumab
  - Increased height can improve self esteem in self-conscious children
- Burosumab is a step forward in the treatment of XLH, it gives people hope of a normal life

The dosing regimen of burosumab is less burdensome than current treatments

- This helps normalise life at home and improves compliance
- Improved convenience reduces anxiety about missing doses

Improvements in bone deformity will be long-term

- Bone deformity will be mild in adults whose limbs are straight after puberty

Advocated burosumab access for adults

[redacted]

ECD consultation comments

Kyowa Kirin

The company has presented the following additional evidence for consideration:

- The results of the phase 3 study comparing burosumab with conventional therapy (CL301)
- Evidence to support the long-term disease progression of XLH in adulthood
- Updated economic analysis including a patient access scheme (PAS)*

**PAS pending formal approval*

[redacted]

ECD consultation comments

Kyowa Kirin: new clinical evidence (phase 3 study CL301)

Study design:

- CL301 (n=61) is a phase 3 randomised controlled study comparing burosumab (n=29) to conventional therapy (n=32)

Location:

- [redacted]

Key inclusion criteria:

- Age 1 to 12 years
- Rickets severity score (RSS) of 2 or above (severe)
- Pre-treatment with conventional therapy for ≥ 12 consecutive months (for children ≥3 years of age) or ≥ 6 consecutive months (for children <3 years of age)

The primary analysis (week 40)

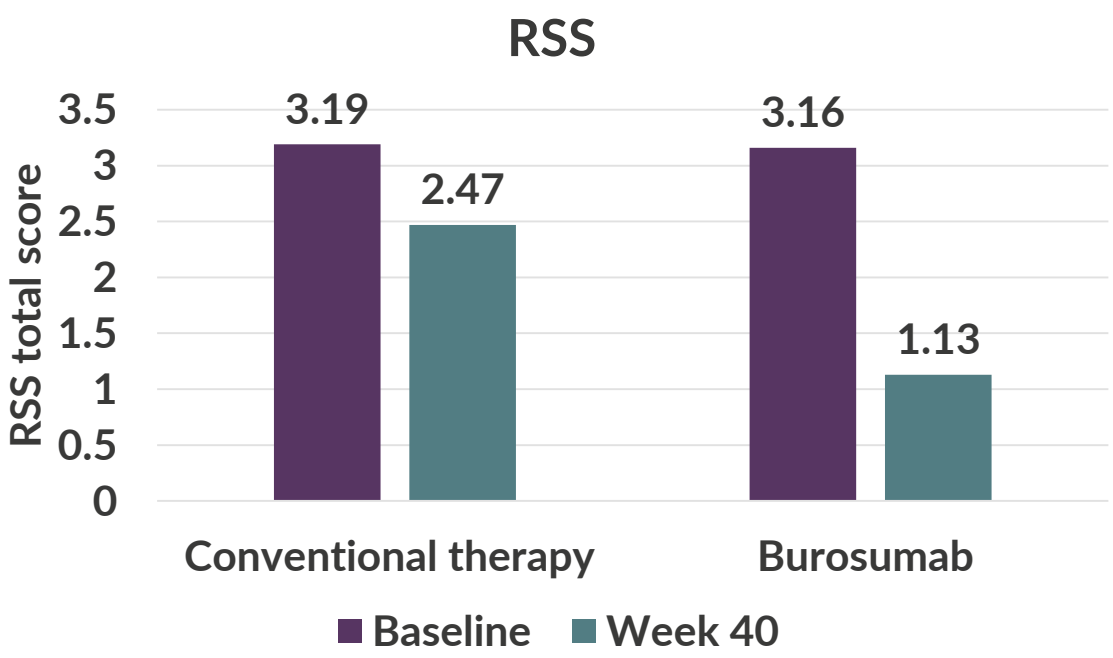
- Bone defect outcomes (RGI-C global score and RSS total score)
- Other outcomes (bone metabolism, growth, walking ability, pain, physical function, fatigue, quality of life)

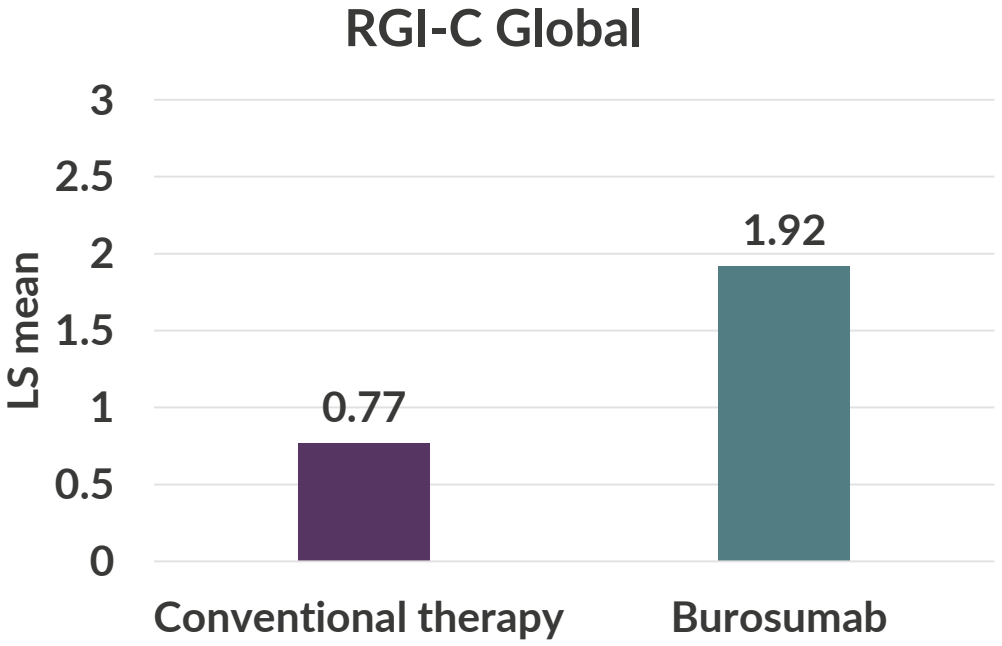
[redacted]

ECD consultation comments

CL301 results (bone deformity outcomes)

- Primary endpoint (week 40) results show that burosumab significantly improved bone deformities compared to conventional therapy:





ECD consultation comments

CL301 results (other outcomes)

People treated with burosumab, compared to conventional therapy, had a greater improvement in:

- Walking ability (6MWT)*
- Growth*
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Burosumab adverse events were generally consistent with those observed in (CL201 and CL205)

6MWT

Figure redacted - AIC

[redacted]

*not a statistically significant difference

ERG comment: study CL301

- Although blinding would be challenging, there is a risk of bias as CL301 is an open-label study
- The follow-up period of the primary analysis (40 weeks) is short for people who will be treated until 16 or 17 years old
- Given small patient numbers (n=61) differences in baseline characteristics between treatment groups can impact results
  - Conventional therapy arm had received prior conventional therapy for [redacted] and were [redacted]
  - Baseline height (z-score) was [redacted] in the burosumab arm
- The results for burosumab do not demonstrate a statistically significant improvement in all aspects of XLH
  - Only improvements in bone defects (RSS and RGI-C) were statistically significant
  - Growth, walking ability, [redacted] were not

[redacted]

Comparison of clinical studies

Differences between studies make the clinical results difficult to interpret

- Differences in baseline characteristics:
  - Study CL301 included more [redacted] children than the other studies
  - Standing height z-score was [redacted] at baseline in CL301
  - More children in CL301 had a renal ultrasound score of [redacted]
  - RSS was [redacted] at baseline in CL301

Disease severity affects effect size

- CL201 subgroup analysis (high v low RSS) found a larger effect in more severe patients
- CL301 only includes people with severe bone deformity (**RSS ≥ 2**)
  - The size of benefit observed in CL301 may not be realised in clinical practice

[redacted]

ECD consultation comments

Kyowa Kirin: Long-term impact of burosumab

ECD	Company response
Long-term impact of burosumab	
• Long-term benefits from fixing skeletal deformities in children are likely • Burosumab won't affect the progression of XLH bone manifestations that occur in adults (such as, increased risk of osteomalacia and accompanying stress fractures and pain) • Burosumab is not expected to have an impact on the metabolic manifestations of XLH after treatment discontinuation (when bones cease to grow)	• Adulthood quality of life detriments are mostly caused by bone deformities which can be corrected by burosumab • In the absence of previous bone deformities, the quality of life impact of osteomalacia is uncertain. Bone deformity and joint inflammation cause painful symptoms, not osteomalacia. – Some people with XLH who have severe osteomalacia, may not be symptomatic • Burosumab treatment improves bone quality more than conventional therapy, which leads to a delay in disease progression and delay in quality of life decline "…burosumab treatment will offer a longer window of improved skeletal health and life quality as the child enters adulthood." • Accept that metabolic aspects of XLH continue when treatment is discontinued • Long-term impact supports the model assumption of disease stabilisation

ECD consultation comments

Kyowa Kirin: revised economic analyses

- Company submitted revised economic analyses including:
  - Transition probabilities
    - Updated to include data from CL301
    - Corrected to use ERG preferred calculation method
  - Updated childhood utilities
  - Updated long-term outcomes / utilities during adulthood
  - Amended age of discontinuation
  - Cost of adverse events
  - Caregiver disutility
  - Patient Access Scheme

[redacted]

Transition probabilities (1)

Burosumab:

- Because CL301 only included people with moderate or severe XLH (RSS ≥ 2) data from CL205 and CL201 was combined with CL301 data to calculate the transition probabilities

From \ To	Healed	Mild	Mod	Sev
Healed	100%	0%	0%	0%
Mild	38.2%	61.8%	0%	0%
Moderate	5.0%	53.1%	41.9%	0%
Severe	0.7%	68.4%	29.7%	1.2%

Source: company model (response to ECD)

Standard of care:

- Data from CL301 was combined with the UK chart review data (assuming last observation carried forward) to calculate transition probabilities

From \ To	Healed	Mild	Mod	Sev
Healed	71%	7%	7%	14%
Mild	9%	70%	11%	9%
Moderate	3%	18%	68%	11%
Severe	3%	7%	16%	73%

Source: company model (response to ECD)

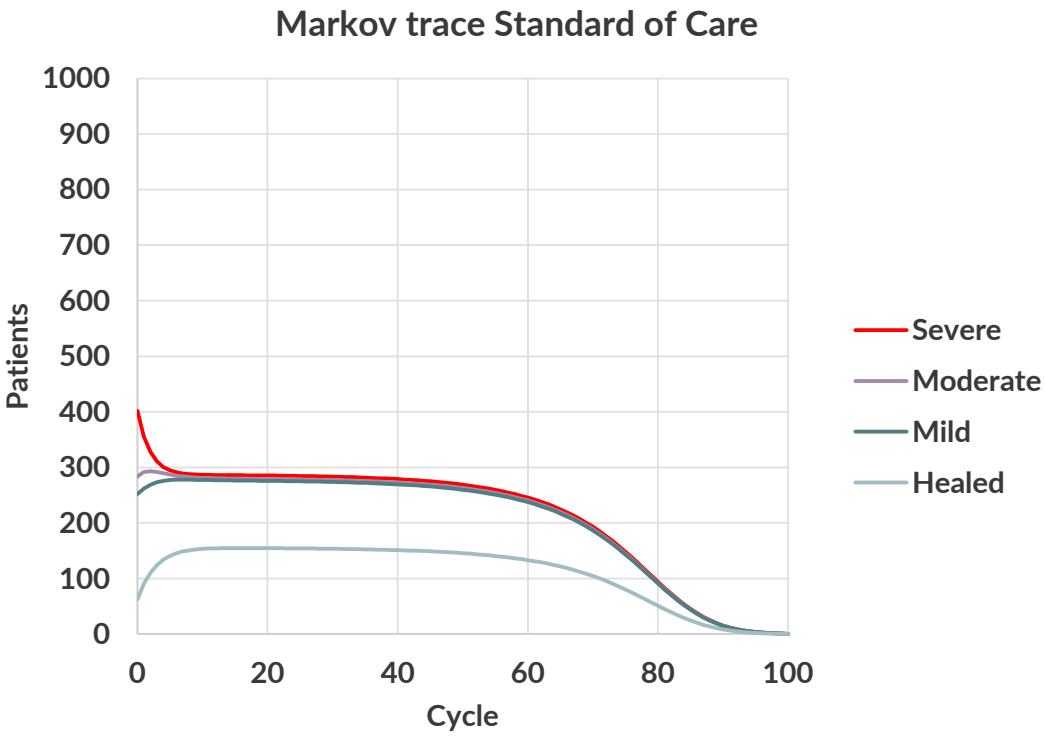
ERG comment:

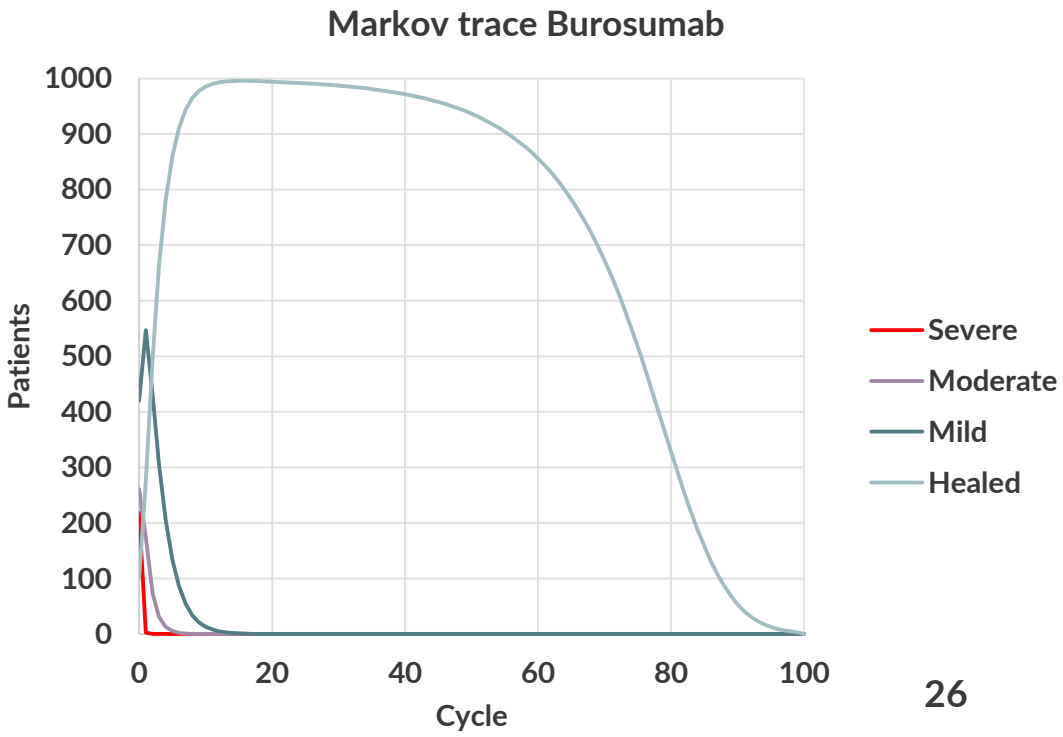
- The company no longer assume treatment effect is age dependent – transition probabilities for 1-4 years and 5+ years are not calculated separately
  - Inconsistent with the company's original base case - not expected to have a large impact
- An imbalance in baseline disease severity can impact outcomes when studies are combined to calculate transition probabilities

[redacted]

Transition probabilities (2)

- Committee previously noted that transition probabilities implied that people having burosumab could not deteriorate (as measured by RSS)
  - Remains true with updated transition probabilities
  - *Decline in health over time explored through adult utilities (following slides)*
- Model assumes that when treatment stops, patients remain in current health state – nearly all burosumab-treated patients in 'healed' state
  - Committee queried the plausibility of this prediction





ECD consultation comments

Kyowa Kirin: updated childhood utility values

ECD	Company response
Childhood utility values	
• Committee preferred to use the unadjusted utility values published in the vignette utility study report	• In the revised base case the company did not adjust the utilities for missing values (as preferred by committee) • The company inferred one missing value in the healed health state to be valued at 1.0 (based on the responses of the same individual in the moderate and mild health states)
ERG comment:	
• The company approach for the estimation of the missing value in the healed health state is appropriate • Limitations in the estimation of the utility values have not been addressed and the uncertainties remain	

[redacted]

ECD consultation comments

Kyowa Kirin: updated childhood utility values

	Company submission (adjusted)	ERG (unadjusted)	Revised company submission
Age 1-4			
Healed rickets	0.872	0.800	0.834
Mild		0.774	
Moderate		0.685	
Severe	0.546	0.610	0.610
Age 5-12			
Healed rickets	0.969	0.890	0.909
Mild		0.757	
Moderate		0.613	
Severe	0.521	0.602	0.602
Age 13+			
Healed rickets	0.861	0.811	0.843
Mild		0.671	
Moderate		0.575	
Severe	0.462	0.479	0.479

ECD consultation comments

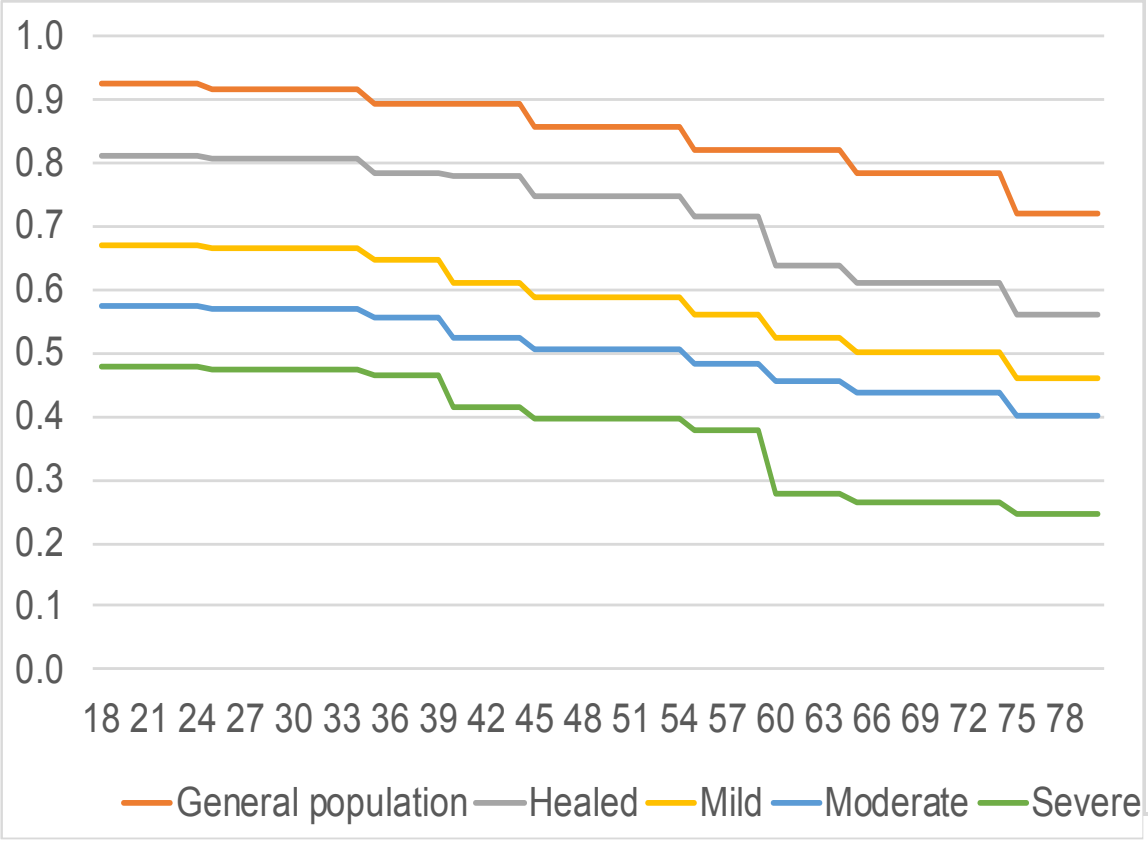
Kyowa Kirin: long-term outcomes / utilities during adulthood

Long-term outcomes / utility values in adulthood	
ECD	
• The committee considered that complete disease stabilisation was unrealistic and agreed that there would likely be a reduction in quality of life later in adulthood	
Company response:	**ERG comment:**
• The company conducted an extension to the vignette utility study to estimate long-term utility values • Health-related quality of life in people with XLH aged 18, 40 and 60 years was considered by experts • Progressive decline in utility is applied in the model • A database (RUDY) of XLH patients was also used [redacted]	• Vignette study extension cannot be validated • Decline in quality of life is greater than that of the general population • Those with severe XLH had the greatest decline in quality of life. Supports the hypothesis that a fixed skeleton will result in fewer adulthood complications • Results are more favourable to burosumab than when no utility decline was considered. Probably a result of a greater decline in quality of life in the severe health state

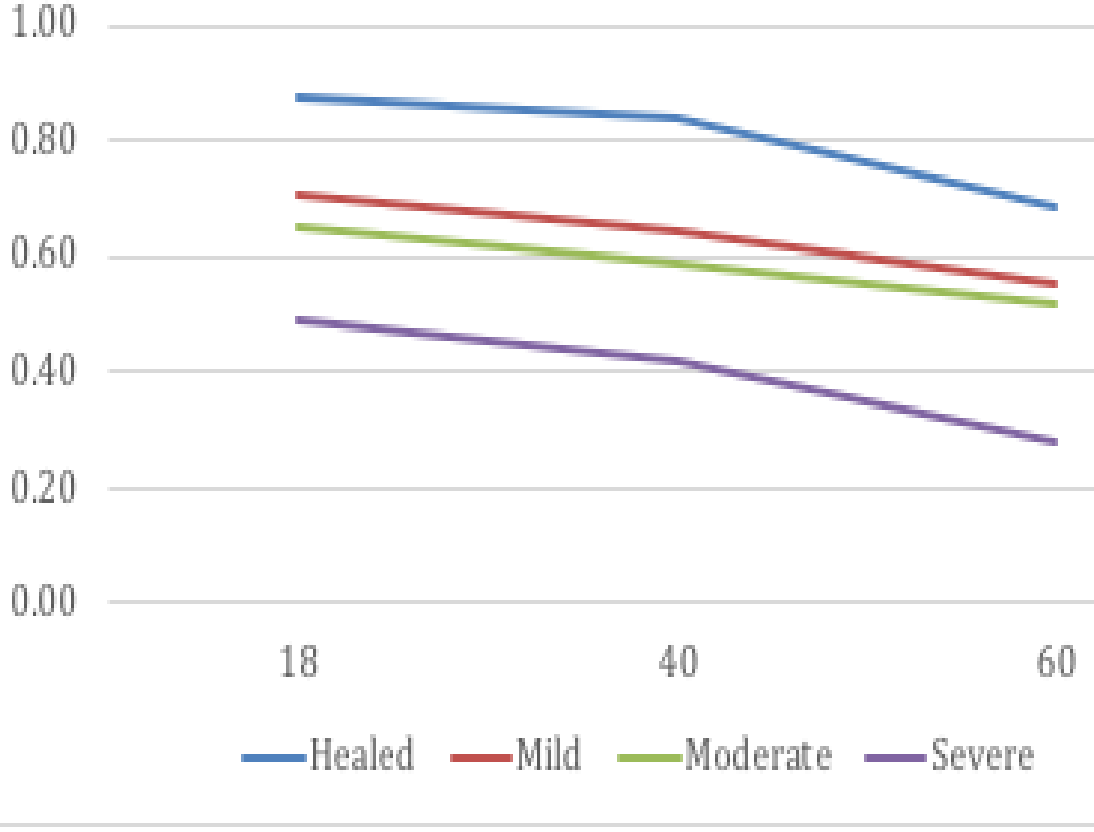
ECD consultation comments

Kyowa Kirin: long-term outcomes / utilities during adulthood

Vignette study extension: progressive utility decline



Estimated EQ-5D-5L scores at 18, 40 and 60 years by disease severity



⊙ ***Is the company method to estimate long-term utility decline preferred to the ERG scenario analysis (utility decline after 20 years)?***

Age of treatment discontinuation

ECM1	Company revised analysis
Age of treatment stopping (age when growth stops)	
• In the original model it was assumed treatment (growth) stopped at ages 16 years in girls and 17 years in boys • A clinical expert noted that a growth velocity < 2cm per annum year indicated final height	• To align with TA188 (growth hormone) the company assumed that treatment is discontinued at 14 years in girls and 16 years in boys (based on growth charts)
ERG comment:	
According to the definition of final height (growth velocity < 2cm per year): • The UK growth chart showed that before the age of 17 growth velocity for boys is 3cm per year - boys should stop treatment at age 17 not 16 • UK growth charts show that annual growth in girls aged up to age 15 is 2cm – girls should stop treatment aged 15 not 14	

⊙ ***What is the committee's preferred treatment stopping age?***

Other factors

- Adverse event costs have been included in the model
- Caregiver disutility:
  - An estimate of caregiver disutility was identified in the literature based on the experience of one caregiver of a person with limited mobility
  - In a scenario analysis a disutility value of -0.08 is applied to people in the moderate and severe health states up to 18 years old
- Company preferred discounting rate – 1.5%:
  - Disease progression in adulthood will not be significant in those with a healed skeleton at the end of growth. Therefore, quality of life will be closer to that of the general population.
  - The effect of burosumab is likely to be sustained (30 years or more)
  - Burosumab does not commit the NHS to significant irrecoverable cost
  - 1.5% accepted in HST7 (Strimvelis) because costs were incurred up-front but benefits accrued over a longer period. This is a comparable situation.

[redacted]

ECD consultation comments

Kyowa Kirin: revised economic analysis

Scenario	Incremental cost	Inc QALYs	ICER (with PAS)*
Committee preferred ICER (with utility decline)	[redacted]	3.95	£209,112
Committee preferred ICER (without utility decline)	[redacted]	4.91	£168,233
Step-by-step to revised base case			
Company original base case (without PAS)*	[redacted]	10.30	[redacted]
Company original base case	[redacted]	10.30	£88,363
ERGs preferred transition probability calculation + adverse event costs	[redacted]	10.32	£88,216
Including CL301 data in the transition probabilities	[redacted]	10.08	£90,292
Amendment to treatment stopping age	[redacted]	10.08	£71,432
Revised childhood utility values	[redacted]	9.04	£79,637
Progressive utility decline in adults	[redacted]	9.35	£76,996
Revised base case (1.5% discount rate)	[redacted]	9.35	£76,996

ECD consultation comments

Kyowa Kirin: scenario analysis

Scenario	Incremental cost	Inc QALYs	ICER (with PAS)
Revised base case	[redacted]	9.35	£76,996
3.5% discount rate	[redacted]	5.52	£120,419
Stopping treatment age is 16 for girls and 17 for boys	[redacted]	9.35	£97,324
Including caregiver disutility	[redacted]	9.78	£73,622
Conservative scenario: • ERG method for calculating transition probabilities • Inclusion of adverse event costs • CL301 data incorporated in transition probabilities • Treatment stops at age 16 for girls and 17 for boys • Revised childhood utilities • 3.5% discount rate	[redacted]	5.38	£153,265

[redacted]

Revised economic analysis: comparison with committee preferred scenario (1)

Scenario: step-by-step to revised base case	Incremental QALYs (undiscounted)	ICER (PAS)
Committee preferred ICER – *with 20 year utility decline*	8.29	£209,112
Committee preferred ICER – *no utility decline*	13.55	£168,233
Including CL301 data in the transition probabilities	13.21	£172,216
Progressive utility decline in adults	13.87	£167,319
Revised childhood utility values	15.53	£149,565
1.5% discounting	15.53	£97,324
Stopping treatment age 14 for girls and 16 for boys	15.53	£76,996
Company revised base case	15.53	£76,996

[redacted]

Revised economic analysis: comparison with committee preferred scenario (2)

Committee preferred ICER – *with utility decline*	£209,112
Committee preferred ICER – *no utility decline*	£168,233

Assumption	Committee preferred (ECM1)	Company deviation (response to ECD)	Approx effect on ICER *(vs with utility decline)*	Approx effect on ICER *(vs without utility decline)*
Transition probabilities	Based on CL201, CL205 and chart review data	Add CL301 data	+£6k	+£4k
Childhood utilities	Unadjusted (Lloyd et al)	Unadjusted + inferred value	-£18k	-£18k
Discounting rate	3.5%	1.5%	-£51.5k	-£57.5k
Decline in adulthood	With/without ERG utility decline at 20 years	New decline in adulthood (vignette study extension)	-£46k	-£5k
Age at discontinuation	16 girls and 17 boys	14 girls and 16 boys	-£40.5k	-£33k

**Figures calculated by the NICE team, to be confirmed by the ERG*

Additional ERG scenarios

Scenario	Incremental cost	Inc QALYs	ICER (with PAS)
Committee preferred ICER (with utility decline)	[redacted]	3.95	£209,112
Committee preferred ICER (without utility decline)	[redacted]	4.91	£168,233
Company revised base case	[redacted]	9.35	£76,996
Treatment stopping age: 15 girls and 17 boys *(see slide 29 for info)*	[redacted]	9.35	£90,136
Utility decline 20 years after end of treatment *(see slide 28 for info)*	[redacted]	6.04	£119,325

[redacted]

QALY weighting

Scenario	QALY gain	
	Undiscounted	Discounted (discount rate)
Company original base case	17.01	10.30 (1.5%)
ERG original base case	8.29	3.95 (3.5%)
Committee preferred analysis	13.55	4.91 (3.5%)
Company revised base case	15.53	9.35 (1.5%)
Company conservative scenario	14.92	5.38 (3.5%)
Utility decline 20 years after end of treatment	8.47	6.04 (3.5%)

[redacted]

Key issues

- Has the evaluation captured all the key issues raised in the comments by patients, parents and the public?
- Does the new clinical evidence (CL301) address clinical uncertainty outlined in ECM1?
- Utility values:
  - Does the committee accept the company amendment to childhood utility values?
  - Is the extension to the vignette utility study an appropriate way to model long-term utility decline?
  - Was caregiver disutility estimated in a robust way? Should it be included?
- At what age does growth stop? What is the appropriate treatment stopping age?
- Is there sufficient justification to deviate from a discount rate of 3.5%?
- What is the committee's preferred ICER? Does QALY weighting apply?
- Other factors

[redacted]