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

For public – contains no confidential information

Technology appraisal committee B [15 February 2024]

Second committee meeting

Chair: Baljit Singh

External assessment group: CRD and CHE Technology Assessment Group, University of York

Technical team: Summaya Mohammad, Yelan Guo, Richard Diaz

Company: Kyowa Kirin

Burosumab is not recommended for XLH in adults (1)

Committee's key conclusions, clinical :

- **Treatment population:** People ≥18 years with XLH and chronic hypophosphataemia symptoms including BPI 'worst pain in last 7 days' ≥4; usual treatment unsuitable because ineligibility, intolerance, insufficient efficacy
- **Population generalisability – Age and weight distribution:** EAP reflects eligible population in NHS
- **Treatment effect:** Burosumab effective at normalising serum phosphate; some PROs may be affected by placebo effect or regression to mean

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Committee's key conclusions, economic :

- **Stopping criteria:** No stopping rule – there may be benefits despite not meeting WOMAC threshold
- **Tapering of treatment effect:** Same tapering to mortality and morbidity
- **Adjusting utilities for placebo-effect:** Placebo-adjusted utilities
- **Utility benefit for carers/family:** Utility benefit to 1 carer – may be overestimated

Abbreviations: BPI: Brief Pain Inventory; EAP: expanded access programme; PRO: patient-reported outcome; WOMAC: Western Ontario and McMaster Universities Arthritis Index; XLH: X-linked hypophosphataemia

Burosumab is not recommended for XLH in adults (2)

Committee's key conclusions where *further analyses requested,* economic :

- **Excess mortality risk from XLH:** HR = 2.33 vs general population
  - Unclear if association with social deprivation – prefer adjusting if linked
- **Mortality benefit with burosumab:** Likely less than 50% in absence of evidence
  - Need evidence on relationship between XLH and factors increasing mortality risk in XLH, and extent burosumab may reduce any mortality risk
- **Modelling excess fracture incidence:** Uncertainty assuming 100% reduction
  - Real-world evidence and explore differing morbidity benefits from reducing fractures
- **Utility source:** Not include data beyond week 96
  - Explore fitting hierarchical/smoother on data beyond week 96
- **Disutility for incident fractures:** Vary depending on fracture
  - More information on length of time fractures in different bones affect quality of life

All cost-effectiveness estimates are above range considered an acceptable use of NHS resources

- **Unmet need:** For a well-tolerated treatment that normalises phosphate levels in adults

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Abbreviations: HR: hazard ratio; XLH: X-linked hypophosphataemia

Burosumab efficacy on patient reported outcomes – CL303 trial

Background: EAG note potential baseline imbalances between arms (burosumab: older on average, fewer fractures, higher 'worse WOMAC physical functioning', more severe pain) – limited evidence beyond 24 weeks; some PROs may have placebo-effect or regression to mean
DG: Placebo-effect noted, company used non-placebo adjusted utility values in model

EAG:

- Some outcomes (e.g. worst pain) have [redacted]
- Most outcomes show modest benefit for burosumab – most benefits small and [redacted]

Clinical expert: Benefits accumulate over time – stopping burosumab affects pain, stiffness, functioning, fatigue

[redacted]

Abbreviations: BPI-SF: Brief Pain Inventory short form; SD: standard deviation; WOMAC: Western Ontario and McMaster universities osteoarthritis index

Draft guidance consultation responses

Responses received from:

- **Company** – Kyowa Kirin: Response to the key issues/uncertainties, provided scenario analysis for stopping rule
- **XLH UK** (patient group): Response based on a survey among 116 people with XLH and their carers
- **Clinical expert**: Response on several key issues based on an online survey among 9 clinical experts prescribing burosumab for 137 people with XLH
- **Charles Dent Metabolic Unit, University College London Hospitals Foundation Trust:** Responses to key issues
- **Web comments:** 58 responses from people affected by XLH – symptomatic impact of XLH, financial impact, economic impact of not providing burosumab, inequality concerns

Abbreviations: XLH: X-linked hypophosphataemia

Stakeholders' comments:

Burosumab eligible population size (1000 people) is overestimated:

- Burosumab better for moderate to severe symptoms – XLH UK provide support to people with XLH and have approx. 320 contacts
- **Clinical expert:** Survey among 9 expert centres managing most adults with XLH – 137 prescribed burosumab, 71 additional would be eligible, 35 additional people each year
- **Web**: Previous literature 1 in 20,000, but recent is 1 in 100,000 XLH population

XLH impact (web): Progressive condition with lifetime daily pain, fatigue, mobility problems, weak muscles, no energy, stiff and painful joints, diarrhoea, hearing problems, dental problems, osteoporosis, anxiety, depression, stress, low self-esteem, suicidal thoughts

- Some have symptoms later in life; de novo mutations may be worse off if diagnosed late (progressive)

Transformative health impact on burosumab (XLH UK and web):

- Pain is more manageable, more independence, more energy, less fractures, less fear of falling, less hearing problems, more confidence walking
- Less pain means more mobility and muscle strength – lower risk of fractures and accidents

Economic impact (XLH UK and web): XLH affects ability to work – can result in early retirement, claiming disability and carer benefits, loss of independence, time at appointments, scans, surgery, therapy, dentist

- *Section 4.4 NICE manual: Costs should relate to resources under control of NHS and PSS*

Abbreviations: XLH: X-linked hypophosphataemia

Key unresolved issues after consultation

= Large impact on ICER

= Small impact on ICER

Key issue		Slide	
Clinical trial	Are CL303 age and weight distribution reflective of NHS practice?	8	
Modelling of mortality and morbidity	Which hazard ratio of excess mortality associated with XLH is appropriate – company or EAG?	9	
	Is 50% reduction in excess mortality with burosumab appropriate?	10 and 34	
	Is a 100% reduction in new fractures if serum phosphate is normalised appropriate?	11	
Treatment tapering effect	Should the same or different treatment effect assumptions be applied to mortality and morbidity?	12	
Stopping rule	Which treatment stopping criteria and discontinuation rates are appropriate?	13	
Utility	Which data should inform long term utility in the model?	14	
	Should utility be adjusted for placebo effect?	15	
	Should disutility for incident fractures continue >1 year?	16 and 35	
	How much utility benefit should be applied to carers/family?	17 and 36	

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Abbreviations: XLH: X-linked hypophosphataemia

Key issue: Age and weight distribution of population

Background: Company prefer age and weight distribution from CL303 – consistent with efficacy and utility data; EAG prefer the UK EAP – better represent NHS, CL303 were younger and weighed less than in EAP
DG: EAP is more appropriate to reflect eligible population in NHS

Company prefer

EAG prefer

		Source			Weight in EAP after starting burosumab at month:				
		CL303	BUR02	EAP	Baseline (n=133)	3 (n=17)	6 (±3) (n=21)	12 (±3) (n=9)	18 (±3) (n=10)
Mean age (SD)		40 (12.2)	40.1 (12.1)	42.8 (14.6)					
Weight, kg	Mean (SD)	67.2 (EU)		70.3	73.6 (16.9)	69.3 (11.6)	72 (15.4)	66.8 (10.6)	65.6 (13.7)
	Median				69.6	64.5	70.3	63.5	62

Company response: Maintains using CL303 – provide evidence of weight distribution in EAP
- Most lose weight after burosumab with less stiffness, fatigue, and improved muscle strength
- Observations from EAP show mean weight <70 kg after burosumab

EAG: Does not consider company's response sufficient to address the issue – maintain using EAP
- Variability in weight changes – mean weight at month 6 similar to baseline
- Small patient numbers at month 18 (65.6kg, n=10) compared with baseline (73.6 kg, n=133)

Clinical expert: EAP show mean weight of all adults (n=57) = 67 kg; and burosumab (n=19) = 63 kg;
- Provide breakdown of adults in EAP by, age band, sex, current strongest pain score

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Abbreviations: EAP: Early access programme; kg: kilogram; XLH: X-linked hypophosphataemia

Key issue: Excess mortality risk associated with XLH

DG: Committee prefer HR = 2.33 vs. general population based on larger sample with more recent data

- Extent of social deprivation associated with XLH unclear, if linked then adjusting for deprivation is preferred

	HR (95% CI)	Source
Company	2.88 (1.18 to 7)	Hawley et al., 2020 – UK CPRD 1995-2016
EAG	2.33 (1.16 to 4.67)	Hawley et al. extended on larger UK sample, CPRD GOLD and AURUM, 1995-2022 (Company's confirmatory study)

Company response: Maintain HR = 2.88 in base case

- Company's confirmatory study controls for deprivation (a matching variable) and is case-cohort study (essentially does not need adjustment for matching variables)
- Analysis of confirmatory study (preferred by EAG) – Use Index of Multiple Deprivation (IMD) quintile added as factor covariate in Cox PH model: HR = 2.49 (95% CI: 1.23 to 5.02)

EAG: Maintain HR = 2.33

- Cannot confirm company analysis (no access to model/data); note HR=2.49 not in model
- In confirmatory study, 10 non-XLH controls of same age, gender, IMD and ethnicity matched to each XLH case, resulting in HR for overall survival between likely and highly likely XLH population and matched cohort

Clinical expert: HR = 2.88 reasonable – company's confirmatory study matches for age/sex/practice/IMD (so expect a lower mortality)

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Abbreviations: CI: confidence interval; HR: hazard ratio; PH: proportional hazards; XLH: X-linked hypophosphataemia

Key issue: Mortality benefit of burosumab

Background:

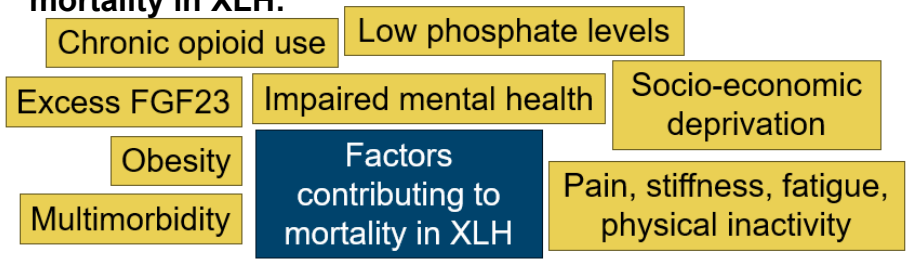
- **Company**: assume 50% reduction in excess mortality risk from XLH with burosumab vs standard care
- **EAG**: No structural link between fractures/morbidities and mortality in model – explore 0%, 11%, 25% reductions in excess mortality

DG: Likely reduction in excess mortality below 50% – direct/indirect evidence needed; explore relationship between XLH and factors that may increase mortality risk e.g. opioids, mental health, social deprivation in XLH and extent burosumab may reduce any mortality risk

Company response: Maintain 50% reduction in excess mortality

- Provide evidence on multi-system effects of hypophosphataemia and factors that may drive increased mortality in XLH
- Burosumab has potential to improve all factors associated with increased mortality, so excess mortality in XLH will reduce

Factors identified by company that may increase mortality in XLH:



EAG: Potential effects of burosumab on excess mortality reduction remains unknown

- Company provided some details on associations between factors that may increase mortality risk and mortality, but none are used in the model to quantify how burosumab could reduce excess mortality risk

Clinical expert survey: 5/9 choose 25% mortality reduction from burosumab; 3/9: 10%; 1 no answer
Stakeholder: Concern more emphasis on mortality than improving QoL – No burosumab studies on mortality effect; biochemistry normalisation, skeletal growth, fracture healing, symptom reduction reasonable as surrogate for eventual life-expectancy

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Abbreviations: QoL: quality of life; XLH: X-linked hypophosphataemia

Key issue: Reduction in fracture incidence with burosumab

Background: Company: assume 100% reduction in excess fracture incidence (i.e. to general population)

- **EAG**: Likely overestimated and not based on any evidence – include 75% and 50% scenarios
- **DG**: High uncertainty assuming 100% reduction – RWE needed to support and exploring morbidity benefits associated with reduction in excess fracture incidence with burosumab

Company response: Maintain 100% reduction in excess fractures assumption

- Estimate annual fracture rate based on CL303 = 0.021 (2 fractures over 90.2 patient-years)
- Model: Burosumab fracture rate = gen. population (0.024 to 0.05 by the end of period), greater than CL303
- RWE on fracture incidence for burosumab in EAP: 0 fractures as adverse events over 389 patient-years
- BUR02 long-term follow-up: Mean exposure 166 weeks and no new fractures
- BUR03 phase 3b, open-label, single-arm study in Germany: 0 new adverse event fractures (n=34)
- Expert elicitation (Seefried et al., 2023), burosumab considered very likely to stop all future fractures

EAG: Likely fewer fractures by normalising serum phosphate, but 100% reduction uncertain – short follow-up

- EMA assessment: Bone normalisation may take months/years (CL304 show bone structure not completely normalised at week 48) – may contribute to continued incidence of new fractures despite burosumab

Clinical expert survey (XLH often have wider bones and higher bone density): 4/8 choose burosumab reduces hip fracture risk to general population; 3/8 to below; 1/8 to above

Stakeholder: Report 0 new fractures over 2-year follow-up in adults with burosumab (n=38 to n=22 at 2-years)

Web: '*My peers have developed fractures and use crutches…[since burosumab] I have developed no fractures*'

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Abbreviations: EAP: expanded access programme; RWE: real world evidence; XLH: X-linked hypophosphataemia

Key issue: Tapering of treatment effect

Background: Company use different tapering assumptions for mortality and morbidity when stopping burosumab; EAG assume same treatment effect
DG: Arbitrary assumptions but agree with applying same treatment tapering assumptions

Company response: Assumptions based on clinical expert opinion – maintain base case :

Company	Year 1 on burosumab	Year 2+ on burosumab	1 year after treatment end	2 years after
Morbidity	100%	100%	50%	0%
Mortality	75%	100%	75%	50%

- 2 clinical experts (UK) – suggest time taken for changes in morbidity/mortality/utilities are different
- Morbidity (fractures) and utilities change quickly – tapering should be in shorter time frame
  - Model assume immediate impact on fractures and loss of impact within 1 year (no new fractures in CL303 after 24 weeks, BUR02 and EAP)
- Mortality: Over time burosumab expected to increase physical activity, reduce opioid use, obesity, improve mental health – takes time, so longer tapering period
  - A delay in positive impacts at start of treatment and delay in loss of benefits after treatment end

EAG: No new evidence from company – note that treatment tapering effect has least impact on ICER

Clinical expert survey: Median time for improvement in pain=12 weeks; Time to reach plateau in pain is 1 year (3 experts) or 2 years (3 experts); Symptoms worsening after stopping burosumab: 4 to 12 weeks

- Survey with XLH UK among adults: Strongest pain scores attenuate the longer people have burosumab

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Abbreviations: EAP: expanded access programme; ICER: incremental cost-effectiveness ratio; XLH: X-linked hypophosphataemia

Key issue: Stopping criteria and long-term discontinuation

Background: Continuation criteria: Serum phosphate >LLN at 24 weeks and improved WOMAC at 12 months
DG: Prefer no stopping rule – EAP and CL303 had no stopping rule, implementation is unclear, other benefits of continuing burosumab e.g. fewer side effects and less opioid use

Company response: Maintain stopping rule, but support stopping rule supported by clinical community

- Draft management of XLH in adults (Mohsin et al.) recommend annual review – consider stopping if *average pain over last week not improved and no analgesic use reduction from baseline*
- New scenario based on BPI score: 65.15% continue (43 met criteria at 48 weeks) – reduces ICER

EAG: Company's scenario based on BPI only a proxy for the draft management of XLH – different pain criteria

- Unclear if scenario also includes meeting serum phosphate and WOMAC score criteria (model structure)
- 34.85% discontinue in new scenario vs 16.9% in base case – may be unreasonable considering few treatment options, benefits of serum phosphate normalisation, reduction in opioid use
- Mean utility change from baseline for 43 meeting pain criteria > base case (0.240 vs 0.215) from year 3+
- Substantially reduces ICER
    - Imbalances in baseline characteristics between arms in CL303 – including greater pain intensity in burosumab arm than placebo at baseline leading to greater pain reduction and changes in utility

Clinical expert survey – from the options of stopping at 12 months if no improvement in average pain over last week and no reduction in analgesic use from baseline: 4/9 – stop for both criteria; 2/9 – either criteria; 2/9 – only failed reduction of average pain; 1/9 – only no reduction in analgesic use from baseline

Does the committee consider a stopping rule appropriate? If so, which criteria?

Abbreviations: BPI: Brief Pain Inventory; EAP: expanded access programme; LLN: lower limit of normal; WOMAC: Western Ontario and McMaster Universities Arthritis Index

Key issue: Modelling utility over time/source of values

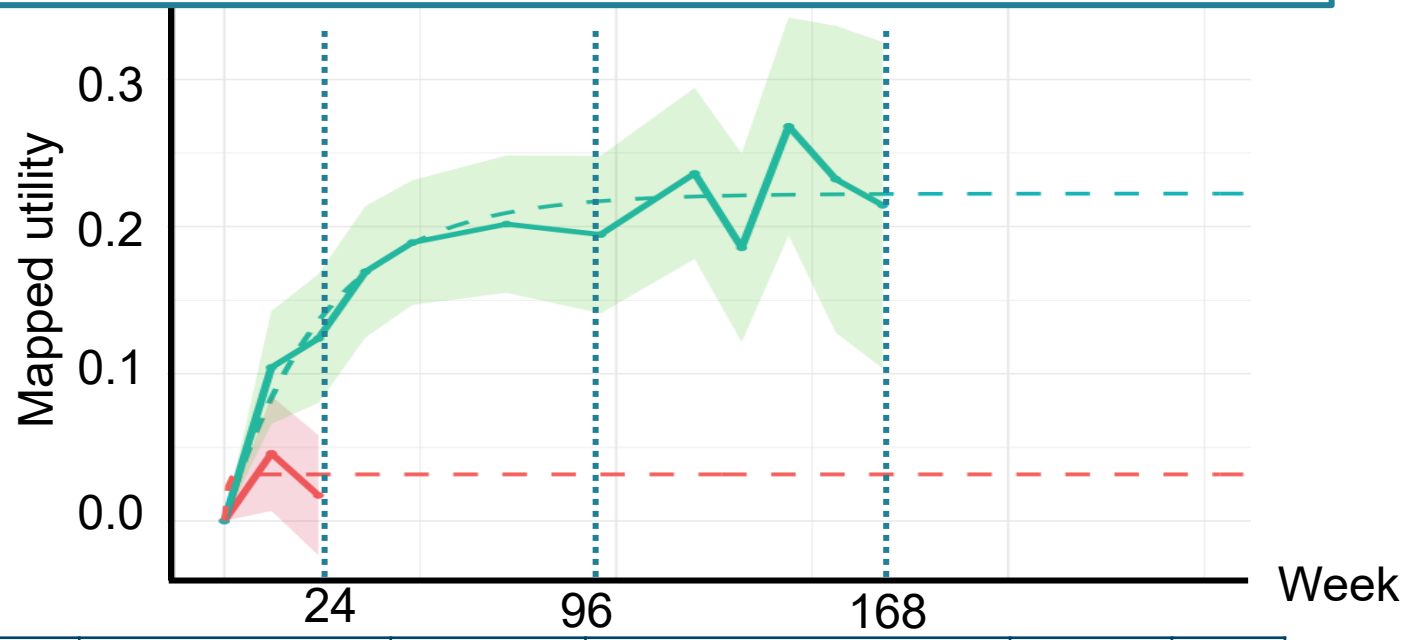
Background: Uncertainty using post-week-96 data – small number of people, data from subsets of original randomised population, including US-only data at timepoints – result in increased variability

- Week 96: Modelled utility lies above observed utility for burosumab, and extrapolated over lifetime horizon
- **Company:** Highlight predicted utilities were within 95% confidence interval predicted by model
- **EAG:** Consider data up to week 96 as reliable (in absence of EAP data) and included in base case

DG: Prefer EAG approach – suggest hierarchical model and/or smoother on data beyond week 96

Company response: Suggested models not feasible to develop/validate in timeframe

- Unclear if a higher parametrised model increases clarity – limited empirical data and scope for elicitation (rare condition)
- Asymptotic model inherently smooths observed curve and avoids extrapolating trends observed within trial period over extended period



Week	Baseline	24	48	96	120	132	144	156	168
Population	CL303 (randomised)		CL303 extension		CL303 US only	BUR02	BUR02 and CL303 US	BUR02	
Bur/Pbo, n	66/65	66/65	66	59	46	11	24	10	10

Abbreviations: Bur: burosumab; EAP: expanded access programme; Pbo: placebo; US: United States

Key issue: Adjusting utility values for placebo effect

Background: Company use non-placebo-adjusted utilities; EAG prefer adjusted and include in scenario
DG: Best practice to consider data from placebo arm in trials – placebo-adjusted values are appropriate

Company response: Maintain non-placebo-adjusted utilities in base case

- Placebo arm utilities show initial improvement at 12 weeks, then return to near baseline levels at 24 weeks – suggest any placebo effect on utility is short-lived
- WOMAC outcomes after burosumab interruption between finishing CL303 and starting BUR02 show return to baseline WOMAC score after treatment withdrawal (Kamenicky et al., 2023) – suggest minimal RTM

EAG: Best practice to use placebo-adjusted utilities – include in scenario

- Kamenicky et al (post-hoc analysis, n=7) give limited evidence to support non-placebo adjusted utilities
- Return to 'similar' baseline score level but how similar is unknown – time to return not mentioned
- Out of 7 people, 4 re-started burosumab within 8 months of discontinuation, 3 within 13-16 months – return to similar baseline utility likely within 1 year of treatment discontinuation
- ICERs very sensitive to utilities, any small placebo effect can have large impact on cost effectiveness

Clinical expert survey – day-to-day symptom variability vs long-term decline: 4/8 agree typically minor variability with no significant worsening over 6 months; 2/8 significant worsening over 6 months; 2/8 agree no/minor general worsening

- Unreasonable to expect pain reduction from placebo to be maintained given low day-to-day variability, minimising regression to mean

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Abbreviations: ICER: incremental cost-effectiveness ratio; RTM: regression to mean; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Disutility for incident fractures

Background: Company apply disutility for incident fractures over lifetime; EAG concern it is overestimated – explore scenario applying disutility in first year only
DG: Disutility duration depends on fracture – information on duration different fractures would affect QoL

Company response: Incident fractures to tibia, fibula, femur, pelvis, foot or spinal vertebrae have lifetime disutility decrement – all other fractures have decrement in first year only

- Impaired bone mineralisation in XLH means fractures likely slow-healing and associated with long-term HRQoL impact – supported by CL303 (no fracture healing between week 12-24 in placebo arm)
- Evidence search for impact of various bone fractures on utility (osteoporosis or at risk of fragility fractures)
  - 3 studies – show prolonged HRQoL impact, and differences between fracture sites

EAG: Lifetime disutility does not reflect fracture healing over time or adjust for fracture-specific mortality – potential double-counting morbidity effects as treatment-specific utilities are extrapolated over lifetime

- Model structure allows changes for separate disutility in first year only
- Borhan 2019 from company's evidence search considered relevant to address committee concern:
  - Suggest hip fractures have negative long-term impact on HRQoL
  - Fractures closer to follow-up assessment associated with significant impact on HRQoL vs fractures a long time before – impact on HRQoL over lifetime unlikely appropriate

Clinical expert survey: 7/9 agree healing XLH-related fractures of proximal femur with ECM is >1 year

- Median recently diagnosed symptomatic pseudo-fractures remaining symptomatic with ECM for:
- 1-year: 80%, 2-years: 50%; 5-years: 25%; Lifelong: 10%

Abbreviations: ECM: established clinical management; HRQoL: health-related quality of life; XLH: X-linked hypophosphataemia

Utility benefit on caregivers and family

Background: Company apply total 20% spillover utility benefit to 2 carers/family members; EAG apply to 1
DG: Prefer applying any utility benefit to 1 carer/family but note this may overestimate utility benefit

- Any benefit on carer utility should only include carers without XLH to avoid double-counting
- Uncertainties to address: Average number of carers an adult with XLH would have; impact of caring for an adult with XLH on quality of life; how burosumab would affect the quality of life of carers

Company response: Maintain utility benefit for 2 carers/family members

- Family members impacted by XLH whether they have caregiving role or not – physical, mental, daily living
- Double counting only possible where 2+ adults within same family with XLH have burosumab in CL303 and some improvement in WOMAC is indirectly due to improvements in other adult in family

EAG: Not appropriate to include informal caregiver and/or family member with XLH because spillover effect is added to patient utility benefit with burosumab in model – likely double-counting of treatment benefits if family with XLH (informal carer) have burosumab too (also benefit from patient benefit associated with burosumab)

- Limited treatment options means family members with XLH likely also considered suitable for burosumab

Patient expert survey: Of 24 carers, 3 report no change in wellbeing after burosumab; 2 report moderate improvement; 19 report significant improvement

- After burosumab, total average carer hours per week decrease by 61% (19 to 7.5 hours per week)
- Number of carers for adults with XLH and no burosumab (n=46): 0 carers (16); 1 carer (10); 2+ carers (18)
- After burosumab (n=24, at least 1 carer): No carer needed (9); 1 carer (10); 2+ carers (5)

Abbreviations: WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; XLH: X-linked hypophosphataemia

Equality and other factors

DG: XLH affects ability to do paid work – Some increased likelihood of higher social deprivation

- Committee agree this was not an equality issue because its recommendation does not restrict access to treatment for some people over others

Company: No further equality issues raised during draft guidance consultation

Stakeholder comments:

Age discrimination (XLH UK, clinical expert, web comments):

- Denying access based on age could disproportionately affect the livelihoods and economic well-being, exacerbating inequalities and hindering ability to contribute to society
- XLH has a higher symptom burden in older people

Geographical inequality (XLH UK, clinical expert, web comments):

- SMC recommend burosumab for adults with XLH (ultra-orphan framework*) – geographical disparity
- XLH disproportionally affects people living with greater deprivation

Gender (clinical expert, web comments):

- XLH disproportionally affects women (2:1 ratio),

Any other factors for additional consideration from committee? E.g. Rarity, unmet need, innovation?

*Note: SMC recommend burosumab within ultra-orphan pathway while further evidence is generated – review in 2026

Abbreviations: SMC: Scottish Medicines Consortium; XLH: X-linked hypophosphataemia

Summary of differences in base case assumptions

Assumption	Company base case	EAG base case
Age and weight distribution	CL303	EAP
Excess mortality risk due to XLH	HR = 2.88	HR = 2.33
Tapering treatment effect on mortality and morbidity	Morbidity: • On treatment year 1 & 2: 100% • After discontinuation: year 1: 50%; year 2: 0% Mortality: • On treatment year 1: 75%; year 2+ 100%; • After discontinuation: year 1: 75%; year 2: 50%	Same tapering effect on mortality and morbidity: On treatment year 1: 75%; year 2+: 100% After discontinuation: year 1: 50%; year 2: 0%
Utility change from baseline and extrapolation/source of utility values	Include post-week 96 data from BUR02	Extrapolating WOMAC using data up to week 96 from CL303
Caregiver/family utility benefit	2 caregivers/family	1 caregiver/family

Abbreviations: HR: Hazard ratio; EAP: expanded access programme; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; XLH: X-linked hypophosphataemia

Committee's preferred assumptions at ACM1

Base case assumption	Company	EAG	Committee
Age and weight distribution	CL303	EAP	EAP
Excess mortality risk from XLH	HR = 2.88	HR = 2.33	HR = 2.33
Tapering of treatment effect on mortality and morbidity	Different tapering effect for both	Same tapering effect for both	Same treatment effect assumptions
Utility change from baseline and extrapolation	Include post-week 96 data from BUR02	Do not include	Not include – suggest hierarchical/smoother on post-week 96 data
Caregiver/family utility	2 caregivers/family	1 caregiver/family	1 caregiver/family
Stopping criteria	Serum phosphate>LLN and improved WOMAC		No stopping rule
Modelling of utility	Should it be adjusted for placebo?		Placebo-adjusted
Burosumab reduces excess mortality 50%	Should this benefit be reduced? No reduction? 25%? 11%?		50% arbitrary – direct or indirect evidence needed
Fracture incidence if normal serum phosphate	Same as general population? 75% or 50% decrease in excess?		Real-world evidence needed to support
Disutility of fractures	Life-long or for 1st year only?		More information needed

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Abbreviations: EAP: expanded access programme; HR: hazard ratio; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Cost-effectiveness results

In summary:

- All cost effectiveness results are substantially above £100k per QALY gained and the maximum acceptable threshold that represent an effective use of NHS resources (£30k per QALY gained)
- **EAG preferred assumptions increase ICER**
    - Biggest known increase associated with EAG assumptions (applied individually) was from assumptions on carer utilities, only using data from CL303 to extrapolate utility values, and age and weight distribution
    - Assumptions on tapering treatment effect and excess mortality risk with XLH have less effect
- **EAG scenarios** all increase ICER (<50% reduction in excess mortality, <100% reduction in incident fractures, disutility of incident fractures applied in first year only, using placebo-adjusted utilities)

Company and EAG's base case results

Burosumab vs standard care		Total		Incremental		ICER (£/QALY)
		Costs (£)	QALYs (£)	Costs (£)	QALYs	
Company deterministic	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard care	9,493	7.83			
Company probabilistic	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard care	9,514	7.83			
EAG deterministic	Burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard care	8,841	7.10			

Note: Company deterministic base case include EAG's programming corrections in model (company accepted changes)

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Abbreviations: ICER; incremental cost-effectiveness ratio; QALY: quality-adjusted life year

EAG's cumulative results

Burosumab vs standard care	Incremental		ICER (£/QALY)
	Costs (£)	QALYs	
Company base case	[redacted]	[redacted]	[redacted]
EAG preferred assumptions			
• Age and weight distribution from EAP	[redacted]	[redacted]	[redacted]
• Excess XLH mortality risk (HR: 2.33)	[redacted]	[redacted]	[redacted]
• Same tapering effect on mortality and morbidity	[redacted]	[redacted]	[redacted]
• Utility data up to week 96 extrapolated	[redacted]	[redacted]	[redacted]
• Utility benefit 1 caregiver/family member only	[redacted]	[redacted]	[redacted]
EAG base case	[redacted]	[redacted]	[redacted]

Abbreviations: HR: hazard ratio; ICER; incremental cost-effectiveness ratio; QALY: quality-adjusted life year; XLH: X-linked hypophosphataemia

Company scenario analyses

Parameter	Base case	Scenario
Time horizon	Lifetime	20 years
Annual discount rate	3.5%	6%, 5%, 1.5%, 0%
Age distribution	CL303	CL001
Weight distribution	CL303 EU	CL303 All
Mortality	Hawley et al. at least likely (50% reduction in morality with burosumab)	Hawley et al. at least possibly (50% reduction); and least likely (0%)
Spill-over burden	Yes	No
Morbidities in model		Spinal stenosis, spinal surgery, dental abscess
Mortality taper	Yes	No
Morbidity taper	Yes	No
Utility taper	Yes	No
Treatment continuation	Stopping rule	No stopping rule
Morbidity reduction (normal serum phosphate)	100%	0%
Stopping rule	Serum phosphate>LLN and improved WOMAC at 12 months	BPI score criteria

EAG's alternative assumptions

Burosumab vs standard care	Incremental		ICER (£/QALY)
	Costs (£)	QALYs	
EAG base case	[redacted]	[redacted]	[redacted]
Morbidity benefit with burosumab (100% fracture incidence reduction)			
• 75% reduction	[redacted]	[redacted]	[redacted]
• 50% reduction	[redacted]	[redacted]	[redacted]
Mortality benefit with burosumab (50% reduction excess mortality)			
• No reduction	[redacted]	[redacted]	[redacted]
• 11% reduction	[redacted]	[redacted]	[redacted]
• 25% reduction	[redacted]	[redacted]	[redacted]
Utility benefit (non-placebo-adjusted utility values and disutility for incident fractures in subsequent years)			
• Placebo-adjusted + disutility for incident fractures in first year only	[redacted]	[redacted]	[redacted]

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Abbreviations: ICER; incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Key unresolved issues after consultation

= Large impact on ICER

= Small impact on ICER

Key issue		Slide	
Clinical trial	Are CL303 age and weight distribution reflective of NHS practice?	8	
Modelling of mortality and morbidity	Which hazard ratio of excess mortality associated with XLH is appropriate – company or EAG?	9	
	Is 50% reduction in excess mortality with burosumab appropriate?	10 and 34	
	Is a 100% reduction in new fractures if serum phosphate is normalised appropriate?	11	
Treatment tapering effect	Should the same or different treatment effect assumptions be applied to mortality and morbidity?	12	
Stopping rule	Which treatment stopping criteria and discontinuation rates are appropriate?	13	
Utility	Which data should inform long term utility in the model?	14	
	Should utility be adjusted for placebo effect?	15	
	Should disutility for incident fractures continue >1 year?	16 and 35	
	How much utility benefit should be applied to carers/family?	17 and 36	

Abbreviations: XLH: X-linked hypophosphataemia

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Thank you.

Back-up

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Draft consultation comments

"I have gone back to working full time, my overall level of pain has dropped significantly and crucially my night pain has almost completely resolved…I can sleep and function…I have recently climbed Mount Snowdon and taken part in a 10k run. Before treatment I struggled to walk 500m slowly. I had multiple stress fractures and other complications including chronic pain, diarrhoea from the alternative medications and massive fatigue…"

"To know that my XLH should not regress further is something I cannot put into words, especially as my many surgeries have given me to have several other severe medical issues, causing further pain, complications, mobility and social issues."

"I can now shop, wash the clothes, change the bedding, walk the dogs etc. much easier as my pain, stiffness and fatigue has all reduced…"

"My body was so painful I could barely walk upstairs or exercise. I am now able to run upstairs and regularly attend a gym."

"I am healthy, fitter, and happier since taking this drug [burosumab]. I used to have to see my GP and hospital so frequently - this is no longer the case."

Key clinical trial – CL303

Design	Phase 3, placebo-controlled, randomised trial
Population	134 adults with XLH (18 to 65 years of age)
Intervention	Burosumab (1 mg/kg) every 4 weeks
Comparator	Placebo
Duration	• 24-week placebo-controlled treatment period • Open-label treatment continuation period (week 24 to 48) with burosumab • Open-label treatment extension – week 48 to 96 • Open-label treatment extension 2 (US only) – week 96 to 149 • After week 96, people treated in European study centres could take part in BUR02 open-label continuation study
Primary outcome	Serum phosphate levels • Proportion with mean serum phosphate concentration above lower limit of normal (2.5 mg/dL or 0.81 mmol/L) – average value at midpoints of 4-weekly dosing intervals
Key secondary outcomes	To week 24: skeletal pain (BPI), stiffness (WOMAC), physical functioning (WOMAC)
Locations	Asia (Japan, South Korea); Europe (Ireland, Italy, France, UK); North America (USA)

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Abbreviations: BPI: Brief Pain Inventory; mmol: millimole; XLH: X-linked hypophosphataemia

Burosumab efficacy on serum phosphate – CL303 trial

DG: Burosumab is clinically effective at normalising serum phosphate

Company: Increase in serum phosphate with burosumab sustained over time –

[redacted]

- 84% in burosumab-burosumab group (open-label extension period, week 24 to 48) had mean serum phosphate above LLN across midpoints of dose intervals
- After cross-over to burosumab, 89% of placebo-burosumab group had mean serum phosphate above LLN across midpoint dose intervals

Week 24	Burosumab (n=68)	Placebo (n=66)
Achieved mean serum phosphate >LLN, n (%)	64 (94.1%)	5 (7.6%)
95% CI	85.8, 97.7	3.3, 16.5
P-value	<0.0001	

[redacted]

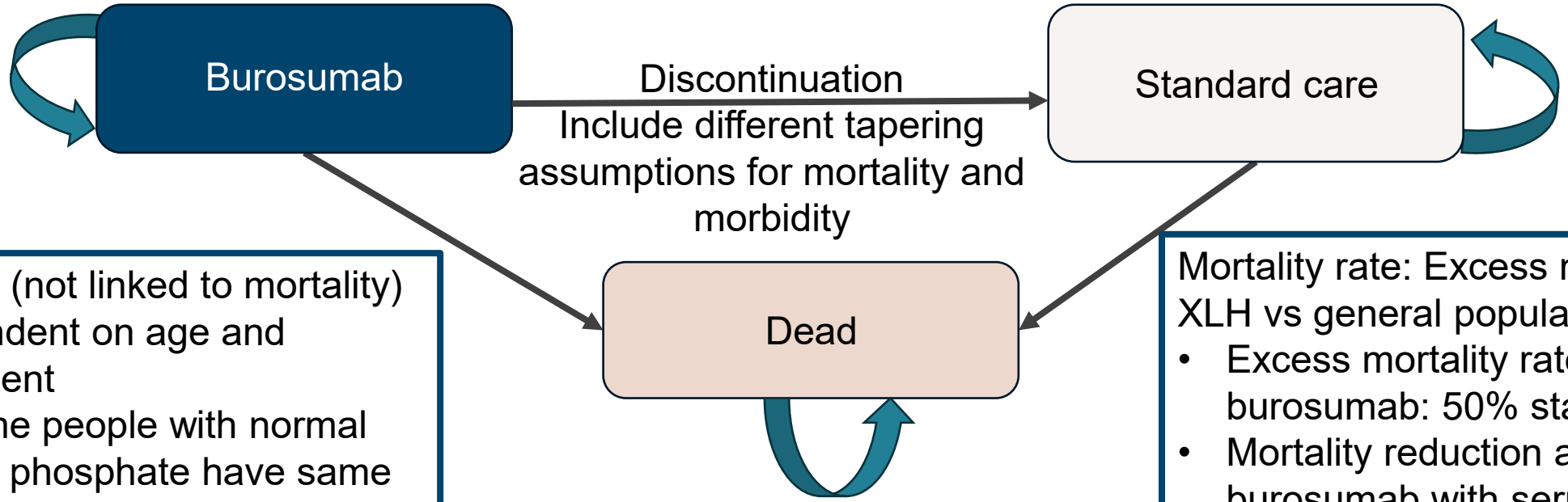
KRN23 = burosumab

Abbreviations: BPI: brief pain inventory; LLN: lower limit of normal; mmol: millimole; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; XLH: X-linked hypophosphataemia

Company's model overview

- State transition cohort model – Using CL303 age and weight distribution (EU cohort); 65% female
- Burosumab modelled to improve serum phosphate levels, reduce fractures and improved HRQoL with better physical functioning and reducing pain and stiffness and fewer fractures

Continuation at 1 year based on reaching serum phosphate above LLN after 24 weeks and improved WOMAC score at 12 months after treatment start



Morbidity (not linked to mortality)
- Dependent on age and treatment
- Assume people with normal serum phosphate have same rate of fractures as general population

Mortality rate: Excess mortality for XLH vs general population HR
- Excess mortality rate for burosumab: 50% standard care
- Mortality reduction applied to burosumab with serum phosphate normalisation (probability 92.4%)

Abbreviations: HR: hazard ratio; HRQoL: health-related quality of life; LLN: lower limit of normal; WOMAC: Western Ontario and McMaster universities osteoarthritis index; XLH: X-linked hypophosphataemia

Key issue: Burosumab efficacy on PROs

Background: WOMAC stiffness and physical function greater in burosumab at week 24 but below MCID; Limited efficacy evidence on pain, physical functioning, fatigue (after possible regression to mean/placebo effects)

Issue	Company	EAG
Statistical significance	CL303 show statistically significant improvements from baseline vs placebo at week 24 (Insogna et al., 2018) – maintained at week 48 and 96 for WOMAC and BPI	Only WOMAC stiffness score statistically significant difference from placebo at 24 weeks (Insogna et al.), maintained effect need comparison with placebo rather than absolute effect
Baseline imbalances	Pre-specified 24-week trial analyses adjust for baseline imbalance; any placebo response or regression to mean would happen in both arms	Change from baseline analysis only corrects imbalances when no association between baseline values and intervention effect – not the case in XLH treatment e.g. beginning with unusual high pain
Clinically meaningful results	MCID thresholds used do not represent meaningful change – not accounting for combined endpoint effect	0.5 standard deviation improvement for MCID appropriate – no further information on meaningful threshold
	EMA accept HRQoL benefits with burosumab as meaningful	EMA may refer to absolute effects not comparison with placebo

Clinical expert: Benefits accumulate over time – stopping burosumab affects pain, stiffness, functioning, fatigue

Abbreviations: BPI: brief pain inventory; EMA: European medicines agency; MCID: minimal clinically important difference; HRQoL: health-related quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; XLH: X-linked hypophosphataemia

Mortality benefit of burosumab (2)

Factor in XLH identified by company	Association to mortality
Hypophosphatemia	Higher risk of complication in chronic idiopathic hypophosphataemia (cardiovascular, CKD, hyperparathyroidism, fractures, periodontitis, depression, mortality, hospitalisation)
Excess FGF23	Associated with shortened life expectancy in people with dialysis
Multimorbidity	Associated with increased all-cause mortality (Hypertension, left ventricular hypertrophy, high blood pressure, hypertension, renal problems, hyperparathyroidism)
Higher prevalence of obesity	Established risk-factor in diabetes, with reduced life expectancy
Physical inactivity: Pain, stiffness, fatigue	High and moderate physical activity levels associated with lower
Mental health: 3x more likely to have depression [Hawley et al.]	Distress associated with greater mortality risk including after adjusting for somatic comorbidity and socioeconomic factors
Opioids: 67% take opioids ≥1 per week [CL001 natural history study] 22% taking opioids at baseline in CL303	Chronic opioid use effects – fractures, sleep issues, hyperalgesia, immunosuppression, chronic constipation, bowel obstruction, myocardial infarction – increase mortality risk
Socio-economic deprivation: 65% below IMD national average	Deprivation associated with increased mortality risk

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Abbreviations: FGF: fibroblast growth factor; CKD: chronic kidney disease: IMD: index of multiple deprivation

Disutility for incident fractures (2)

Study identified by company		Fracture impact on HRQoL	EAG
Adachi 2010	Impact of fractures on QoL from global longitudinal study of osteoporosis in women	Spine (0.62), hip (0.64), upper leg (0.61) fractures have largest reduction in EQ-5D (0.79 no fracture)	• No follow-up period stated • Does not examine duration fractures in different bones affect quality of life
Griffin 2015	Based on a trauma centre in England: Recovery of HRQoL for hip fracture (up to 1 year follow-up, n=403)	After 1 year, 0.22 (95%CI: 0.17 to 0.26) mean reduction in EQ-5D-3L vs pre-fracture quality of life (retrospective)	• Impact post-1 year not examined • Only hip fractures considered
Borhan 2019	Impact of incident fragility fractures (spine, hip, rib, shoulder, pelvis, forearm) on HRQoL for people 50+ years old (n=7753) • Using 10-year prospective data from Canadian Multicentre Osteoporosis Study	• Incident spine and hip fractures associated with significant negative impact on Health Utilities Index scores, negative impact on mobility, self-care, ambulation • Fractures occurring closer to follow-up assessment associated with significant impact on HRQoL vs fractures occurring a long time before it – except hip fracture where negative impact lasted 5 years or longer • Women with hip fracture never recovered to pre-fracture level score (odds ratio = 0.41 [95% CI 0.19 to 0.98)	Relevant study to consider

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Abbreviations: HRQoL: health-related quality of life

Previous NICE guidance applying utility benefit to caregivers for adults

NICE manual 4.3.17: Evaluations should consider all health effects for patients, and, when relevant, carers. When presenting health effects for carers, evidence should be provided to show that the condition is associated with a substantial effect on carer's health-related quality of life and how the technology affects carers

Evaluation	Marketing authorisation	Number of carers
TA804 Teduglutide for treating short bowel syndrome	1 year and above with short bowel syndrome	1 carer for adults; 2 carers for children
TA808 Fenfluramine for treating seizures associated with Dravet syndrome	2 years of age and older	1.8 carers
TA614 Cannabidiol with clobazam for treating seizures associated with Dravet syndrome	2 years of age or older	1.8 carers
TA615 Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome	2 years of age or older	1.8 carers

HST8: Company apply 0.08 caregiver disutility for moderate and severe health states up to age 18 – based on 1 caregiver of a person with XLH with limited activity (Kuhlthau et al. 2010)

- Committee: important to consider carer burden and the quantitative assessment, but it was not robust so would also consider the burden qualitatively (using analyses in which quantitative burden omitted)

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Abbreviations: XLH: X-linked hypophosphataemia