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

For Public – contains no confidential information

Technology appraisal committee B [8 November 2023]

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Company: Kyowa Kirin

Background on X-linked hypophosphataemia

Causes of X-linked hypophosphataemia (XLH)

- Rare, genetic condition, characterised by low phosphate in the blood – caused by excess activity of FGF23 signalling protein → kidneys abnormally process phosphate → loss of phosphate in the urine (phosphate wasting)
- Calcitriol (vitamin D) production also reduced

Epidemiology

- Around 300 to 500 adults with XLH in England; including unregistered and undiagnosed is around 1,000

Symptoms and prognosis

- Symptoms onset generally at 12-15 months old but often misdiagnosed as vitamin D deficient rickets
- For adults: osteomalacia (soft, weak bones) bone pain, fractures, pseudo-fractures, joint stiffness, restricted movement (from enthesopathy), neurological complications, hearing problems, spinal cord compression, many develop hyperparathyroidism
- Mental health impact – may lead to anxiety and depression

Abbreviations: FGF23: Phosphate-regulating hormone Fibroblast Growth Factor 23

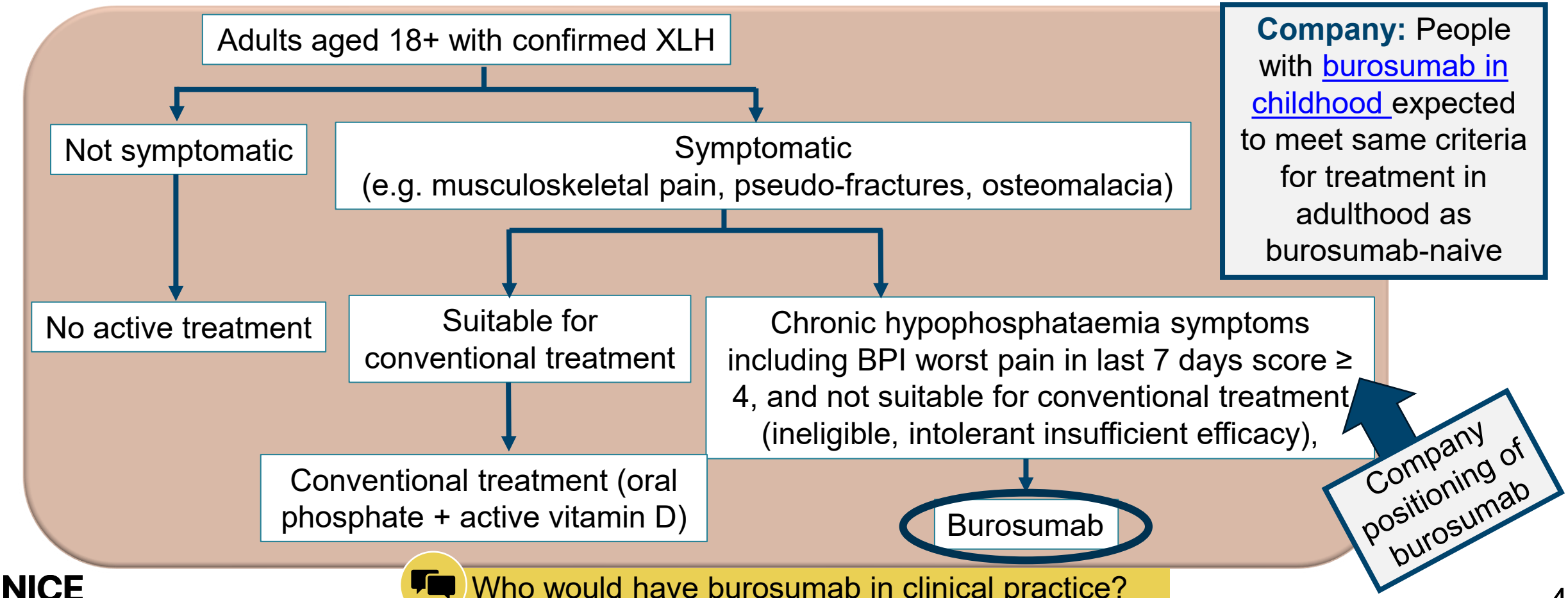
Burosumab (Crysvita, Kyowa Kirin)

Marketing authorisation (MA)	• Initial marketing authorisation for paediatrics, with extension to include adult population: October 2020 • Standard MA in UK for treatment of XLH in children (1-17) and adults: October 2022 • "For the treatment of X-linked hypophosphataemia in children (aged 1 to 17) with radiographic evidence of bone disease, and adults" (MHRA March 2023)
Mechanism of action	• Monoclonal antibody that binds and inhibits the activity of fibroblast growth factor 23, increasing reabsorption of phosphate from the kidneys to increase serum phosphate levels and restore phosphate homeostasis
Administration	• Subcutaneous injection • Recommended starting dose in adults: 1 mg/kg, rounded to nearest 10 mg up to a max dose 90 mg, every 4 weeks • Initiation and dose change under healthcare professional supervision, but subsequent self-administration may be possible
Price	• Single-use solution for injection vials list price: £2,992 (10 mg); £5,984 (20 mg); £8,976 (30 mg) • Patient access scheme applicable

Burosumab positioning in the treatment pathway

HST8 (2018): Burosumab recommended for treating XLH with radiographic evidence of bone disease in children aged 1 year and older and young people with growing bones – Can continue until bones stop growing

- ID3822 covers extension of licence for adult population
- Company presents evidence for narrower adult population than MA based on expected use in NHS



Who would have burosumab in clinical practice?

Abbreviations: BPI: Brief Pain Inventory; HST: Highly specialised technology; MA: marketing authorisation; XLH: X-linked hypophosphataemia

Patient perspectives

"I feel like [burosumab] gives me the freedom to be much more like a normal 19-year-old at university."

"I now have zero anxiety about my ageing process for the first time."

"Since starting burosumab my mobility has improved…I now walk with crutches so a big improvement."

"Since being on burosumab I am able to work longer hours…I need less breaks. I am able to participate in local/community activities. I have been able to travel solo for the first time…Prior to burosumab…I would have not considered having children…"

"I am terrified that my health would deteriorate back to where it was or even worse if the treatment were stopped, as the benefits now are beyond words"

"Increased mobility is the biggest advantage…helped me lose weight…improved health all round and reduced depression"

"[burosumab] has given me my life back… not being in pain is huge…My self-esteem was low…"

Submission from XLH UK

XLH is progressive and affects self-care, parenting, education, employment – impacts physical and emotional wellbeing

Unmet need for treatments targeting XLH cause:

- Limited and suboptimal symptom management (oral phosphate supplements, activated vitamin D) – Many find ineffective
- Treatment difficulty because of bad taste, dose frequency, adverse effects, e.g. GI distress, diarrhoea, kidney stones, nephrocalcinosis, hyper-parathyroidism
- Greater potential benefit treating more severe XLH (also for carers)

Impact on family and caregivers:

- Frequently take time out of work to support – impact wellbeing
- More than 1 family member may have XLH (genetic)
- Other benefits: Productivity, convenience, independence

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Abbreviations: GI: gastrointestinal; XLH: X-linked hypophosphataemia

Clinical perspectives

XLH in adults:

- Causes progressive complications with significant impact on physical and mental wellbeing
- Wider impact in adults underestimated by research because lack of standardised assessment pathway
- Unmet need for adults with XLH for effective treatment for pain, function, pseudo-fractures
- Aim of treatment: Stop progression, prevent complications, improve physical and mental wellbeing
- Clinically significant response: Reduction and prevention of complications, improved physical and mental function

Burosumab: First-in-class and improves physical outcomes in adults with significant XLH

- People with significant clinical disease and those treated in childhood expected to have added benefit (prevent onset of complications) [outside scope of this evaluation]
- Burosumab impacts caregiver and family health-related benefits
- Side effects can usually be well managed
- NHS implementation framework in progress through RDCN for Adult Rare Bone Diseases and XLH

Abbreviations: RDCN: Rare disease collaborate network; XLH: X-linked hypophosphataemia

Equality considerations

Any recommendations apply to the population in the decision problem

- Subgroup of licensed indication in adults: Adults with confirmed XLH, chronic hypophosphataemia symptoms including BPI worst pain over last 7 days score ≥4 and conventional therapy is unsuitable (ineligibility, intolerance, insufficient efficacy)

Company:

- XLH is very rare and adults with symptomatic XLH have long-term disability
- People with XLH in UK are more likely to have higher levels of social deprivation than general population
- Likely from negative impact of XLH on education, career, work
- Heredity nature likely to worsen deprivation and add to cumulative mutigenerational burden on families

Clinical expert:

- XLH in adults is a condition of deprivation, probably due to disability
- Excluding access to burosumab will increase disability from physical and mental wellbeing perspectives, worsening inequality in adults

Abbreviations: XLH: X-linked hypophosphataemia

Key issues

* Back up slide

= Large impact on ICER

= Unknown impact on ICER

Key issue		Slide
Population	Defining population, who is eligible for burosumab?	12
Clinical trial	Do imbalances in trial arms have an impact on clinical effectiveness estimates?	13
	Are CL303 age and weight distribution reflective of NHS practice?	14
	Do patient-reported outcomes show efficacy?	15, 35*
	Are data and CE estimates generalisable to burosumab-experienced population?	33*
Modelling of mortality and morbidity	Is modelling morbidity and mortality incidence as independent events, appropriate?	17
	Which hazard ratio of excess mortality of XLH is appropriate – company or EAG?	19
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Stopping rule	Are the treatment stopping criteria and discontinuation rates appropriate?	21
Utility	Which data should inform long term utility model?	22
	Should utility be adjusted for placebo effect?	22, 39*
	Should disutility for incident fractures continue >1 year?	23
	How much utility benefit should be applied to carers/family?	24

Clinical effectiveness

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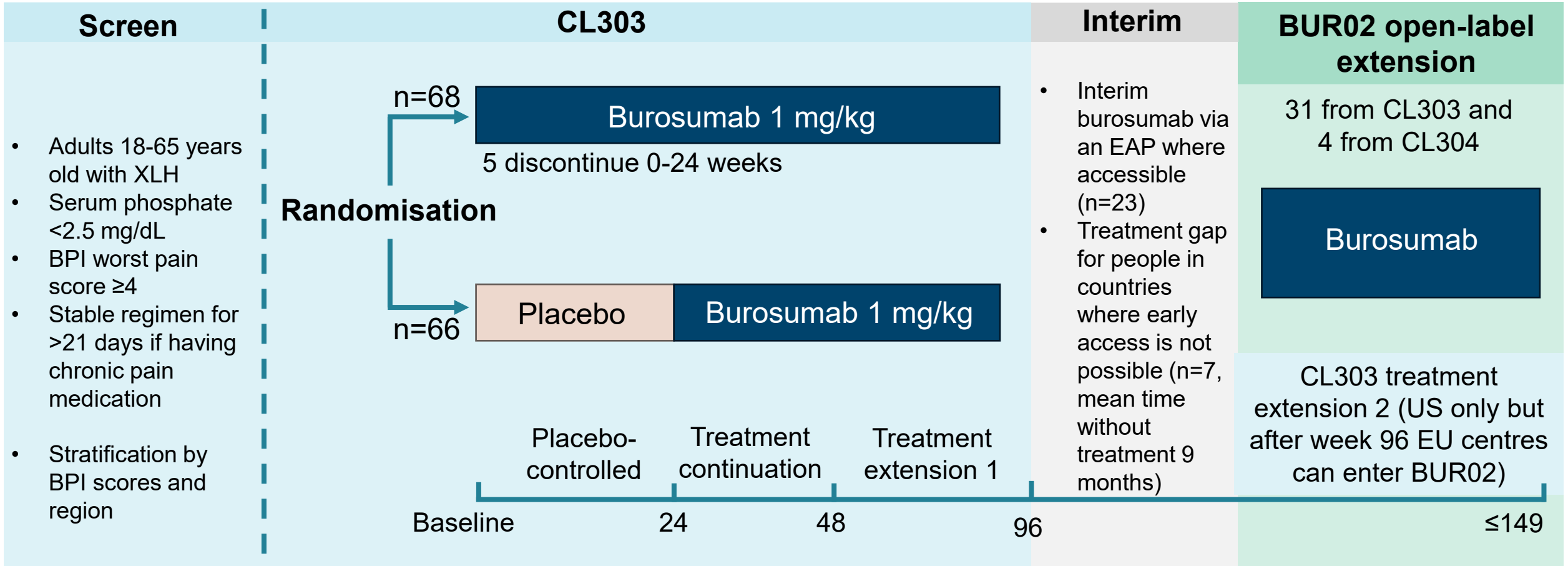
Clinical evidence sources

Trial	Aim	Location	Eligibility	Use
CL303: Phase 3, randomised, multicentre placebo-controlled, 96-weeks, n=134	Efficacy and safety of burosumab	Asia (Japan, South Korea); Europe (Ireland, Italy, France, UK); North America (USA)	BPI worst pain score ≥4 and if on chronic pain medications, stable >21 days before screening	Model
BUR02: Phase 3b, multicentre, open-label extension to CL303 (+48 weeks), n=35*	Monitor long-term safety and efficacy of burosumab in adults	European sites of CL303	Subset treated in EU centres from CL303 and CL304	Model
Early access programme: For inclusion in multicentre, single-arm, retrospective RWD, n=[redacted] (as of April 2023)	RWD collection in adults	England, across sites	Presence of debilitating symptoms, including, but not limited to, pain, stiffness, and fatigue	Model – baseline weight and age distribution inform EAG base case
CL001: Global natural history survey, n=232 adults	XLH manifestations, treatment history, PROs	>30 countries (67% from US)	Adults with XLH and parents/caregivers of children with XLH	Scenario: Morbidity rates for non-burosumab-treated people and utility source

*Included people from CL304 (single-arm study evaluating the effect of burosumab on osteomalacia in 14 adults with XLH)

Abbreviations: BPI: brief pain inventory; PRO: patient reported outcome; RWD: real world data; XLH: X-linked hypophosphataemia

Pivotal trials: CL303 and BUR02 extension



Primary outcome (24 weeks): Proportion with mean serum phosphate concentration above lower limit of normal (2.5 mg/dL or 0.81 mmol/L)

- 94% burosumab arm and 8% in placebo arm met primary outcome at 24 weeks – Summary of CL303 results

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Abbreviations: BPI: Brief Pain Inventory; dL: decilitre; EAP: Early access programme; mg: milligram; L; litre; mmol: millimole; XLH: X-linked hypophosphataemia

Key issue: Defining the eligible population

BPI-SF worst pain score
1-4 (mild); 5-6 (moderate);
7-10 (severe)

Background: Defining symptoms sufficiently severe for burosumab treatment
Defining unsuitability or treatment failure with conventional treatment

Company: Population – adults with confirmed XLH with chronic hypophosphataemia, symptoms include BPI≥4, and conventional treatment unsuitable, intolerance or insufficient efficacy → Burosumab second-line

EAG: Symptoms for burosumab:
Company's population reflects current guidelines but does not reflect other broader criteria:

- UK EAP: *"Presence of debilitating symptoms…pain, stiffness, fatigue"*
- CL303: *"If on chronic pain medication, regimens stable for 21 days before screening"*

Treatment failure for burosumab:

- Uncertainty if people who could have phosphate treatment in principle, are eligible for burosumab
  - UK EAP allow stopping phosphate treatment to have burosumab
- Some may discontinue conventional treatment (inefficacy) but restart later (persistent symptoms)

Clinical expert: Prefer including pseudo-fractures (may not meet BPI≥4); Treatment failure could include intolerance; insufficient efficacy needs assessment of defined pain reduction after reasonable duration of treatment trial

- Draft guidelines: If not tolerated or no benefit after 3 months, and average pain over the last 7 days ≥4/10 and clinically attributable to XLH then refer to consider burosumab

Abbreviations: BPI: brief pain inventory; EAP: early access programme; XLH: X-linked hypophosphataemia

Key issue: Baseline imbalances in CL303

Background: Potential imbalances between treatment arms

- EAG: Could be because of using 2 stratification factors at randomisation in a relatively small sample
- Concern regression to mean may imply burosumab effectiveness is overestimated (further information)

Characteristic at baseline		Burosumab (n=68)	Placebo (n=66)	How burosumab arm differs
Age	Mean (SD)	41 (12)	39 (13)	Older
	Range	20 to 63	19 to 66	
Fractures	Fractures/pseudo-fractures, n	65	91	Fewer fractures
	• Unhealed, n (%)	32 (47)	38 (58)	
WOMAC mean (SD)	Total score	52 (18)	46 (18)	Worse physical function
	Physical function	51 (20)	44 (20)	
	Stiffness	65 (20)	61 (21)	
	Pain	51 (18)	48 (16)	
BPI-SF worst pain (average)	Mean (SD)	7 (1)	7 (1)	More people with severe pain
	<6, n (%)	15 (22)	23 (35)	
	≥6, n (%)	53 (78)	43 (65)	

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

Key issue: Age and weight distribution in CL303

Background: Age and weight distribution in CL303 may not align with adults with XLH in NHS

- People in CL303 were younger (max age restriction 65) than burosumab in EAP in England
- Weight distribution of EU participants in CL303 lighter than in EAP – affect burosumab dosing and costs

Trial	Mean age (SD)	Mean weight, kg
CL303	40 (12.2)	67.2 (EU)
BUR02	40.1 (12.1)	
EAP (n=40 from UCLH)	42.8 (14.6)	70.3

Company: Average dose: 65.2 mg – aligns with EAP (average dose = 65 mg)

Age/weight	CL303	EAP
<50 years of age	76%	58%
> 75kg	28% (EU)	40%

EAG: EAP more representative of population expected in NHS practice than CL303

- Age and weight distribution for adults likely to change over time with burosumab availability – e.g. larger population of people had burosumab in childhood, so identifying eligible people in adulthood may be easier, and baseline characteristics may change
- Using age and weight distributions from EAP increase ICER

Clinical expert: EAP population over time will be less representative of adult population as more continue burosumab following transition from childhood – reduce age and potentially weight

Which age and weight distribution is more appropriate to use?

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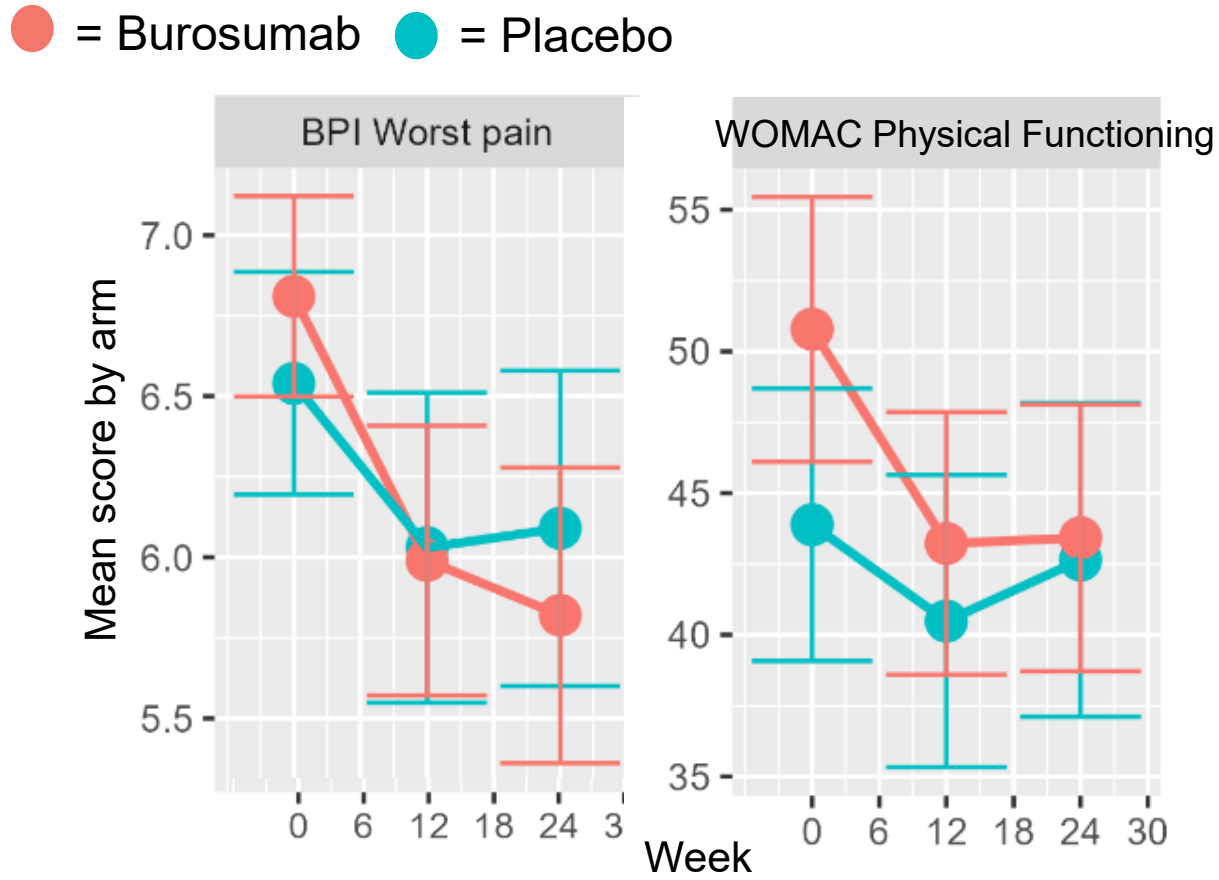
Abbreviations: EAP: Early access programme; XLH: X-linked hypophosphataemia

Key issue: Burosumab efficacy on patient reported outcomes

Background: EAG note limited evidence for clinical effectiveness of burosumab vs placebo on these outcomes

- Some outcomes (e.g. worst pain) have [redacted]
- Most outcomes show modest benefit for burosumab – most benefits small and [redacted]
- Scores at baseline such as WOMAC physical function higher in burosumab than placebo
- Although function improves with burosumab – may be because of regression to mean



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

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

Cost effectiveness

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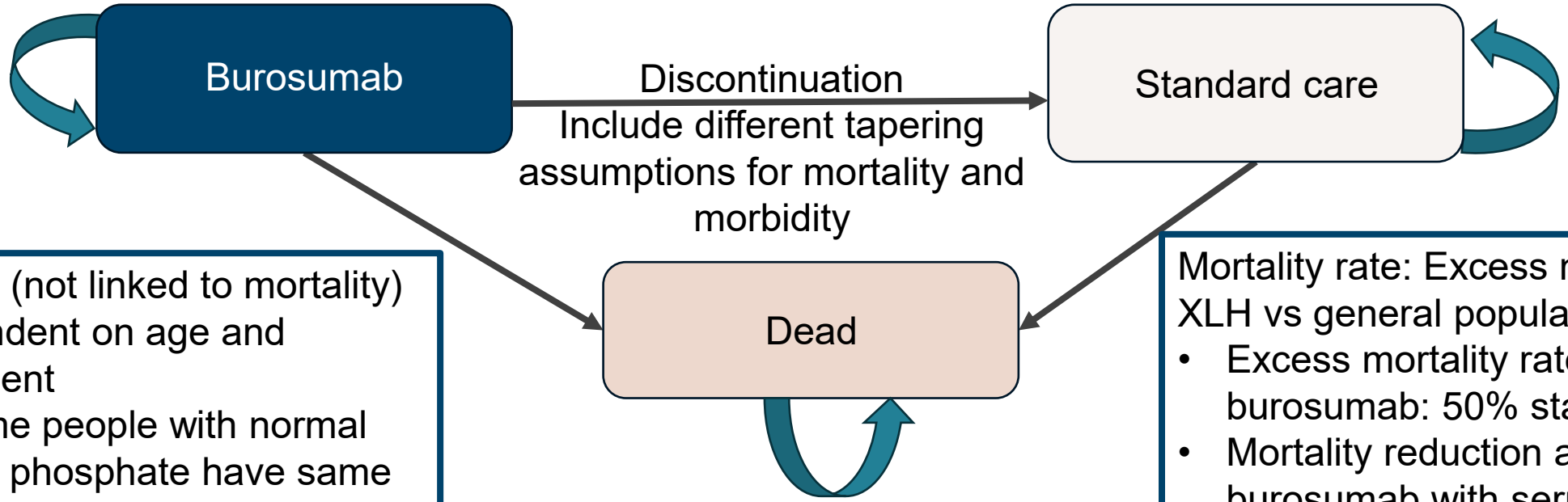
Company's model overview

- 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

How company incorporated evidence into model

Treatment efficacy

- Normalisation of serum phosphate: CL303 burosumab arm or placebo (for standard care at 24 weeks) assumed to persist whilst on burosumab
- Risk of mortality: assumed 50% lower excess mortality with burosumab
- Tapering treatment effect differs for morbidity and mortality after stopping over 2 years

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

Discontinuation

Year 1: 16.9% (100% - %people in CL303 meeting continuation rule); Year 2+: 3% (clinical opinion and discontinuation rate EAP)

Time horizon; cycle length

Lifetime (up to age 100); annual cycle length

Utilities (utility values used in model)

- WOMAC from CL303 and BUR02 mapped to EQ-5D (Wailoo et al. 2014)
- Disutility applied for incident fractures (source TA204 post-menopausal osteoporosis)
- 20% of utility benefit for burosumab applied to 2 caregivers

Costs

- Mean weight calculation (from EU cohort CL303, dose = 1 mg/kg), n=47
- 95% self-administer; otherwise administered by hospital nurse (20 minutes)

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Abbreviations: EAP: early access programme; WOMAC: Western Ontario and McMaster universities osteoarthritis index

Key issue: Excess mortality and mortality benefit

Standard care

Hazard ratio for excess mortality risk from XLH compared with general population

Company base case:

- HR = 2.88 (95% CI: 1.18 to 7) (Hawley et al., 2020) using UK Clinical Practice Research Datalink database 1995-2016

Supportive data for higher excess mortality:

- HR = 3.26 (95% CI: 1.83 to 5.81) assessment of mortality in Korean people with XLH

EAG: Prefer HR = 2.33 (95% CI: 1.16 to 4.67)

- Hawley et al. extended on larger sample from UK CRPD GOLD and AURUM databases with more recent data (1995-2022) (Company's confirmatory study)

Burosumab

Hazard ratio for burosumab vs general population

Company base case: Assume 50% reduction in excess mortality risk from XLH vs standard care

- i.e., HR = 1.94
- Normalising serum phosphate, reduce side effects, and potential opioid use

EAG: No structural link between fractures/morbidities and mortality in model – not possible to assess link between normal serum phosphate with fracture events and mortality

Scenarios explored (increase ICER):

- No mortality benefit of burosumab
- 11% reduction (meta-analysis treating osteoporosis on mortality)
- 25% reduction

Clinical expert: Explore 20%, 40% 60% reduction

Which hazard ratio of excess mortality is appropriate to apply?

Abbreviations: CI: confidence interval; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; XLH: X-linked hypophosphataemia

Key issue: Burosumab reduction in fracture incidence

Background: Company assume 100% reduction in excess fracture incidence rates with burosumab (normalised serum phosphate) = general population (based on Curtis et al. 2016)

- Incidence of fractures for standard care predicted from baseline CL303 data
- 94.1% burosumab arm and 7.6% placebo achieved >LLN mean serum phosphate normalisation
- After 24 weeks, probability of normal serum phosphate for burosumab = 92.4% (100% - 7.6%)
- Model assumes serum phosphate normalisation at week 24 will persist while on burosumab

New fractures/pseudo-fractures in CL303:

Week		Placebo (burosumab after week 24)	Burosumab
Fracture	0-24	[redacted]	[redacted]
	36-48	[redacted]	[redacted]
Pseudo-fracture	0-24	[redacted]	[redacted]
	36-48	[redacted]	[redacted]

Is 100% reduction in excess fracture incidence appropriate?

EAG: 100% reduction not based on any evidence – likely overestimate burosumab effect

- Burosumab targets reducing hypophosphatemia-driven osteomalacia and fragility fracture incidence, not fractures from people without XLH (Curtis et al.)
- 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 treatment

Clinical expert: Adult bones with burosumab are wider, often higher density than no XLH – adults starting burosumab may have high reduction in fracture risk

Abbreviations: LLN: lower limit of normal; XLH: X-linked hypophosphataemia

Key issue: Treatment stopping criteria and long-term discontinuation rates

Background: Criteria for continuing in model: 1) Serum phosphate >LLN at 24 weeks
2) Improvement in WOMAC total score at 12 months after start of treatment

EAG: Question if WOMAC criterion appropriate – not commonly used in UK

- Additional criterion may be unreasonable if maintained phosphate levels have potential to reduce morbidities and mortality
- May be other advantages with burosumab treatment, e.g. less opioid use for pain management even if WOMAC improvement criterion not met
- No stopping criteria in CL303 trial or EAP in England

Data informing year 1 assumption		Year 1	Year 2+
Company (stopping)	% normalised phosphate week 24 and improvement in WOMAC CL303 week 48	16.9%	3%
EAG scenario (no stopping)	CL303 burosumab discontinuation rate at week 24	7.35%	3%
EAG scenario (no stopping)		7.35%	0%

Clinical expert: (draft for musculoskeletal pain, stiffness) review burosumab annually, consider stopping after 12 months if no improvement in average pain over last week and no reduction in analgesic use from baseline

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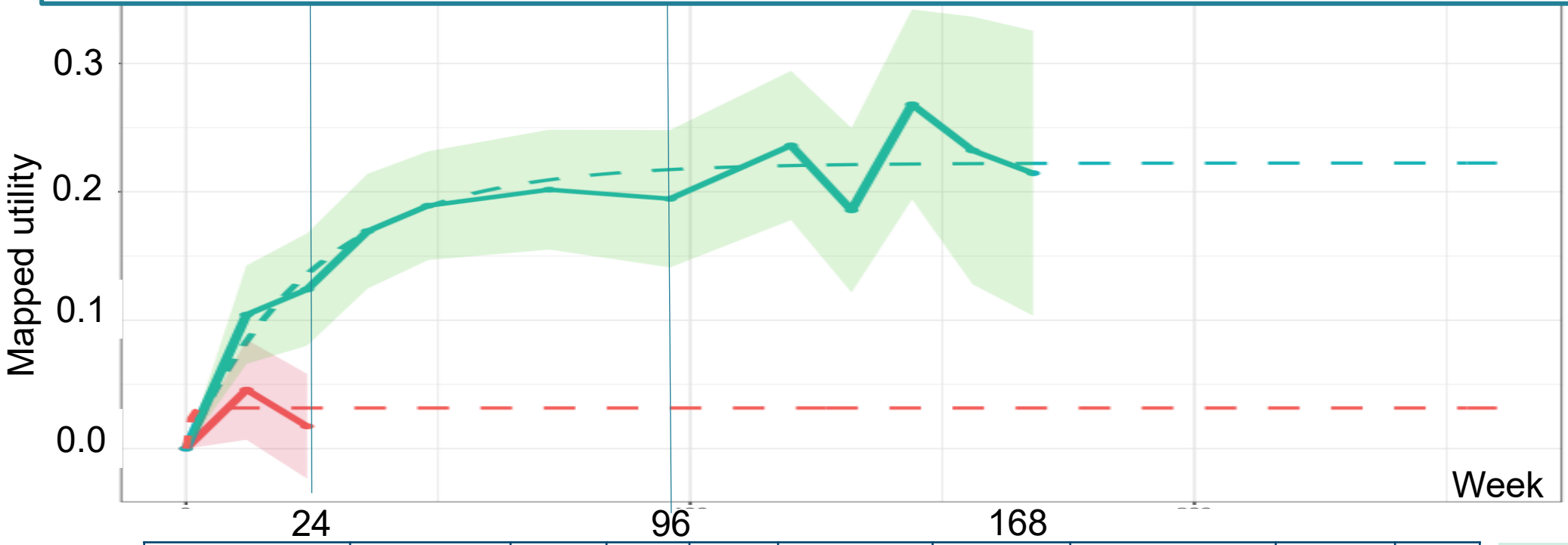
Abbreviations: EAP: early access programme; LLN: lower limit of normal; WOMAC: Western Ontario and McMaster universities osteoarthritis index; XLH: X-linked hypophosphataemia

Modelling utility over time

Background: WOMAC scores from CL303 and BUR02 mapped to EQ-5D

- Company fit non-linear asymptotic model to each arm independently to predict change in utility post observed
- No adjustment for placebo effect over 24 weeks (further information)



EAG: Concern post week 96 data comes from different population to baseline – uncertain and large impact

- Prefer data up to 96 weeks in model

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

Clinical expert: Week 96 data should be included – Cumulative benefit over time

Abbreviations: Bur: burosumab; Pbo: placebo

Key issue: Disutility for incident fractures

Background: Model applies disutility for incident fractures over lifetime

- Uncertainty on size and duration of disutility associated with incident fractures and assuming independent effects when multiple events may occur over a lifetime horizon

Company: Disutility from fractures in XLH may continue for more than 1 year (although no data)

- Impaired bone mineralisation in XLH likely mean fractures have long-term impact on HRQoL
- Fractures in XLH are slow healing, and some untreated are non-healing
- Skrinar 2019: Pain scores higher in XLH with history of fracture (long term impact)
- Osteoporosis – potential long-term impact on HRQoL (but bone structure/mineralisation different to XLH)

EAG: Possible overestimation of disutility – scenario assume disutility in first-year only

- Some fractures accrue lifetime utility decrement (tibia/fibula; femur/pelvis; foot; vertebrae/spinal)
- Not reflecting fracture healing over time – potential for HRQoL improvement
- Mortality and morbidities modelled independently; Lifetime disutility with fractures not adjusting for fracture-specific mortality
- Potential double-counting morbidity effects as treatment-specific utilities are extrapolated over lifetime

Clinical expert: Pseudo-fractures in XLH often longstanding and unreasonable to expect majority to heal

- ~8% healed at 12 and 24 weeks in placebo, vs 20%, 43%, 63% (12, 24, 48 weeks) for burosumab

How should disutility for fractures be modelled?

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Abbreviations: HRQoL: health-related quality of life; XLH: X-linked hypophosphataemia

Key issue: Utility benefit on caregivers and family

Background: Uncertainty in the size of treatment benefit on caregivers and family, and the number of caregivers

- Concern overestimating spillover effect with 2 caregivers/family – may not be reasonable for adults (administration supports independence and reducing burden)

Company: Spillover benefit on caregiver/family = 20% patient utility benefit, to 2 caregivers/family

- 20% estimate from HRQoL research study (19 people but including caregivers with XLH too)
- Caregivers/family can be affected by: Dependence, increased responsibilities, restriction in family activities
- Utility improvement for caregiver/family in model < loss of utility for impact of caring for an adult with XLH from research study (0.081)

Company base case	Mean utility
Spillover effect for 2 caregivers/family	
Year 1	0.059
Year 2	0.085
Year 3	0.086

EAG: Use utility benefit for 1 caregiver/family only

- Mean difference in observed (when excluding caregivers without XLH) vs expected EQ-5D utilities compared with age-linked UK general population utilities = -0.081 (95% CI: -0.19 to 0.029) – not statically significant

Clinical expert: Progressive caregiver burden over time – increasing impact of XLH on adults

How should utility benefit be applied to caregivers?

Abbreviations: HRQoL: health-related quality of life; 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 with increased duration and after stopping burosumab	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 (Company's mortality assumptions applied to both)
Utility change from baseline and extrapolation	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

Note: Case for severity modifier explored by company but not included in base case

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

Cost-effectiveness results

All ICERs are marked confidential

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 (applied in first year only), using placebo-adjusted utilities)

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Thank you.

Committee's preferred assumptions

- Is the committee satisfied that company's eligibility criteria for burosumab appropriate?
- Is the continuation rule appropriate?

Assumption	Company base case	EAG base case	Committee
Age and weight distribution	CL303	EAP	
Excess mortality risk due to XLH	HR = 2.88	HR = 2.33	
Tapering of treatment effect on mortality and morbidity	Different assumptions for mortality and morbidity	Same tapering effect on mortality and morbidity	
Utility change from baseline and extrapolation	Include post-week 96 data from BUR02	Do not include	
Caregiver/family utility benefit	2 caregivers/family	1 caregiver/family	
Burosumab reduces excess mortality 50%	Should this benefit be reduced? No reduction? 25%? 11%?		
Fracture incidence if normal serum phosphate	Same as general population? 75% or 50% decrease in excess?		
Modelling of utility	Should it be adjusted for placebo?		
Disutility of fractures	Life-long or for 1st year only?		
Other assumptions	Any other preferences on modelling assumptions?		

Back-up

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Decision problem (1)

	Final scope	Company	EAG comments
Population	Adults with XLH	Adults ≥18 years with XLH with chronic hypophosphataemia, symptoms that include BPI "worst pain in last 7 days" score of ≥4 (upper limit of mild pain), and conventional treatment is unsuitable because of ineligibility, intolerance or insufficient efficacy	• Population differs from scope • UK Early Access Programme criteria do not include phosphate treatment unsuitability or a BPI of 4 or above • CL303 trial inclusion criteria also different – chronic pain medication regimens must be stable for >21 days before screening
Intervention	Burosumab		
Comparators	Established clinical management without burosumab (including vitamin D analogues and phosphate supplementation)	Best supportive care = mainly fracture treatment (established clinical management in submission)	• Company exclude vitamin D analogues and phosphate supplementation – EAG consider reasonable as burosumab is only considered where phosphate treatment is not appropriate

Abbreviations: BPI: brief pain inventory

Decision problem (2)

	Final scope	Company	EAG comments
Outcomes	• Fractures • Pain (including bone, joint and joint stiffness) • Motor skills • Tooth loss and pain • Neurological complications (including problems with hearing and balance, and spinal cord compression) • Renal function • Parathyroid hormone levels • Alkaline phosphatase levels • Mortality • Adverse effects • HRQoL (including carers)	Base case: • Fracture incidence • Stiffness, pain and fatigue (WOMAC scores) • Mortality • HRQoL (including informal caregivers and close family) • Serum phosphate levels Scenario analyses: • Dental problems • Spinal stenosis and need for spinal surgery • Tinnitus and hearing loss	• Broadly in line with scope • WOMAC and BPI scales not routinely used in NHS to assess people with XLH (clinical advice) • Serum phosphate levels used instead of alkaline phosphatase

Abbreviations: BPI; brief pain inventory; HRQoL: health-related quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; XLH: X-linked hypophosphataemia

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

Key issue: Generalisability of trial evidence and cost-effectiveness data to burosumab-experienced population

Background: Burosumab recommended for XLH with radiographic evidence of bone disease in children aged 1 year and over and in young people with growing bones

- Subgroup of adults previously having burosumab in childhood

Company: 7 people in CL303 had prior burosumab use as adults in earlier clinical study

- People having burosumab in childhood (1 to 17 years old) expected to meet same eligibility criteria as other adults during adulthood
- Adult dose and regimen used from 18 years old (lower total dose on average for adults than for children)

EAG: Uncertainty on generalising results to burosumab-experienced population

- Uncertainty which criteria will be used for appropriate treatment in burosumab-experienced population
- Equity considerations for burosumab access when having burosumab and reaching 18 years of age
- No data or outcomes specific for burosumab-experienced population (in adulthood or childhood)
- Generalisability of cost-effectiveness data or trial evidence not explored by company

Clinical expert: Lack of trial data from childhood to adults with burosumab – reasonable expect stopping burosumab in young adult leading to sudden and persistent lower serum phosphate

- Ongoing hypophosphatemia: progressive, irreversible musculoskeletal effects (osteoarthritis, spinal conditions)

Abbreviations: XLH: X-linked hypophosphataemia

Key clinical trial CL303 primary outcome results

Primary outcome: 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

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

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

Comparison of company model with CADTH, SMC and PBAC models

Differences from the company's cost effectiveness analysis		
CADTH	PBAC	SMC
Comparator include conventional treatment or no treatment		
Incorporates structural link between morbidity events and mortality	-	CL001 (global XLH natural history study) used to inform incidence of morbidity events
Increased mortality risk associated with fractures is only after 50 years of age	-	-
Discontinuation in first year based on CL303 (lower rate) and no discontinuation from year 1 onwards	Lower annual discontinuation rate for burosumab (7% in first year and 1% in subsequent)	-
Utilities do not include BUR02 (WOMAC from baseline in CL303 up to week 96 mapped to EQ-5D)		
No utility benefit for caregivers and family		-

Abbreviations: CADTH: Canadian agency for drugs and technologies in health; PBAC: Pharmaceutical benefits advisory committee; SMC: Scottish medicines consortium; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; XLH: X-linked hypophosphataemia

Key issue: Burosumab effect on mortality

Background: No mortality benefit for burosumab in CL303 or BUR02 (short trial and small population)

Company: Assume 50% reduction in excess XLH mortality risk with burosumab

- HR = 2.88 for standard care vs general population; HR = 1.94 for burosumab vs general population
- Normalising phosphate homeostasis and mitigating multi-system effects of hypophosphataemia, potential reducing opioid use – drivers of mortality in XLH and extend life expectancy
- Mortality reduction applied to burosumab arm with serum phosphate normalisation (probability 92.4%)
- So, survival model is function of age, sex, treatment received

EAG: No evidence supporting mortality benefit with burosumab – unknown effect and size of benefit

- No structural link between fractures/morbidities and mortality in model – not possible to assess link between serum phosphate normalisation with fracture-related events and mortality
- CADTH model: only people with fractures have increased mortality risk (after 50 years of age)
- 11% reduction in mortality with treatment (relative risk: 0.89, 95% CI: 0.8 to 0.99)) – from meta-analysis of treatment effect for osteoporosis on mortality
- Scenarios (increase ICER): No mortality benefit; 11% reduction; 25% reduction (accounting for additional multi-system effects other than fractures)

Clinical expert: Challenges comparing relative mortality rates in long-term burosumab use – reasonable include mortality benefit with range of values from 20%, 40%, 60%

Is a mortality benefit appropriate to assume?

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Abbreviations: CADTH: Canadian agency for drugs and technologies in health; XLH: X-linked hypophosphataemia

Key issue: Burosumab effect on utility change from baseline and extrapolation of effect over time

Background: After week 24, only open-label and single arm data < 3 years for long-term treatment

- Utility improvement for duration on treatment; For discontinuation: 50% utility year after treatment end
- Additional data – combining US data from open-label, uncontrolled CL303 and BUR02 – mean change from baseline utility up to week 168 for burosumab and up to week 24 for placebo

Company: Appropriate to use all long-term data post week 96 and BUR02 follow-up in rare condition

EAG: Data up to week 96 from treatment continuation of CL303 only reliable data for asymptotic model

- Concern on data used to inform asymptotic model:
- Trial imbalances may affect statistical significance of WOMAC scores
  - From week 96 – based on different population with different baseline characteristics and WOMAC
- No comparison of baseline characteristics for each population to explain increase in utility at week 120, 144
- People in EAP in England more representative of modelled population than CL303

Clinical expert: Unreasonable to exclude the week 96 data - adults in the trial had XLH >40 years

- Cumulative benefit over time – progressive healing of pseudo-fractures

Should post-week 96 data inform utility changes?

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

Key issue: Adjusting utility values for placebo effect

Background: If the change from baseline in mapped utility values should be adjusted for placebo effect observed in 24-week period of CL303

Company: Use non-placebo-adjusted utilities (placebo effect in control period of CL303 not deducted from mean change from baseline utility for burosumab)

- 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 regression to mean

EAG: Use non-placebo adjusted utilities but important uncertainty – scenario with placebo-adjusted

- Kamenicky et al give limited evidence to support non-placebo adjusted utilities – 7 people
- Mention return to 'similar' baseline score level but how similar is unknown
- Mean difference in WOMAC total and subscale scores between people having compassionate burosumab (23) and those without burosumab (7) during interim period was statically non-significant in WOMAC total score and subscale scores (except for stiffness)

Clinical expert: Reasonable to adjust pain outcome for placebo-effect (BPI pain show placebo effect)

Should the utilities be adjusted for placebo-effect?

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

Utility values in company base case

	Mean utility	Source
Baseline utility		
Intercept	0.543	Linear regression model using CL303 data
Age	-0.003	
Utility increments for burosumab applied to baseline utility		
Year 1	0.147	Asymptotic model – not adjusted for placebo effect
Year 2	0.211	
Year 3+	0.215	
Utility multipliers associated with fractures		
All lower limb/hip fractures first year	0.7	NICE TA204 (Denosumab for prevention of osteoporotic fractures in post-menopausal women)
• Subsequent years	0.8	
Vertebrae/spinal fractures first year	0.91	
• Subsequent years	0.99	
Upper limb fractures first year	0.934	
• Subsequent years	1	
Other fractures first year	0.934	
• Subsequent years	1	

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

Severity modifier

Mean age:
- CL303: 40.1 (SD: 8.7)
- EAP: 42.8 (SD: 14.6)
- Model: Age-specific results aggregated according to proportion adults with XLH in each age category to estimate total population costs and effects

Thresholds for severity weighting:

QALY weight	Proportional shortfall	Absolute shortfall
1	<0.85	<12
1.2	0.85 to 0.95	12 to 18
1.7	≥0.95	≥18

Starting ages that meet 1.2 severity threshold:

Analysis	Baseline	QALYs		QALY shortfall	
	Age	Expected (general population)	Total (people with XLH)	Absolute	Proportional
Company	18	23.47	11.02	12.46	0.53
Company	21 (13% CL303)	23.01	10.62	12.39	0.54
Company	27 (13% CL303)	21.95	9.84	12.11	0.55
EAG	21 (7% EAP)	23.01	10.77	12.23	0.53

Company: Do not include QALY weighting but 1.2 severity may apply depending on data estimating general population utilities
- Severity of XLH should be considered General population QALYs: Schneider et al., (2021) reference case, and Ara and Brazier (2010)

EAG: Severity modifier 1x is appropriate
- Severity modifier not met for any starting age using Schneider et al.

Abbreviations: EAP: early access programme; SD: standard deviation; XLH: X-linked hypophosphataemia

Company and EAG's base case results

Burosumab vs standard care		Total		Incremental		ICER
		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)

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

EAG's cumulative results

Burosumab vs standard care	Incremental		ICER
	Costs (£)	QALYs	
Company base case	[redacted]	[redacted]	[redacted]
EAG preferred assumptions			
• Age and weight distribution from EAP	[redacted]	[redacted]	[redacted]
• Excess XLH mortality risk	[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: 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 (serum phosphate normalisation)	100%	0%

EAG's alternative assumptions

Burosumab vs standard care	Incremental		ICER
	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