Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Kyowa Kirin Ltd

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. XLH UK
   b. National Hospital for Neurology and Neurosurgery Charles Dent Metabolic Unit, UCLH

3. **Comments on the Draft Guidance from experts:**
   a. Kassim Javaid – Clinical expert, nominated by XLH UK
   b. Supplemental Data

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Consultation on the draft guidance document – deadline for comments 5pm on 3 Jan 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kyowa Kirin Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Ahmed Sowdani, Kyowa Kirin Ltd

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Issue 3.15 Adjusting utilities for placebo effect** ***The committee concluded that it is best practice to take into account data from the placebo arm of clinical trials. The committee therefore concluded that the EAG scenario using placebo-adjusted utility values was appropriate.*** Comment: We note the EAG's response to the Company's technical engagement response, which states that "the EAG's preferred base case assumption is the same as the company's assumption (use of non-placebo adjusted utility values) but the EAG considers this a remaining important

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	uncertainty, with a scenario presented using placebo-adjusted utility values." [Committee Papers, Issue 13] We also note that "the committee agreed that the potential placebo effect observed at week 12 in CL303 seemed to diminish at week 24, although this did not return to exactly baseline value". We would like to emphasise that: • Any placebo effect on utility appears to be short-lived: placebo arm utilities in the CL303 trial showed an initial improvement at 12 weeks, followed by a return to near baseline levels at 24 weeks. • WOMAC outcomes following burosumab interruption between finishing study CL303 and starting study BUR02 (reported in Kamenicky [2023])[1] show that patients returned to baseline WOMAC scores following withdrawal of treatment. This suggests that there is minimal regression to the mean. If there were significant regression to the mean, there would be a residual treatment effect following treatment interruption. We acknowledge that the number of patients in this analysis is small, but nevertheless it supports the evidence from CL303, cited above, that any placebo effect is likely to be minimal and short-lived. Therefore, we suggest that the unadjusted values should be used, as per the company base case.
2	**Issue 3.17 Utility benefit for carers and family members** ***The committee suggested that any exploration of the potential benefit of burosumab on carer utility should only include carers without XLH, to avoid potentially double-counting the utility benefits of burosumab. The committee agreed that, based on the evidence currently provided, it preferred the EAG's assumption to only include carer utility benefit for 1 carer. But, it noted that this assumption may overestimate carer utility benefit associated with burosumab.*** Comment: The company strongly disagrees with the committee's observation that inclusion of utility benefit for *one* carer may overestimate carer utility benefit associated with burosumab. We would like to note that the utility benefit proposed in the company base case was for two family members, not necessarily two carers. Family members are impacted by XLH whether or not they have a caregiving role for the person with XLH. Furthermore, family and carers both with and without XLH stand to benefit from an improvement in the condition, in terms or reductions in pain and stiffness, and improvement in physical functioning, of adults with XLH. This is because the impact of XLH on physical and mental health (pain, stiffness, fatigue, mobility issues) affects many activities of daily living that the affected person can undertake within the household, both for themselves and for the benefit of other family members. Thus, • **Children with and without XLH** will benefit from improvements in the condition of their parent (with XLH) arising from treatment with burosumab**.** • **Partners without XLH** will benefit from improvements in the condition of their partner (with XLH) arising from treatment with burosumab. • **And wider family members, both with and without XLH**, stand to benefit from the adults with XLH being treated with burosumab. The only case where "double counting" might conceivably occur would be where two or more adults within the same family with XLH received burosumab in the CL303 trial, and some of the improvement

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	in WOMAC score observed in these adults was indirectly due to improvements in the other adult rather than due to burosumab treatment. In practice the scope for double counting within the CL303 trial would seem to be minimal (especially given that the partners of adults with XLH are extremely unlikely to have XLH themselves). Therefore, we suggest that utility benefit for two carers/family members should be taken into account.
3	**Issue 3.16 Disutility of incident fractures** ***In its model, the company applied a disutility for incident fractures that continued over the lifetime of the model. The EAG acknowledged that some fractures may accrue a lifetime utility decrement, such as fractures to the tibia, fibula, femur, pelvis, foot or spinal vertebrae. However, the EAG had concerns that the disutility may be overestimated because there is potential for an improvement in health-related quality of life for other fractures healing over time.*** ***The committee acknowledged the high uncertainty with assuming a lifetime disutility for incident fractures in the model. It concluded that a disutility for incident fractures is appropriate to include but the duration of disutility in the model would vary depending on the type of fracture included. It further concluded that it would welcome more information on the length of time that fractures in different bones would affect quality of life.*** Comment: It should be noted that only incident fractures to the tibia, fibula, femur, pelvis, foot or spinal vertebrae had a lifetime disutility decrement in the model. All other fractures had a decrement in the first year only. Impaired bone mineralisation in XLH means that fractures are even more likely to be slow-healing (without appropriate treatment) and therefore likely to be associated with a long-term HRQoL impact. This is supported by the CL303 trial, where there was no fracture healing between week 12 and 24 in the placebo arm. Furthermore, the burden of disease survey published by Skrinar et al.[2] found that pain ratings were higher for adults who reported a history of fracture (at any time) compared with those who did not.The Company made an additional search for evidence on the long-term impact of fractures of different bones on utility. XLH is a rare disease, and XLH-specific data were not available. The search focused on fracture impact in populations with, or at risk of, impaired bone function (patients with osteoporosis, or at risk of fragility fracture); fractures in populations with normal bone composition were not considered generalisable to people with XLH, because normal bones would be expected to heal more quickly. Three relevant papers were identified, summarised below. All show a sustained HRQoL impact from fractures for prolonged periods of time (at least ten years in two of the studies), with differences between different fracture sites. These findings are from populations who have impaired bone function, but have fewer issues in bone healing compared to people with XLH. The finding of long-term impact of fractures even in these populations suggests that the modelling approach is likely to be conservative, as patients in the SoC arm are likely to experience the impact of fractures for an even longer period of time due to the slow- or non-healing nature of fractures associated with XLH. Therefore, we maintain that the assumption of a long-term HRQoL impact from fractures is reasonable and we suggest that this should be retained. **Adachi 2010** The Global Longitudinal Study of Osteoporosis in Women (GLOW) was conducted in 10 countries in Europe, North America and Australia. Information on fractures which had occurred since the age of 45 years were collected from the enrolled population of women ≥55 years old at a risk of fragility

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

Draft guidance comments form

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fractures. Mean age of respondents was 69±9 years. EQ-5D scores declined corresponding with the number of multiple fractures. There was a HRQoL reduction across all fracture sites, with spinal, upper leg and hip fractures corresponding to the greatest impact on long term quality of life. The exact follow-up period was unclear, but given that the study analysed fractures from age 45 years, and the mean age is 69 years, we assume that follow-up was >1 year.[3]

Fracture	N	Mean age standardised EQ-5D-3L	SD	Mean Difference vs No fracture	L95%CI	H95%CI	p-value
No fracture	42577	0.79	0.2				
Clavicle	761	0.68	0.3	0.04	0.02	0.05	<0.001
Arm	1755	0.71	0.3	0.3	0.2	0.4	<0.001
Wrist	4825	0.73	0.3	0.01	0.001	0.01	<0.05
Rib	2318	0.69	0.3	0.03	0.2	0.04	<0.001
Spine	1197	0.62	0.3	0.09	0.07	0.1	<0.001
Hip	1074	0.64	0.3	0.07	0.06	0.08	<0.001
Pelvis	604	0.64	0.3	0.04	0.02	0.05	<0.001
Upper leg	609	0.61	0.3	0.07	0.06	0.08	<0.001
Lower leg	1440	0.7	0.3	0.03	0.02	0.04	<0.001
Ankle	3574	0.72	0.2	0.04	0.3	0.4	<0.001
0	42577	0.79	0.2				
1	9815	0.74	0.2				
2	2425	0.68	0.3				
≥3	966	0.58	0.3				

Griffin 2015
Study from a single major trauma centre in England. University Hospitals Coventry and Warwickshire NHS Trust patients referred for a hip fracture, were aged >60 years treated with surgery, and followed up for a period of 1 year (n=403). After 1 year follow up, compared to pre-fracture quality of life (retrospectively determined post-fracture, pre-surgery) there was a 0.22 mean reduction (95%CI 0.17-0.26, p<0.001) in EQ-5D-3L.[4]

Borhan 2019
This study provides some information on the effects of fractures at different sites on HRQoL over time. CaMos was a longitudinal population-based study, originally designed to assess the burden and risk factors for osteoporosis and fracture in Canadian men and women aged 50 years and older at baseline.[5] There were 2187 men (median age 66 years) and 5566 women (median age 67 years). Incident fractures caused by minimal trauma were documented at the year 5 and 10 interviews (and annual mailed questionnaires); HUI-2/3 were administered by interviewers at baseline and year 10. A logistic regression analysis was conducted determining the recovery to baseline/pre-fracture levels of quality of life determined by HUI-2/3. The same analysis was conducted for women who had fractures during each of the 5 year periods (see below). The authors stated that their analysis suggests that single and multiple hip fractures, and multiple spine and rib fractures, strongly impact the HRQL of older people over a prolonged period of time.

NICE National Institute for Health and Care Excellence

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

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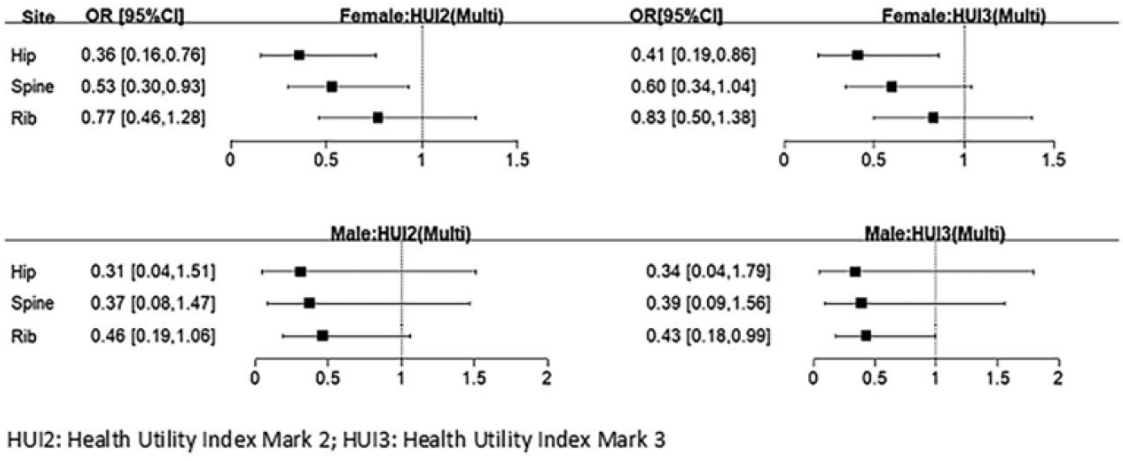

Fig. 5. Results of logistic regression analyses of recovery to baseline of multi-attribute HUI scores for both women and men.

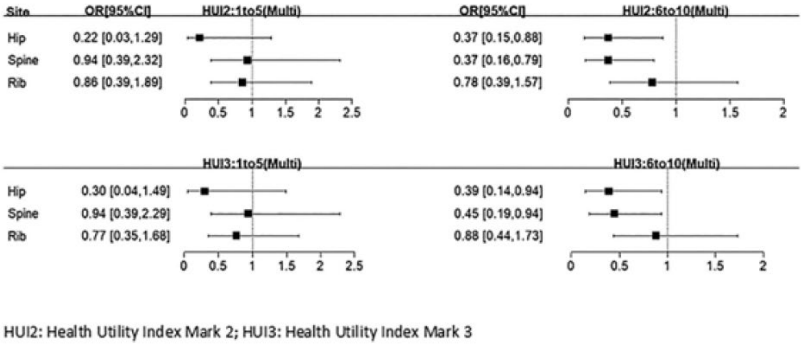

Fig. 6. Results of logistic regression analyses of recovery to baseline for multi-attribute HUI scores for women who had fractures only in year 1 to 5 or year 6 to 10.

4	**Issue 3.14 Source of utility values** ***The committee agreed that in the absence of any other scenarios, it preferred the EAG's approach. However, the committee valued including extra data on a rare condition such as XLH. The committee suggested that the company explore fitting a hierarchical model, a smoother on the data beyond week 96, or both.*** Comment: We note that the DRM R package used to fit the AR2 asymptotic model uses a maximum likelihood approach to fit the model and so applies more weight to the earlier timepoints where there are more data and less weight to the later timepoints when estimating the model parameters. The asymptotic model was selected as it inherently "smooths" the observed curve and avoids extrapolating trends observed within the trial period over extended periods. The suggestion of developing new models including hierarchical aspects is interesting, but the development and validation of such models is not feasible within the time available for a submission and it is not clear that more highly parameterised models would provide more clarity given the limited empirical data available and limited scope for truly informative elicitation for XLH which is a rare disease.

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

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Consultation on the draft guidance document – deadline for comments 5pm on 3 Jan 2024. Please submit via NICE Docs.

<table>
<tr><td>5</td><td>
Issue 3.6 Population
The committee concluded that using the age and weight distribution from the early access programme is more appropriate than the trial because it better reflects the eligible population in NHS clinical practice.
Comment: After the start of burosumab treatment, with the reduction of stiffness and fatigue and improvements in muscle strengths, most people with XLH experience a reduction in their weight. Kyowa Kirin has requested an analysis of weight changes recorded after the start of burosumab treatment in the EAP. Observations were grouped into categories to capture weight changes recorded up to 3 months after treatment start, at month 6 (±3 months), month 12 (±3 months), and at month 18 (±3 months). Please note, weight is not routinely collected in the EAP, therefore numbers of observations are small.

Weight of EAP participants according to length of treatment
<table>
<tr><td>Observation</td><td>n</td><td>Mean (SD), kg</td><td>Median, kg</td></tr>
<tr><td>Baseline</td><td>133</td><td>73.6 (16.92)</td><td>69.6</td></tr>
<tr><td>Month 3</td><td>17</td><td>69.3 (11.64)</td><td>64.5</td></tr>
<tr><td>Month 6</td><td>21</td><td>72.0 (15.41)</td><td>70.3</td></tr>
<tr><td>Month 12</td><td>9</td><td>66.8 (10.62)</td><td>63.5</td></tr>
<tr><td>Month 18</td><td>10</td><td>65.6 (13.70)</td><td>62.0</td></tr>
</table>

Based on these observations, mean weight of the cohort seems to be below 70kg after start of burosumab treatment. Therefore, we maintain that using European patients from CL303 with a mean calculated weight of 67.2 kg is a better representation of the weight of the treated XLH population in the long term than the baseline weight obtained from the EAP.
</td></tr>
<tr><td>6</td><td>
Issue 3.13 Excess fracture incidence
The committee noted the high level of uncertainty in assuming a 100% reduction in excess fracture incidence rates. This was because there was a lack of data on long-term fracture rates for people with XLH with normalised serum phosphate, as well as how people may change their behaviour if having burosumab and the effect of this on their fracture risk. The committee concluded that real-world evidence is needed to support the assumption and exploring different morbidity benefits from a reduction in excess fracture incidence with burosumab is appropriate.

We want to emphasise that the assumption refers to the <u>excess</u> fracture incidence rates, i.e. burosumab treated patients are still assumed to be at risk for fractures, only their fracture rates are assumed to be reduced to the rate that would be experienced by members of the general population at the same age.

It is important to note that the fracture rates referred to in the committee slides, with the exception of one fracture reported in the placebo->burosumab arm of the CL303 trial as an adverse event, refer to “new findings” detected by x-ray rather than reports of traumatic fractures and include pseudofractures.

The model explicitly includes fractures only (pseudofractures are radiological findings and only their impact on patients’ quality of life were assumed to be included in the model as part of the improvements observed in WOMAC scores). There was one new fracture identified in the burosumab -> burosumab group during a 48 week observation period (68 patients * 48 weeks = 62.7692 patient-years of observation) and one new fracture found in the placebo -> burosumab group between weeks 24 and 48 (24 week observation period) while they were taking burosumab (66 patients * 24 weeks = 30.4615 patient-years of observation). The estimated annual fracture rate based on the CL303 trial
</td></tr>
</table>

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	would have been 0.02145 (2 fractures over 90.2308 patient-years). The model assumes that patients treated with burosumab would be experiencing fracture rates observed in the general population. The general population fracture rate applied in the model for 18-year-olds is 0.024 increasing to above 0.050 by the end of the modelled time period. Therefore, the model actually assumes a higher annual fracture rate than observed in CL303 in its calculations for burosumab treated patients. It should also be noted that there is considerable intra-rater variation in the assessment of fractures detected by the review of x-rays.[6] [6] Therefore, some of the new findings reported may be just that, new findings on the x-rays as opposed to new fractures reported by the patients themselves. Furthermore, the rate of new active fractures reported during CL303 as part of safety outcomes is very low and decreases over time. After 24 weeks, there were no new fractures or pseudofractures reported in patients who have been taking burosumab since study start (the burosumab to burosumab group), and only one fracture in the placebo to burosumab group.

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

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Table: Number of active fractures and pseudofractures healed over time (primary analysis set)

Number of Active Fracture/ Pseudofractures	Active Fractures		Active Pseudofractures		Total	
	Placebo (N = 66)	Burosumab (N = 68)	Placebo (N = 66)	Burosumab (N = 68)	Placebo (N = 66)	Burosumab (N = 68)
Baseline	13	14	78	51	91	65
Week 12 grade – n (% baseline)						
Healed	0	2 (14.3)	7 (9.0)	11 (21.6)	7 (7.7)	13 (20.0)
Partially Healed	2 (15.4)	8 (57.1)	22 (28.2)	18 (35.3)	24 (26.4)	26 (40.0)
Unchanged	11 (84.6)	3 (21.4)	26 (33.3)	13 (25.5)	37 (40.7)	16 (24.6)
Worse	0	0	10 (12.8)	0	10 (11.0)	0
Missing	0	1 (7.1)	13 (16.7)	9 (17.6)	13 (14.3)	10 (15.4)
New Finding	2	0	6	3	8	3
Week 24 grade – n (% baseline)						
Healed	0	7 (50.0)	7 (9.0)	21 (41.2)	7 (7.7)	28 (43.1)
Partially Healed	6 (46.2)	3 (21.4)	19 (24.4)	13 (25.5)	25 (27.5)	16 (24.6)
Unchanged	2 (15.4)	3 (21.4)	39 (50.0)	6 (11.8)	41 (45.1)	9 (13.8)
Worse	3 (23.1)	0	8 (10.3)	2 (3.9)	11 (12.1)	2 (3.1)
Missing	2 (15.4)	1 (7.1)	5 (6.4)	9 (17.6)	7 (7.7)	10 (15.4)
New Finding	0	1	0	2	0	3
	Placebo→ Burosumab	Burosumab→ Burosumab	Placebo→ Burosumab	Burosumab→ Burosumab	Placebo→ Burosumab	Burosumab→ Burosumab
Week 36 grade – n (% baseline)						
Healed	3 (23.1)	7 (50.0)	18 (23.1)	26 (51.0)	21 (23.1)	33 (50.8)
Partially Healed	3 (23.1)	2 (14.3)	29 (37.2)	9 (17.6)	32 (35.2)	11 (16.9)
Unchanged	3 (23.1)	4 (28.6)	14 (17.9)	5 (9.8)	17 (18.7)	9 (13.8)
Worse	2 (15.4)	0	3 (3.8)	2 (3.9)	5 (5.5)	2 (3.1)
Missing	2 (15.4)	1 (7.1)	14 (17.9)	9 (17.6)	16 (17.6)	10 (15.4)
New Finding	0	0	2	1	2	1
Week 48 grade – n (% baseline)						
Healed	6 (46.2)	8 (57.1)	26 (33.3)	33 (64.7)	32 (35.2)	41 (63.1)
Partially Healed	4 (30.8)	2 (14.3)	32 (41.0)	9 (17.6)	36 (39.6)	11 (16.9)
Unchanged	1 (7.7)	2 (14.3)	10 (12.8)	4 (7.8)	11 (12.1)	6 (9.2)
Worse	0	0	0	0	0	0
Missing	2 (15.4)	2 (14.3)	10 (12.8)	5 (9.8)	12 (13.2)	7 (10.8)
New Finding	1	0	0	0	1	0

New finding identifies "New Finding" Grades at each post-baseline time point. End of Study is the last post-baseline visit for all subjects in the study.

Source: CL303 Clinical study report

Real-world evidence on fracture incidence in patients receiving burosumab is available from the UK Early Access Programme (EAP). No fractures have been reported as AEs over 389 patient-years of burosumab treatment on the EAP (Kyowa Kirin, Data on File). In addition, the BUR02 study provided long-term follow-up (mean burosumab exposure 116 [SD 30.7] weeks) and no new fractures were observed.[7] Similarly, BUR03 (BurGER; NCT04695860) was an investigator-sponsored, Phase 3b, open-label, single-arm study to confirm the safety and efficacy of burosumab in adults with XLH. It was carried out at a single centre in Germany. It enrolled 34 patients, who received burosumab 1 mg/kg body weight every 4 weeks for 48 weeks. The study is now completed, and the investigators

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

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<table>
<tr><td></td><td>reported that there were no fractures reported as adverse events in this study either (Kyowa Kirin, Data on File).

Furthermore, in the expert elicitation carried out to inform the economic model in the absence of long-term data in this rare disease and published by Seefried et al. 2023, treatment with burosumab was considered ‘very likely’ to stop the development of all future fractures regardless of fracture history. Burosumab was expected to ‘more likely than not or very likely’ prevent future fractures in adults with a misaligned skeleton; prevention would be even more likely in adults with an aligned skeleton.[8]

The company therefore maintains that the approach taken to modelling the reduction of excess fracture risk is conservative, and both the trial evidence as well as real world evidence from the EAP and BUR02 on the lack of fractures reported suggest that people with XLH treated with burosumab would have a very low risk of fractures.</td></tr>
<tr><td>7</td><td>Issue 3.12 Mortality benefit of burosumab
The committee suggested that evidence on the following may inform assumptions in the model:
• the relationship between XLH and the factors proposed to increase mortality risk in XLH (opioid use, effects on mental health, social deprivation, side effects of currently available treatments and consequences of reduced mobility)
• the mortality risk associated with factors proposed to increase mortality risk
• the extent that burosumab may reduce any mortality risk.

Comment: We draw the committee’s attention to the evidence on this topic presented in the Company Submission (Document B, Section 1.3.4, Table 4). This table is reproduced below, with additional information found in an additional search carried out in response to the committee’s comment.

Quantitative evidence of the effect of the relevant issues on mortality is presented where available. Treatment with burosumab has the potential to ameliorate all of these factors, thus reducing the magnitude of the excess mortality seen in people with XLH.

<table>
<tr><th>Contributing factor</th><th>Rationale</th></tr>
<tr><td>Hypophosphataemia and excess FGF23</td><td>As described in the CS, phosphate plays an essential role in metabolic processes and tissue structure and function throughout the body.[9–12] Excess FGF23, which is the root cause of hypophosphataemia, is also thought to have adverse effects independently of hypophosphataemia.[10] Life-long phosphate insufficiency, together with reduced production of active vitamin D and an excess of FGF23, may have systemic effects that predispose patients to earlier death. Excess FGF23 levels have been associated with shortened life expectancy in dialysis patients, though the authors note that this may not be generalisable to other groups.[13,14]

A Korean study of 154 patients with chronic idiopathic hypophosphataemia (independent of Kyowa Kirin) found that hypophosphatemic patients had a higher risk of any complication (adjusted hazard ratio [aHR], 2.17; 95% confidence interval [CI], 1.67–2.69) including cardiovascular outcomes, chronic kidney disease, hyperparathyroidism, osteoporotic fractures, periodontitis, and depression. Hypophosphatemic patients also had higher risks of mortality and hospitalization than the controls (aHR, 3.26; 95% CI, 1.83–5.81; and aHR, 2.49; 95% CI, 1.97–3.16, respectively).[15]</td></tr>
</table>
</td></tr>
</table>

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	Multimorbidity, including obesity	Adults with XLH live with multiple, often complex, co-morbidities, as evidenced in the life course analysis study by Javaid et al.[16] Multimorbidity is associated with increased all-cause mortality.[17] Obesity: adults with XLH have a higher prevalence of obesity than the general population.[18] Obesity is a well-established risk factor for diabetes and a range of other morbidities associated with reduced life expectancy. The association between obesity, the development of risk factors and mortality from a UK Biobank study is shown:[19]

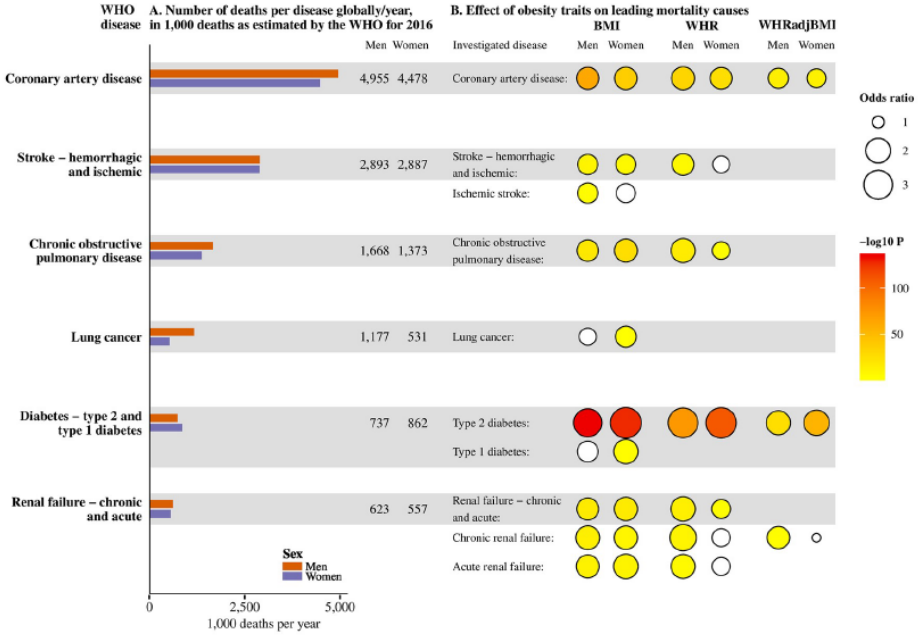

Fig 4. Overview of the sex-specific effect magnitudes and strengths of association of obesity traits on leading causes of death. Leading causes of death defined as non-communicable diseases on the WHO top 10 lists of causes of death, globally and in high-income countries, with additional separate analyses for subclasses of stroke, diabetes, and renal disease. No obesity trait (BMI, WHR, or WHRadjBMI) genetic risk score associated with dementia, colorectal cancer, breast cancer (investigated in women only) or hemorrhagic stroke–these are not shown on the plot (for the regression results see Table F in S1 Text). (A) Total number of deaths globally, in 1,000 deaths, as estimated by the WHO for 2016 [64], stratified by sex. For diabetes, estimates for annual number of deaths are for type 1 and type 2 diabetes combined. (B) Obesity trait-disease combinations taken forward for Mendelian randomization showed with circles. Mendelian randomization associations with P-values surpassing our threshold in yellow to red fill depending on P-value (-log10 P-value), white fill indicates a P-value not surpassing our threshold. The size of the circles corresponds to the magnitude of the odds ratio estimate for the Mendelian randomization estimate. Estimates and P-values from the MR analyses of the obesity traits with the disease outcomes using the sex-specific estimates approach. BMI, body mass index; P, P-value; WHR, waist-hip-ratio; WHRadjBMI, waist-hip-ratio adjusted for body mass index; WHO, World Health Organization.

https://doi.org/10.1371/journal.pgen.1008405.g004

Further, Bhaskaran 2018 was a study of UK primary care with data on 3.6 million adults from the CPRD linked to the national mortality database. It fitted adjusted Cox regression models to demonstrate the associations between BMI and mortality. The study found a J-shaped association with overall mortality with an estimated hazard ratio per 5 kg/m² increase in BMI of 0.81 (95% CI 0.80–0.82) below 25 kg/m² and 1.21 (1.20–1.22) above this point 25 kg/m².[20] In addition, the impact on life expectancy compared to a healthy individual was calculated:

Never-smoker aged 40 years:	Men	Women

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

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		<table><tr><th></th><th>Expected age of death at age 40 years (years)</th><th>Reduction in life expectancy (years)</th><th>Expected age of death at age 40 years (years)</th><th>Reduction in life expectancy (years)</th></tr><tr><td>Underweight <18.5 kg/m^2)</td><td>77.9</td><td>4.3</td><td>79.8</td><td>4.5</td></tr><tr><td>Healthy weight (18.5—24.9 kg/m^2)</td><td>82.2</td><td>..</td><td>84.3</td><td>..</td></tr><tr><td>Overweight (25.0-29.9 kg/m^2)</td><td>81.2</td><td>1</td><td>83.5</td><td>0.8</td></tr><tr><td>Obese (all, >=30.0 kg/m^2)</td><td>78</td><td>4.2</td><td>80.9</td><td>3.5</td></tr><tr><td>Obese class 1 (30.0—34.9 kg/m^2)</td><td>78.7</td><td>3.4</td><td>81.9</td><td>2.4</td></tr><tr><td>Obese class 2 (35.0-39.9 kg/m^2)</td><td>76.2</td><td>5.9</td><td>79.6</td><td>4.7</td></tr><tr><td>Obese class 3 (>=40.0 kg/m^2)</td><td>73.1</td><td>9.1</td><td>76.6</td><td>7.7</td></tr></table> Other comorbidities: The consensus statement by Trombetti et al. notes that XLH may be associated with hypertension and possibly left ventricular hypertrophy.[18] More recently, a study of 50 adults with hereditary hypophosphataemia (including XLH) by Espersen et al. found their blood pressure (BP) was significantly higher than matched controls (systolic BP 128 [95%CI: 124-133 mmHg] versus 118 [95% CI: 114-121 mmHg], p<0.001; diastolic BP was also significantly higher).[21] In the UK, Maronga et al. (2023) analysed 64 patients with XLH, including children, identified through the CPRD database. They identified 'a strong signal indicating higher prevalence of hypertension' compared with controls (OR=2.31, p=0.2).[22] People with XLH have a higher prevalence of kidney stones and other renal abnormalities, and hyperparathyroidism; these are adverse effects of conventional treatment.[18]
	Physical inactivity	The pain, stiffness, fatigue and impaired physical function associated with XLH lead to an increased prevalence of physical inactivity. In a study of 26 UK adults with XLH, almost three-quarters reported a low level of physical activity.[23] Physical inactivity is associated with a higher risk of mortality: Lear et al. 2017 studied 130,000 people from 17 countries and found that compared to low physical activity levels, those with moderate and high activity levels had lower mortality (hazard ratios of 0.80 and 0.65, respectively).[24] A SLR/MA of prospective cohort studies (n=39) assessing physical activity and sedentary time by accelerometry and its association with mortality found mortality increased with inactivity: HR (95%CI) 1.00 (reference) in the first quarter (least active), 0.48 (0.43-0.54) in the second quarter, 0.34 (0.26-0.45) in the third quarter, and 0.27 (0.23-0.32) in the fourth quarter (most active).[25]
	Impaired mental health	Hawley et al. found that adults with XLH in the UK were three times as likely to have a diagnosis of depression compared to the general population.[26] Patient testimonies and clinical consensus statements[18] confirm that living with XLH exerts a toll on mental health for many adults. A study of 68,222 community-

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 3 Jan 2024. Please submit via NICE Docs.

		dwelling adults aged 35+ in the UK found that psychological distress was associated with an increased risk of mortality, which rose with increasing distress scores: HR (age and sex adjusted) versus General Health Questionnaire-12 score 0 ranged from 1.20 (95% CI 1.13 to 1.27) to 1.94 (95% CI 1.66 to 2.26; P<0.001 for trend). This association remained after adjustment for somatic comorbidity and behavioural and socioeconomic factors.[27] Conversely, several SLR/NMAs have been conducted looking at the association between positive mental well-being and its protective factor in all-cause mortality; in Chida et al. 2008 (SLR of prospective, observational cohort studies, n=35) in a healthy population, the HR was 0.82 (95%CI 0.76-0.89),[28] in Cohen et al. 2016 (SLR of prospective, observational cohort studies, n=10) it was 0.83 (0.75-0.91),[29] and in Martín-María et al. 2017 (SLR of prospective, observational cohort studies, n=62) it was 0.92 (0.905-0.934).[30]
	Opioid use	Many adults with XLH are long-term users of prescription opioids in order to manage their pain. In the CL001 natural history study, 67% reported taking opioids at least once a week, and 22.4% of participants in CL303 were taking opioids at baseline.[31] Chronic opioid use is associated with adverse effects including fractures, breathing problems during sleep, hyperalgesia, immunosuppression, chronic constipation, bowel obstruction and myocardial infarction.[32] Inoue et al. 2022 analysed data on 13,884 US adults of whom 2168 suffered from chronic pain. Opioid prescriptions significantly increased the risk of all-cause mortality (Odds ratio = 1.5 [95% CI 1.1, 1.9] at 3 years and 1.3 [1.1, 1.6] at 5 years.[33]
	Socio-economic deprivation	People with XLH in the UK face disproportionately high levels of social deprivation compared with the general population, with 65% falling below the Index of Multiple Deprivation (IMD) national average. [26] A 2018 analysis of 328,594 participants in the UK Biobank aged 40–69 years found that deprivation was associated with increased mortality risk: each one-quintile increment in deprivation was associated with a HR for trend of 1·11 (95% CI 1·08–1·13) for all-cause mortality for distribution of IMD quintiles in people with XLH).[34] A further UK study utilising ONS population and mortality estimates between 2002 and 2018 in England (period was selected due to the availability of Lower Super Output Area [LSOA] level mortality data) found that in 2003 in the poorest 10% of LSOAs, the total rate of deaths were for men was 1.4 times those observed in the richest 10% of LSOAs, rising to 1.6 times in 2017. Similarly for women, there were 1.3 times more deaths in 2003, rising to 1.5 times more deaths in 2017.[35] The number of deaths by the total inequality index by age group is provided below:

	Age group	Total inequality index	Deaths TI accounted for (per 1000), 2017
Male	25-39	2.192	0.788
Male	40-54	3.306	3.548
Male	55-64	2.771	8.179
Male	65-79	2.268	22.554
Male	80+	1.442	47.666
Male	All ages (0-80+)	1.631	4.544

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 3 Jan 2024. Please submit via NICE Docs.

		Female	25-39	2.032	0.367
		Female	40-54	2.58	1.865
		Female	55-64	2.362	4.65
		Female	65-79	2.217	14.861
		Female	80+	1.376	35.348
		Female	All ages (0-80+)	1.543	3.141

The mortality rates for each broad age group are age adjusted using the 2018 population data, to keep the age composition constant over time. 'Deaths TI accounted for' shows the difference in the deaths (per 1,000) in the bottom and top 10% of LSOA in 2003 and 2017

The Total Inequality (TI) index is defined as the mortality rate ratio comparing the most deprived 10% of LSOAs to the least deprived 10% of LSOAs. A ratio of one indicates no difference between the two groups, a ratio above one indicates higher mortality rates in the more deprived areas.

8

Issue 3.9 Stopping criterion and discontinuation

The committee considered uncertainty on the stopping criteria and noted that the early access programme does not include a stopping rule. It noted that it was unclear how a stopping rule would be implemented in clinical practice. The committee also noted the additional benefits of burosumab, such as reduced side effects and opioid use, that adults with XLH may benefit from despite their WOMAC total score not meeting the improvement threshold. Therefore, the committee preferred not to include a stopping rule in the model.

Comment: The draft document on recommended management of XLH in adults in the NHS (Mohsin et al).[36] recommends that burosumab therapy should be reviewed annually. Stopping burosumab after 12 months should be considered if average pain over the last week has not improved AND there has not been a reduction in analgesic use from baseline. This demonstrates clinical support for stopping burosumab if patients are not experiencing clinical benefit.

A new scenario is provided below, aligning with the continuation criteria suggested by the clinical experts, i.e. based on the requirement of improvement in pain at one year. In the CL303 trial 43 patients fulfilled the criteria suggested by the clinical experts at 48 weeks, i.e. their reported BPI score improved compared to baseline, leading to 65.15% patients continuing treatment after one year, The table below reports mapped utility values for this population. Applying a continuation criteria leads to lower proportion of patients continuing burosumab treatment, but their mean utility levels are higher.

Predicted mean utilities mapped from WOMAC whilst receiving treatment with burosumab

	Burosumab (pain-based stopping rule applied) - unadjusted Mean (SE)	Burosumab (pain-based stopping rule applied) – placebo adjusted Mean (SE)
Year 1 on treatment	0.147 (0.011)	0.115 (0.016)
Year 2 on treatment	0.239 (0.014)	0.207 (0.018)
Year 3+ on treatment	0.240 (0.015)	0.208 (0.019)

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 3 Jan 2024. Please submit via NICE Docs.

The table below shows the impact of the new, pain-based discontinuation rule on the ICER, leading to a 6.5% decrease in the ICER.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company submission base case – one-year discontinuation based on WOMAC, HST8 PAS price							
SoC	£9,493	18.90	7.83				
Burosumab	[redacted]	19.42	[redacted]	[redacted]	0.52	[redacted]	[redacted]
New scenario – one-year discontinuation based on pain, HST8 PAS price							
SoC	£9,493	18.90	7.83				
Burosumab	[redacted]	19.32	[redacted]	[redacted]	0.42	3.44	[redacted]

[redacted]

The company suggests that the model should reflect the stopping rule proposed by UK clinicians in their recommended pathway. However, the company would support whichever stopping rule is supported by the clinical community in England.

9

Issue 3.11 XLH mortality

The extent of social deprivation associated with XLH and its link to mortality rates remained unclear. The committee agreed that if such a link did exist, an analysis adjusting for deprivation would be preferred. The committee concluded that it preferred a larger sample with more recent data, as seen in the company's confirmatory study, to estimate excess mortality associated with XLH. It therefore preferred a hazard ratio of 2.33 to model the excess mortality risk from XLH compared with the general population.

Comment:

We would like to clarify that the company's mortality analysis **does** control for deprivation, as this was one of the matching variables. This is a case-cohort (rather than a case-control) study. Unlike in case-control studies, adjustment for the matching variables *per se* is not needed in case-cohort studies (Sjölander & Greenland 2012[37]). However, to explore this question, an analysis of the company's confirmatory study was undertaken with IMD quintile added as a factor covariate the Cox PH model (allowing it to have four dummy categories). The hazard ratio for mortality from this analysis was 2.49 (95% confidence interval 1.23 – 5.02), compared with 2.33 (95% confidence interval 1.16 – 4.67) from the original analysis.

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

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Consultation on the draft guidance document – deadline for comments 5pm on 3 Jan 2024. Please submit via NICE Docs.

10	**Issue 3.10 Tapering of treatment effect** ***The company included different tapering assumptions for mortality and morbidity when stopping burosumab. Alternatively, the EAG assumed the same treatment tapering effect on morbidity and mortality and applied the company's mortality tapering assumptions to both. The committee concluded that the assumptions were arbitrary but agreed with the EAG's approach to using the same assumptions for both morbidity and mortality treatment effect tapering.*** Comment: The tapering assumptions made in the model were informed and validated by clinical expert opinion. Two UK-based clinical experts with experience in treating and managing adults with XLH were engaged to validate the model structure, resource utilisation and to inform model assumptions, including the assumptions around tapering of the impact of burosumab treatment on morbidities, mortality and utilities (the interview details were provided in Appendix P of the company submission). The experts have suggested that time it takes for burosumab to change these factors should be different according to the time it takes to influence the outcomes. Morbidity (i.e. fractures) and utilities change quickly, and the tapering should therefore happen in a shorter period of time. The company model therefore assumed an immediate impact on fractures (note, there were no new fractures reported in CL303 after 24 weeks, no fractures in BUR02 and no fractures in the EAP), and a within one-year disappearance of the impact. The impact on mortality, however, is more complex. Over time, burosumab treatment is expected to increase physical activity levels, reduce opioid use, reduce obesity and improve mental health. These effects take time, so the experts suggested a longer time period of tapering: both a delay in the positive impacts at the start of treatment as well as a delay in the loss of benefits after treatment discontinuation. The company suggests that the approach recommended by clinical experts for the modelling, i.e. different tapering assumptions for morbidity and mortality, should be retained as per the company base case. However, the company would support wider clinical opinion on this issue.

Insert extra rows as needed

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	XLH UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**XLH UK**'s financial year runs from February 1st – January 31st. From February 1st, 2022 – January 31st, 2023 XLH UK received £21,000 in financial support from Kyowa Kirin which represented 95% of its income. The financial support, received in January 2023, from Kyowa Kirin has been allocated to deliver on three priorities identified in our 2023 strategic plan: Patient event: £3,000 for venue, equipment and marketing; £6,000 towards evidence underpinning fresh insights. Improve awareness of the charity in UK NHS specialist centres: £2000 for materials and printing. Upgrade of website: £10,000 for design of a secure, off the shelf wireframe which can be maintained by non-specialist volunteers. (Kyowa Kirin were not involved in any of the above priorities) In our current financial year, from February 1st, 2023 – January 31st, 2024 XLH UK has received no financial support from Kyowa Kirin during our current financial year. Our income to date from public donations and support has been £14,292. ********** **The International XLH Alliance** (IXLHA) is also a registered charity in England and Wales and is a collaborative network of XLH patient organisations. It's financial year also runs from February 1st – January 31st From February 1st, 2022 – January 31st, 2023 IXLHA received a restricted grant of £57,280 from Kyowa Kirin which represented 71% of its income. The financial support, received in 2022 from Kyowa Kirin helped support us in being able to: Create the 3rd International XLH Symposium in Dublin, Ireland in 2022. To bring together IXLHA member organisations for a face-to-face strategy, improvement and training meeting also in Dublin, Ireland in 2022. (Kyowa Kirin were not involved in the programme or planning of either event) In our current financial year, from February 1st, 2023 – January 31st, 2024, IXLHA received: £515 from Kyowa Kirin Australia as unrestricted donation in May. £175 compensation from Kyowa Kirin for speaking at a private industry event. (as declared on .2 below)

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Burosumab for treating X-linked hypophosphataemia in adults

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Has all of the relevant evidence been taken into account?** XLH UK, a charitable trust registered in England and Wales, representing patients, their families and clinical experts, of those suffering with X-Linked Hypophosphataemia (XLH), are disappointed that NICE does not recommend burosumab for adults with XLH following the draft guidance ID3822. Burosumab offers a life-changing moment for XLH patients as it is the first and only treatment that targets the underlying mechanism of their hypophosphataemia. Adults with XLH who have been prescribed burosumab through the Early Access Programme (EAP) have shared with us powerful insights on how their treatment has significantly improved their lives; including reductions in chronic daily pain, stiffness in the major joints, improvements in the prevention of fractures, healing of fractures, reduction in fatigue and mental health. Since 29/11/2023, following the publication of the draft guidance ID3822, XLH UK has collaborated with the patient community and clinical experts from across the country to address each of the 12 uncertainties raised in the draft guidance to aid in the final guidance. We identified two of these uncertainties for XLH UK to help with, providing more evidence from a community survey. • Applying a carer utility benefit of burosumab to 1 carer (see section 3.17). • The number of carers an adult with XLH would have, the extent to which caring for people with XLH affects quality of life, and how caring for people who are having burosumab impacts quality of life. The committee considered that the company assumptions may overestimate the benefit of burosumab on carer quality of life (see section 3.17). From 29/11/2023 to 13/12/2023, 116 patients and family members completed XLH UK's Carer Survey.

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Burosumab for treating X-linked hypophosphataemia in adults

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All survey participants are currently living in the UK, are 16-years or older and were:

- an adult with XLH without carer roles (n=44)
- an adult with XLH and carer of at least one adult with XLH (n=11)
- an adult with XLH caring for a child with XLH (n=16)
- a family member without XLH and carer of at least one adult with XLH (n=31)
- a family member without XLH but not a carer of at least one adult with XLH (n=14)

Adults with XLH not prescribed burosumab: n=46
16/46 have no carer.
10/46 have a carer count of 1.
18/46 have a carer count of 2 or greater.
2/46 gave n/a.

Total carer hours per week due to their XLH?	Count
0	21
1-10	10
11-50	14
51-100	1

Average hours per week: 11.8 hours.

Adults with XLH prescribed burosumab: n=24 (the majority having been receiving burosumab for greater than 1.5 years).

Prior to starting burosumab all 24 respondents reported having at least 1 carer. Now on burosumab, 9 reported no longer requiring support from a carer and 10 only required support from 1 carer. 16 reported a reduction in the number of carers they required support from since being on burosumab.

Number of carers	**Before burosumab**	**While on burosumab**
None	0	9
1	8	10
2	8	2
3	4	2
4	1	0
5 or greater	3	1

The total average carer hours per week decreased by 61% since being on burosumab.

Group of hours per week	**Before** you started burosumab, how many hours in total per week did carer(s) or family member(s) spend caring for you? (number in hours only, put 0 if n/a)	While on burosumab, how many hours in total per week do carer(s) or family member(s) currently spend caring for you? (number in hours only, put 0 if n/a)	
0	4	11	
1-10	10	8	

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11-50	9	4	
51-100	0	1	
101-200	1	0	
	Average hours pw 19.3	Average hours pw 7.5	-61.1%

When asking a similar question to 24 carers surveyed, similar care hours were reported before the person they cared for started to receive burosumab.

Before the person you care for started burosumab, how many hours per week, on average, did you spend providing care? (number in hours only, put 0 if n/a)	
Group	**Count**
0	5
1-10	10
11-50	7
51-100	1
101-200	1
	Average hours pw 20.1

We also asked carers two questions regarding how the levels of care had changed or impacted them since the person they care for started burosumab.

- 15 reported that the level of care they needed to provide had decreased significantly, 3 reported that the level of care had decreased moderately, 4 reported the level of care staying the same, none reported a moderate increase, and one reported a significant increase.
- No carers reported that their well-being had decreased significantly or moderately following the person they care for starting burosumab and 3 reported no change to their well-being, 2 reported a moderate improvement in their wellbeing and 19 reported their well-being as a carer improving significantly.

"My wife s health has dramatically improved physically and mentally because of this she needs less help on a day to day basis, before she had burosumab I had to help her get out of bed in the morning , shower and dress. I had to take care of the house and shopping , it was hard seeing her in pain all the time . Now my wife is a new person she only needs minimal help , we are able to go out and take holidays she has become more independent and happy . Because of the lifting of being a carer to her our relationship has improved , my own life and mental health has really changed for the better. we are able to enjoy life to the full and look forward to a better future and look forward to retiring together thanks to Burosumab.
If Burosumab is denied to my wife the future looks very bleak indeed I fear for our future."

"I find it extremely hard to care for the person with xlh. Her health has deteriorated massively and she struggles to walk all the time. Doing everyday tasks is a hindrance for her and I have

Burosumab for treating X-linked hypophosphataemia in adults

Draft guidance comments form

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	to be around all day just in case she struggles with her tasks or if she falls and hurts herself. It is affecting our mental health as well." We are happy to provide the anonymised data on request.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We are concerned that the NICE EC may be overestimating the number [1000] of adult patients with XLH who may be eligible for burosumab in England. There is a wide range in the burden of symptoms caused by XLH. Therefore, we are mindful that some adult XLH patients have limited symptom burden, or no symptoms at all. So only a part of the population (those who are moderately to severely affected) may be better suited to burosumab treatment, as it does appear to be superior at reducing those symptoms. As a patient organisation we are well known among the clinical experts across the country, have good relationships with those hospitals, and are key in providing additional support to their patients. We have amassed approximately 320 patient contacts, many which have come via their specialist hospitals, which we believe to be a significant portion of the population across the U.K.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The life changing impact that we have seen burosumab have on eligible adult patients is profound and demonstrates an effective treatment for a population likely to experience progressive, significant disability. This includes reduced ability to contribute to society economically, negative mental health impact and high probability of a need for costly surgery and care, including but not limited to adaptions to home and increasing requirements for physical care over time. Patients who have been receiving burosumab reported significant improvements in their total health and day to day life in their own words via our survey: *"I am now back and working as a GP, something I was struggling to do before because significant pain was limiting my functioning and sleep to the point that I could not manage to do this. It has been life transforming and the fact it could be taken away is so very scary both for me and my daughter with XLH too."* *"The pain in my body has decreased hugely, prior to starting this drug I would be woken up multiple times a night in pain, I no longer have this. My body was so painful I could barely walk upstairs or exercise. I am now able to run upstairs and regularly attend a gym."* *"Prior to starting Burosumab, I thought I was going to have to have surgery on my knees and my left thigh, I was also nervous about ending up in a wheelchair due to the pain and stiffness in my spine..."* *"…In addition to this, the improved energy levels has been life changing. I used to get so tired that I could only manage a couple of things a day, I'd drop my son off at school 15mins away and then I would pass out for an hour, now I have so much more energy. I use to struggle to cook because I was so tired , so I'd order take aways, which negatively impacted my health. Now I have energy, I cook my meals from scratch, they are healthy and I can feel the*

Burosumab for treating X-linked hypophosphataemia in adults

Draft guidance comments form

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	difference! I am healthy, fitter, and happier since taking this drug. I used to have to see my GP and hospital so frequently - this is no longer the case." We feel the current recommendations underestimate the total transformational health impact we have seen among eligible adults in the XLH community who have been able to access burosumab via the EAP.
4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** The Scottish Medicines Consortium (SMC) in March 2023 recommended burosumab for adults with XLH in Scotland under the ultra-orphan pathway. The decision to not recommend burosumab to eligible adults in England would cause geographical disparity and raise issues of unequal treatment based on residence, impacting equality, especially for individuals near the border. There are concerns regarding age-related discrimination if burosumab is not recommended for eligible adult XLH patients in England. Denying access once a child reaches adulthood, a critical period that often includes important milestones like A-level exams, raises worries about disrupting continuity of care and potentially compromising academic and personal pursuits. A parent of young adult with XLH raises that this abrupt shift in treatment access during a pivotal life stage had adversely affected the health and well-being of their child. *"…Burosumab was stopped 3 months before his Alevel exams. This undoubtedly had a negative effect in his exam results. His energy levels dropped significantly. He found it extremely difficult to finish the course. While he was taking Burosumab* [name removed] *was enjoying the subjects he was studying and was in course for A/B A-level results. After the Burosumab stopped he found it very difficult to carry on with his studies…"* Restricting access to burosumab may impact individuals' ability to work and stay employed, particularly for those in the working-age population. Effective management of XLH is crucial for maintaining the health and productivity of individuals, preventing potential disability, and supporting their active participation in the workforce. Denying access based on age could disproportionately affect the livelihoods and economic well-being of working-age individuals, exacerbating inequalities and hindering their ability to contribute to society. *"Prior to burosumab I had to stop my ICU job due to fatigue. Now I am working as a specialist nurse and have less fatigue, normal blood biochemistry and bone profile and reduced concern for fractures."* *"Now in my thirties I no longer have the energy or the strength to do 'normal' day to day activities and feel unable to plan for an active future whereby I am pain free and independent. I have become increasingly withdrawn from a social life and worry about my physical and mental health. I feel I will not be able to continue with my current job much longer and do not know how I will provide for myself and my family financially and emotionally."*

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Charles Dent Metabolic Unit, University College London Hospitals NHS Foundation Trust

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the modelling used does not capture the real benefits that adults with XLH receive from treatment with burosumab.

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Burosumab for treating X-linked hypophosphataemia in adults

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	Burosumab is undoubtedly highly effective at healing fractures. Over the past 2 years, we have now treated treated 38 adults (age 43.25±14.22 years) with Burosumab as part of the compassionate use programme. By the end of 1 year of treatment the fracture prevalence in our cohort had halved – from 25 fractures in 9 individuals at baseline, to 12 fractures in 5 individuals at 1 year. In addition, **no** new fractures have developed in this cohort over a 2 year follow up. However, the emphasis of Burosumab should not only be on the efficacy of fracture healing and prevention. Even patients without fracture will have benefits in pain reduction and particularly reduced stiffness and improved mobility. This has a huge effect on the quality of life of our patients. Data from our cohort of adults treated as part of the compassionate use programme confirms this with 18 (of 37 patients studied) having had a clinically significant improvement in their timed up and go test at 1 year; and 19 (of 37 patients studied) having had a clinically significant improvement in their 6 minute walk test (6MWT). For some individuals this improvement can be very marked – 6 individuals improved their 6MWT distance by > 100 m. Importantly, although not all individuals have reached 2 years of treatment, in those who have (N=22), these benefits are maintained at year 2. Improvements in quality of life are also maintained (Baseline ED5Q5L overall health score = 55.4±18.8. This improved to 64.6±19.5 after 1 year of treatment (p=0.013) and was maintained at 67.14±16 after 2 years of treatment).
2	We are concerned that more emphasis is being placed on whether burosumab can reduce mortality than on whether it improves patients' symptoms and quality of life. There is no reliable data available on life expectancy in XLH, and no studies of burosumab were designed to determine any effect of treatment on mortality. For a lifelong genetic disease like XLH, mortality is not a useful outcome measure as you would need to treat patients for decades in placebo-controlled rials before you could see any outcome. It must be reasonable to regard normalisation of biochemistry and skeletal growth, healing of fractures and reduction of symptoms as a surrogate for eventual life-expectancy.
3	We are concerned that this recommendation raises major equality issues. Burosumab has been approved for paediatric patients under an HST process, and the company have reached a pricing agreement with NHSE on that basis. To then assess cost-effectiveness in adults with the same indication for treatment under a standard technology appraisal will inevitably require the company to offer the same drug, for the same indication, at different prices for paediatric and adult patients. This differential will be exacerbated further by the fact that burosumab is dosed by weight. All these patients have the same disease, and the pharmacological effects of burosumab are the same in adults and in children with XLH. The company and NICE should consider a lifetime approach to treating the disease rather than imposing arbitrary age-based cut offs (currently nobody over 18 can receive burosumab from NHSE regardless of whether their bones are still maturing or not).
4	We are concerned that insufficient consideration has been given to the effects of stopping burosumab at the age of 18 years. The committee say that no data has been produced for this, but this is because there are very few children who have been treated with burosumab from an early age who have yet had to stop treatment. Limited reports from patients who have stopped treatment at 18 years suggest that issues with stiffness and impaired mobility are returning.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	Kassim Javaid

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Has all of the relevant evidence been taken into account? To directly address the questions from ID3822 Draft guidance: Burosumab for treating X-linked hypophosphataemia in adults, clinicians within the Rare Disease Collaborative Network for Adult Rare Bone Diseases with expertise in managing adult XLH were asked to complete an online

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Draft guidance comments form

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	survey. Nine experts, including all centres participating in the Early Access Programme, responded. These experts collectively prescribe burosumab for 137 adults. The survey questions have been emailed TA team3 in the supplemental materials and the raw data is available on request. NOT APPLYING A STOPPING RULE FOR BUROSUMAB: From the survey, 9/ 9 experts were able to define a stopping rule. Four experts agreed on the need to have both average pain over the last seven days not improved & no reduction in analgesic used from baseline as a stopping criterion at 12 months, and two experts required either of these criteria; two experts recommended only failed reduction of average pain, and 1 expert-recommended only no reduction in analgesic use from baseline. APPLYING THE SAME TREATMENT EFFECT TAPERING ASSUMPTIONS FOR MODELLED MORBIDITY AND MORTALITY From the survey, four experts were able to provide information, and the median time for improvement in pain was 12 weeks. The time to reach a plateau in improvement in pain was estimated to be one year (3 experts) and two years (3 experts). In comparison, the time for symptoms to worsen after stopping treatment ranged from 4 – 12 weeks. The time to reduction in mortality was unable to be estimated by 8 experts. ADJUSTING FOR PLACEBO EFFECT IN THE MODEL FOR EXTRAPOLATING UTILITY VALUES IN THE ABSENCE OF EVIDENCE SUPPORTING THAT THE PLACEBO EFFECT IS NOT MAINTAINED BEYOND THE TRIAL PERIOD The experts were asked about day-to-day symptom variability vs long-term decline. Minor day-to-day with no significant worsening over 6 months was the most typical pattern (4/8 experts), then minor day-to-day with significant worsening over 6 months (2 experts) and major day-to-day variability with no/minor general worsening over 6 months (2 experts). THE EFFECT OF BUROSUMAB ON THE EXCESS MORTALITY RISK ASSOCIATED WITH BUROSUMAB, WHICH IS EXPECTED TO BE LOWER THAN THE 50% REDUCTION MODELLED BY THE COMPANY Five experts estimated a 25% reduction in mortality from burosumab therapy, and 3 experts estimated a 10% reduction, with 1 expert unable to give an estimate. THE EFFECT OF SERUM PHOSPHATE NORMALISATION ON REDUCING NEW FRACTURES IN PEOPLE WITH XLH AND WHETHER PEOPLE WITH NORMAL SERUM PHOSPHATE WOULD HAVE THE SAME NUMBER OF FRACTURES AS THE GENERAL POPULATION. IT EXPECTED THAT THIS MAY BE OVERESTIMATED IN THE COMPANY MODEL All experts (9/9) agreed fractures associated with XLH are not osteoporotic. Seven experts agreed healing with conventional therapy takes more than a year; 2 experts could not comment. Four out of 8 experts predicted burosumab would reduce the fracture risk to that of the general population, to below the general population (3 experts) and above the general population (1/8 expert). THE DURATION OF DISUTILITY FOR FRACTURES IN THE MODEL AND WHETHER THIS MAY VARY DEPENDING ON THE TYPE OF FRACTURE INCLUDED. THE COMMITTEE CONSIDERED THAT THE COMPANY'S ASSUMPTION OF LIFELONG DURATION OF DISUTILITY MAY BE AN OVERESTIMATE IN THE COMPANY MODEL Seven out of 9 experts agreed healing with conventional therapy takes more than a year, and 2 experts were not able to comment. The median proportion of adults with pseudofractures that

Burosumab for treating X-linked hypophosphataemia in adults

Draft guidance comments form

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	remained symptomatic with conventional treatment was 80% of patients at 1 year, 50% at 2 years, 25% at 5 years, and 10% with lifelong symptoms. In addition, working with XLH-UK, Rudystudy.org was promoted to adults with XLH to consider joining and completing questionnaires. The results from this study were able to add information about the weight of adults and tapering of benefits when starting and stopping treatment. The raw data is available on request. USING THE AGE AND WEIGHT DISTRIBUTION FROM THE EARLY ACCESS PROGRAMME The mean weight of all adults was 67kg and those on burosumab 63kg. A more detailed breakdown by by sex, age band and current strongest pain score is presented in the supplemental file table 1. APPLYING THE SAME TREATMENT EFFECT TAPERING ASSUMPTIONS FOR MODELLED MORBIDITY AND MORTALITY The strongest pain in burosumab users appears to attenuate the longer patients are on burosumab (See Supplemental data Table 2 & Figure 1 emailed to TA team 3). There are 2 ex-users, who had stopped burosumab after transition, and reported high painDETECT strongest pain scores (see supplemental data Figure 2 emailed to TA team 3).
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We are concerned that the draft recommendation is based on unreasonable assumptions around the direct clinical benefit of burosumab in reducing pain and treating and preventing pseudofractures. Further, we believe it is unreasonable to expect the reduction in pain from the placebo to be maintained given the low day-to-day variability as experienced by the experts, minimising the effect of regression to the mean. We are concerned that the draft guidance suggested up to 1000 adult patients may be eligible for burosumab. From the recent survey of 9 expert centres, that manage most adults with XLH, 137 adults are prescribed burosumab, and 71 additional adults would be eligible with 35 additional patients per year. Most patients should be known to expert centres, so 1000 seems unreasonable. APPLYING A 2.33 HAZARD RATIO TO ESTIMATE THE EXCESS MORTALITY RISK FROM XLH COMPARED WITH THE GENERAL POPULATION It is reasonable to expect lower mortality in the larger CPRD GOLD and AURUM study because this study matched age, sex, practice, and index of multiple deprivations (IMD). In contrast, the Hawley paper did not match using the index of multiple deprivation. It is reasonable to assume that by matching on indices of deprivation, as an established predictor of mortality, the causal relationship between XLH and mortality to be attenuated. It is, therefore, reasonable to use the high 2.88 mortality risk in the highly likely population in the Hawley paper.
3	Are the recommendations sound and a suitable basis for guidance to the NHS? XLH is a progressive, severe rare bone disease that significantly reduces quality of life and increases mortality. The draft recommendations are unreasonable and deny a first-in-class, life-changing treatment for a sub-group of adults with severely symptomatic XLH. As a group of experts, we have developed, with the XLH-UK patient groups, a draft clinical pathway (emailed to TA team 3) that integrates start and stopping criteria for burosumab in adults with moderate to severe pain related to XLH and those with pseudofracture and have failed conventional therapy. Eight out of 9 experts agreed on a starting criteria of ≥18 years with worst

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Draft guidance comments form

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	pain in last 7 days ≥4/10 & failed conventional therapy attributable to XLH. Two experts recommended a fixed 12-month duration of therapy for pseudofractures as well as those awaiting orthopaedic surgery. Seven out of 9 agreed failed conventional therapy defined by a 3-month trial of oral phosphate and activated vitamin D unless already tried in the last 24 months for similar symptoms. Only 1 expert recommended extending the duration of conventional therapy to 6 months to permit dose adjustments. Four out of 9 experts agreed with the need to have both average pain over the last 7 days not improved & no reduction in analgesic used from baseline as a stopping criterion at 12 months; 2 experts required either of these criteria, 2 experts recommended only failed reduction of average pain, and 1 expert recommended only no reduction in analgesic use from baseline. Seven experts recommended burosumab treatment decisions should be made by the Rare Disease Collaborative Network for Adult Bone Diseases Multidisciplinary Team meeting structure, 7 experts recommended a formal Managed Access scheme supported to provide clinical outcome data for 3 years, and 6 experts recommended treatment decisions should be made by expert centres.
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? It is recognised that XLH disproportionately affects women, with higher symptom burden in older patients and those living with worse deprivation. A recommendation to not make burosumab available for adults with moderate/ severely symptomatic disease will have a disproportionate impact on these patient groups.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Burosumab for treating X-linked hypophosphataemia in adults

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 03/01/24. Please submit via NICE Docs.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Supplemental data

USING THE AGE AND WEIGHT DISTRIBUTION FROM THE EARLY ACCESS PROGRAMME

Table 1: Adult XLH weight by sex, age band and current strongest pain score:

SUBGROUP	n	Current weight (kg)			
		Mean	Median	IQR 25	IQR 75
ALL ADULTS	57	67	64	56	74
WOMEN	43	70.2	61	55	73
MEN	14	66.1	65	61	77
16-35 YRS	19	67	62	56	69
36-55 YRS	23	69.6	68	59	78
56-85 YRS	15	63.5	60	54	73
Burosumab ever users	19	63	60	54.5	71
Burosumab non users	38	69.3	65	56.2	77.2
Non-Burosumab users: Most recent PainDETECT[1] strongest < 4	3	64.3	65	60	70
Non-Burosumab users: Most recent PainDETECT[1] strongest ≥4	34	69.6	65.5	56	78.5

Legend: [1]As measured by painDETECT questionnaire

APPLYING THE SAME TREATMENT EFFECT TAPERING ASSUMPTIONS FOR MODELLED MORBIDITY AND MORTALITY

Table 2: Current strongest Pain using painDETECT by burosumab user status

SUBGROUP	N=	Age (mean)	Current strongest pain[1]			
			Mean	Median	IQR 25	IQR 75
ALL ADULTS	56	44	6.59	8.0	4.5	9.0
Burosumab ever users	19	47	4.43	3	1.5	7.5
Burosumab current users	17	50.4	4	3	1	7
Burosumab ex-users	2	18.5	9	9	8.5	9.5

Legend: [1]As measured by painDETECT questionnaire

Figure 1: Current strongest pain in current burosumab users using painDETECT by weeks from starting burosumab.

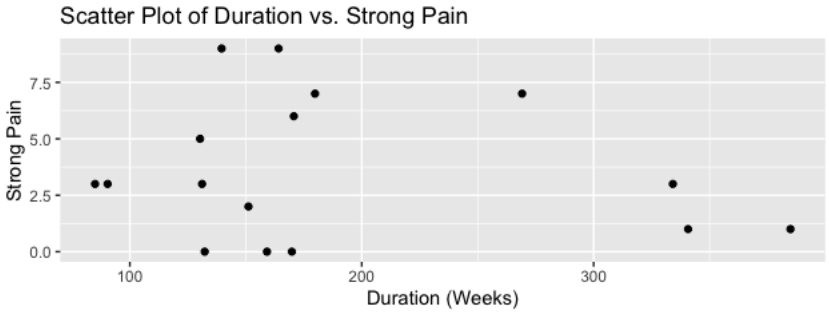
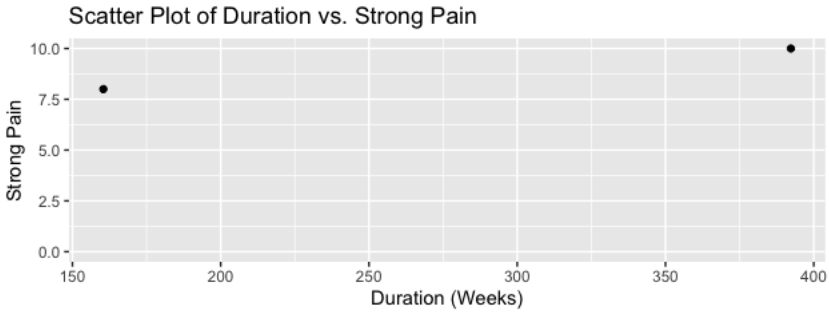


Figure 2: Current strongest pain in Burosumab ex-users using painDETECT by weeks after stopping burosumab.



EXPERT CENTRE SURVEY FOR ADULTS with XLH

Attachments: ACD and proposed adult pathway

Perspectives on use of Burosumab in Adults with XLH Survey
GDPR : This data will be analysed by University of Oxford and XLH UK for the propose of providing information for the potential use of burosumab in adults to NICE and the wider community. Please respond by 22nd of December and we invite as many responses as possible so please do forward on the link:

Email
Centre Name:
Country - England, Wales, Scotland, Northern Ireland.
Primary role (e.g. rheumatology)

Are you an EAP centre: Yes/ No

1. Inclusion criteria
    a. Do you agree with the Inclusion criteria of 18 years and over & worst pain in last 7 days ≥4/10 & failed conventional therapy
    b. Failed conventional therapy as 3 month trial of oral phosphate and activated vitamin D unless already tried in the last 24 months for similar symptoms

    c. If not tolerated or there is no benefit after three months of treatment, and average pain over the last 7 days is ≥ 4 /10 and clinically attributable to XLH
2. Stopping criteria: Review Burosumab therapy annually and consider stopping burosumab after 12 months:
    a. if average pain over the last week has not improved
    b. there has not been a reduction in analgesic use from baseline.
    c. OR (either of the a or b)
    d. AND (both a and b)
    e.
3. Decision making
    a. Should be managed by an expert centre
    b. Should be managed by an RDCN MDT
    c. Should be managed by a formal Managed access scheme supported to provide clinical outcome data for 3 years s
    A
4. Tapering
    a. How long to start improving pain, other QoL after starting
    b. How long to lose pain benefit if stop
    c. How long to improve mortality
    d. How long to lose mortality benefit

5. Benefit of long term use on patient reported outcomes such as pain, stiffness, function - plateau vs ongoing benefit
    a. 6 months
    b. 1 years
    c. 2 years
6. In the clinical trial, there was a reduction in pain in both the placebo and treatment arms over 6 months, in your experience how much variability in pain do you see in adults pain over 6 months
    a. Great day-to-day variability with no/ minor general worsening
    b. Great day-to-day variability with significant general worsening
    c. Minor day-to-day variability with no/ minor general worsening
    d. Minor day-to-day variability with signficant general worsening
7. Fracture in XLH
    a. Have a different mechanism to osteoporotic fracture
    b. What proportion of XLH related fractures of the proximal femur heal with conventional therapy
        i. within one year
        ii. take longer than a year
    c. With conventional therapy, what proportion of adults with XLH with a recently diagnosed symptomatic pseuofractures can expect to remain symptomatic/ lower QoL for
        i. 1 year
        ii. 2 years
        iii. 5 years
        iv. life long
    d. Given XLH adults tend to have wider bones and higher bone density, will burosumab therapy reduce hip fracture risk to
        i. above general population
        ii. same as general population

iii. below general population

e. How many adults have you seen with a classic osteoporotic fracture at the
   i. hip
   ii. spine
   iii. wrist
   iv. humerus
   v. other

8. How many adults with XLH
   a. are currently prescribed burosumab by your centre
   b. are currently not prescribed burosumab but would be eligible based on the criteria of pain ≥4/10 and failure of conventional therapy
   c. how many new patient are you referred every year (excluding transition) who would be eligible
   d. how many transition patients are you referred every year who would be eligible
9. Do you consider XLH adults to more deprived as measured by receipt of benefits, housing and employment status.
10. The mortality of XLH appears elevated and this maybe due to physical and mental symptoms, loss of function, opioid use, limited employment and being poorer as well as a direct effect on comorbidities (not yet determined). Knowing the benefits of burosumab and these potential mechanisms, how much would you expect burosumab on average to reduce mortality
    a. 10%
    b. 25%
    c. 50%
    d. 75%
    e. 90%
11. Please add any other comments you think are relevant here.

Single Technology Appraisal

Burosumab for treating X-linked hypophosphataemia in adults [3822]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Dear Members of the NICE Panel,

I am 38 year old female grappling with XLH, sharing my personal journey. Childhood corrective surgeries and countless hospital stays seemed conquered, allowing me a near-normal life for a number of years. Grateful for education, a steady job, and a happy family , my life took a turn in the last 5 years.

Daily pain, mobility challenges, and secondary conditions like arthritis, hearing and tooth loss now dominate my life.
Daily, I face excruciating pain. It never goes away, in fact it increases during the day. At times I get this sharp, breath taking pain that literally swipes me off my feet. I have to stop, hold onto someone or a piece of furniture and wait for it to pass. I then slowly, through the pain, stretch my limbs- it could be anything from my leg,back or an arm.

Every muscle and joint hurts daily. My mobility has decreased. I wake up so stiff I need to support myself on the furniture to be able to go from room to room. I struggle to sit freely on the toilet. I have to support myself getting on and off the seat.

Mobility restrictions have reshaped my once active life, forcing my partner to take on majority of the household chores we once enjoyed together. I am no longer able to stand, walk or even sit for more than 10 minutes without the pain and stiffness. I struggle to stand up and cook a full meal. When I do, I have a chair next to me to take regular breaks.
Fatigue disrupts my daily life, my work, eroding my independence and leading to a sense of burden on loved ones.

I can be doing nothing and still get so tired , I need to take a nap. Fatigue dictates my schedule ,turning once enjoyable outgoings into carefully planned endeavours . When going out, even for a simple shopping trip, I research closest parking or get dropped of any wait on my own for my companion to join me. Once out, I have to stop and sit down regularly. I can't be out for a whole day anymore, I need to plan to get home on time before I get too tired. I have to decline a lot of social invitations and to many I am no longer being invited. I worry about my decreasing performance at work as I get more tired and less mobile.

From being a happy ,full of live person, I am becoming more house bound and depressed. I worry about the impact of my professing condition on family and friends. I don't want to be a burden to them and to the society. Nothing eases the fatigue or the pain. I have vast amounts of pain medication,creams and tablets ,none of which eases the pain. Current medication I am on (Phosphate Sandoz and Calcitriol) is ineffective and carrying number of side effects . I have not taken it for number or years. I didn't feel any benefits and had a lot of side effects. When my health started to deteriorate, I went back on this medication and has been taking it daily since 2019. I suffer from number of side effects disrupting my daily routine. I get up an hour earlier to what I used to ,to allow my body enough time to recover from some of the side effects. Within 30-60 minutes from taking phosphates I experience nausea and stomach cramps. I have gastrointestinal problems including constipation and diarrhoea. I can not go to toilet for days and when I do I experience loose diarrhoea. I have to empty my bladder too frequent.It is most disruptive in the evening. It takes me anything between 60-90 minutes before I am able to fall asleep without needing to empty my bladder. I don't get enough sleep, I only sleep 4-5 hours a night.

I also get calcification build up in my foot. This was removed in the past but has returned resulting in more pain, stiffness and restrictive movement. I worry I get more calcium deposits elsewhere,on my spine causing paralysis or my kidneys resulting in kidney damage.

My phosphate levels are not stable despite the medication . Only this year, my phosphates dropped at least twice to the dangerously low level resulting in A&E visits. On first occasion I was very weak, in a lot of pain and feeling confused. I lost strength in my right knee, it couldn't bear my own weight, I couldn't walk or stand. I suspected a pseudo fracture ,but I was diagnosed with dangerously low phosphate levels. I was advised to increase the dosage and call 999 if I get worse or don't improve. On second occasion I suddenly felt unwell while being at work. I was driven home from where I was first taken to GP who advised to go to A&E. As minutes went past I was getting worse. I was in excruciating pain, I got a rash, I was very tired and disoriented to the point I struggled to speak. I was diagnosed with low phosphate levels, it was unsafe for me to return back home. I was kept overnight and administered phosphates via IV.

I was set for a CHAOS surgery to my deformed tibia in 2024, but unstable phosphates that could lead to prolonged recovery ,risking permanent disability and looming guidance on burosumab availability has prompted a pause.

Couple years ago I suffered suspected pseudo fracture. I wasn't diagnosed and helped quickly enough , I often face difficulties in diagnosis and medical help due to the condition being so rare and unknown. As a result , I have now deformed foot and an arthritis. I no longer can move it freely , I get steroid injections couple times a year to ease the pain and reduce the inflammation.

I am loosing my hearing. I noticed I couldn't hear clearly. At first I thought my phone speaker was faulty ,I replaced my phone but still couldn't hear properly. I now can only pick up the calls wearing a headset.
I lost most of my teeth , including 4 of my front teeth. I have a front dental bridge and numerous crowns. I suffer from spontaneous abscesses. Until recently , I ,nor my dentist, realise these were caused by XLH. All of my dental treatments are very painful and expensive.

The financial impact associated with managing XLH symptoms is adding more stress and worry. From paying for prescriptions, buying pain relief tools such as massager guns, TENS machine to funding treatments such as various physiotherapy types, massage sessions. I am now in need of more medical care . Only this year I had over 10 specialist appointments , additionally 2 minor procedures, MRI, CT ,countless X-rays and blood tests. Increasing healthcare expenses ,loss time at work add to my layer of stress and ambiguity ,further impacting my mental and overall wellbeing.

Recent NICE guidance rejecting burosumab for adults has shocked me and broken me to the core. I fear for my future and the impact it is going to have on my friends and family. I don't want to be a burden to society.
Thank you for giving me an opportunity to share my experiences with you. Please reconsider your initial guidance. Your reconsideration could be life changing.

Thank you,
[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
Dear Esteemed Members of the NICE Panel,	

I write to you as a 31-year-old woman named [redacted], navigating the relentless challenges of XLH. As a child I suffered with daily pain, and the treatments available (Phosphate Sandoz) were not tolerated by my body (giving me diarrhoea). I've therefore spent most of my life on no specific medication for XLH aside from constant painkillers, physio, acupuncture and massage. I also suffered mentally with the visual difference of the condition, having bowed legs and walking with a waddling gait meant that my self confidence was low and the constant pain was also mentally draining.

As the years have gone by that pain has gotten worse and secondary conditions such as arthritis have set in. Surgeries helped in the short term but long term are not a solution. More surgeries will be required, including repeat surgeries on what has been done as they have only 'patched up' the underlying concern.

Daily, I confront unrelenting pain, intensifying as the day unfolds. Sharp, breath-stealing episodes force me to halt, clinging to any support until the storm subsides. Each day, every muscle and joint aches, curtailing my mobility. Stiffness greets me each morning, requiring support even for basic movements.

Mobility constraints have reshaped my once-active life, shifting household responsibilities to my partner. Fatigue, a constant companion, disrupts my work, threatening my independence and burdening loved ones. Simple outings demand more planning due to the unpredictability of my energy levels and pain.

Medication, such as Phosphate Sandoz and Calcitriol is not effective for me, so I have no dedicated medication to help with XLH. The fear of calcification build-up and unstable phosphate levels adds to my distress.

Despite the recent joy of welcoming a new baby, my challenges persist. Rare and unknown, XLH often delays diagnosis and proper medical assistance, resulting in deformities and complications. I fear for the future of caring for my child given the worsening challenges I face now. I worry I will become a burden to her, as I already am reliant on my husband and family and friends for regular support.

Hearing loss, dental issues, and the financial strain of managing XLH symptoms amplify my anguish. Recent NICE guidance rejecting Burosumab for adults has shattered me. I implore you to reconsider; your decision holds the power to be life-changing.

Thank you for your time and consideration.

Sincerely,
[redacted]

Name	[redacted]

Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a person who has XLH and I have 2 adult children with xlh.
My son has been on burosumab for nearly 3 years and has less pain than before starting it and more energy. He takes less painkillers than before . He also tells me his hearing has improved. The hearing is a little discussed problem which is caused by xlh. But my hearing loss due to xlh has had a massive effect on my life and my work. My children were on the old fashioned treatment growing up ,of oral phosphate and calcitriol. He suffered many side effects such as kidney stones and often felt unwell when blood levels of calcium and parathyroid hormone increased. The old fashioned treatment is no good for adults or children. Better than nothing , but with many side effects.

My daughter has received no treatment since being an adult and has suffering hugely with foot pain and back pain. Is currently having MRI scans and treatment for foot and back pain and has had physiotherapy for her feet and back and has had it recently for arm pain. She suffers greatly with her mental health with all of this pain and immobility. The differences between the 2 of my children is remarkable. One is working and in less pain. The other not on burosumab has no real life at this time. Her life is medical appointments, scans, mri, blood tests, physio etc.

I have been on burosumab for nearly 3 years and initially was taking no pain killers at all and could walk for miles for the first time in my whole life. I am 60. I have more energy and prev to starting burosumab I had 2 fractures in my foot and left tibia. These healed very well on burosumab and I've had no further fractures. I had a short period on calcitriol a few years ago but it made my blood calcium and parathyroid hormone levels increase and I felt awful. Overall unwell with pain and nausea. So that treatment was no good for me.

My son and I can walk more steadily and with more confidence without being aware of every step, as previously. Never before in my life have I chosen to exercise or go for a walk. Ever. have since starting burosumab. Since starting burosumab I can walk more steadily, confidently and without having to think about every step I take. I have had no falls since starting this treatment and before I was having 2-3 per week! This has helped my confidence and going out. I feel it it essential to approve this treatment for adults to prevent the terrible deterioration that happens with xlh. If my body is constantly low in phosphate and other blood levels incorrect as previously mentioned, it causes numerous and calcification in the joints which makes the joints very stiff and painful. The muscles are weak and i have no energy and feel exhausted all the time.

As an adult I have had 4 major joint replacements, osteotomies, multiple arthroscopic surgery, months and months off from work as a nurse and having to claim disability benefits and not work and pay tax and national insurance. If I had been on burosumab I feel my life would have been better and different. I love my job and it's unbelievably frustrating not being able to do it. The lifetime of having xlh and no treatment up until the last few years has taken its toll on my body. The recent treatment has helped a lot. If there is anything that could prevent anyone feeling like I do now, then please give it to them.

I would also like to say about the financial aspect of having xlh with no treatment, having to borrow money from friends and family , claim benefits and all that is required when you live alone and have to have major surgery. It's also a big impact on mental health. At times I have thought about suicide daily. If f there was an effective available treatment, a person with xlh could live a close to 'normal' life without being such a drain on others and the government by multiple operations, inability to work and claiming benefits.

Please reconsider. This is an expensive treatment but there aren't that many adults with xlh and compared to a lifetime of pain, immobility, surgeries, expensive dental treatment , poor mental health and hearing issues which all require intervention from the NHS.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

As someone who had been on burosumab for approximately one and a half years, the difference to the quality of my life has been immense. Prior to taking this medication I was restricted to crutches and walking aids at only 26 years old, my mental health was at an all time low due to the incredible amount of daily pain I was in. I was seen by multiple health care professional from gps, physiotherapists, mental health counsellors and specialists. To say burosumab changed my health is an understatement, it's given me a completely different life and I couldn't imagine others not getting to experience this or it ending for myself. I now no longer need walking aids and my use of painkiller is very rare, I have not suffered any fractures or other issues during my burosumab journey and the amount of hospital care I have needed has reduced dramatically. Not to mention the amount of pain I experience daily has become far more manageable and I almost forget it's there sometime. This is something I never thought I would experienced, I truly believed my life would be unbearable by the sheer amount of daily pain I was in on a daily bases before this medication. It has also allowed me to

work regularly as prior to burosumab I was regularly having to take time off due to pain, almost having to leave working completely. I would like to add I am currently only 28 years old and the fear what will happen to my heath (both mental and physical) without this medication not to mention the typical pains your experience with aging, I just want to experience a good quality of life and with this medication I know I would.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	British Society for Paediatric Endocrinology and Diabetes (BSPED)
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

BPABG (British Paediatric & Adolescent Bone Group) believe it has

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

BPABG agrees with regards the clinical effectiveness interpretations, although would stress that there are emerging anecdotal patient reports that discontinuation of burosumab for adolescents once growth is completed results in deterioration of symptoms and quality of life.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Although the guidance is based on evidence from pivotal trials of adults who started burosumab having previously never received burosumab, BPABG feel it is important to consider in the evaluation and analysis on the maintenance of benefit of continuing burosumab in adolescents who have completed growth so that they do not develop the same adverse consequences (pain, stiffness, fatigue, poor mobility and quality of life) that adults who have not received this treatment demonstrate.

This is particularly true where there are families in which there are either adults who were started on burosumab under the EAM scheme and remain on it, or adolescents who transitioned to adulthood and remained on burosumab under the EAM scheme but in which there are other affected members who have transitioned to adult care but cannot now get treatment with burosumab because the EAM scheme is no longer active. This will also apply to family members who have not yet transitioned and remain on burosumab but will be obliged to stop treatment once they have

transitioned. This would result in the situation where some adult members are on treatment whilst others are not.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

None suggested by BPABG

- Section 1 - Recommendations, point 1.1

BPABG (British Paediatric & Adolescent Bone Group) believes this puts adolescents transitioning into adult services under significant mental and physical distress, having been receiving therapy that has significantly (both anecdotal and evidence-based) improved their symptoms (pain, fatigue, physical functioning) and quality of life. Evidence is clear that on discontinuation of treatment there is a deterioration to baseline, not only biochemically, but also in terms of symptoms and patient reported outcomes. Although there is the option of restarting conventional treatment, there is anecdotal information (presented at the British Society for Paediatric Endocrinology & Diabetes meeting in 2023) that suggests a deterioration in symptomatology (pain, fatigue, stiffness) and psychological well-being even in those restarting conventional treatment on completion of growth.

- Committee-discussion - Treatment population, point 3.4

From BPABG's perspective, it is important to consider the second two categories provided, given that this cohort has already experienced the "game-changer" that is burosumab, having gained benefit from this with regards their pain, fatigue, mobility, well-being and orthopaedic intervention. Although there is no published evidence to support this (MyXLH & XLH Registry will provide some answers on this), it is important to try to consider in modelling the psychological and quality of life impact on these individuals who will have to discontinue this life-changing treatment, with the comparatively suboptimal options of no treatment or restarting conventional treatment.

- Committee-discussion - Normalising serum phosphate levels, point 3.7

BPABG would agree with the clinical and patient experts with regards pain experienced by those discontinuing burosumab being different to those having experienced pain from ineffective conventional treatment their whole life. We would also add that the placebo effect was not seen throughout the PROs, particularly with WOMAC scores.

- Committee-discussion - Adjusting utilities for placebo effect, point 3.5

BPABG would suggest that the placebo effect is likely to be short-lived, which may not be as suitable when considering long-term impact (which is progressive as per anecdotal report from patients). Furthermore, important PRO measures (WOMAC) do not demonstrate any significant placebo effect in the pivotal trial.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	Add details here

Comments on the DG:

I am an adult who received the old treatment growing up but since being an adult I have received no treatment. I was put forward for a trial of burosumab but this never happened. I have felt neglected by medical staff my whole adult life with xlh.
I have constant back pain and can hardly walk as the pain in my feet is so bad. My hips and knees hurt. I am having a lot of medical help now. Some privately as there is no help on NHS for me. I have had surgery, scans, MRI , X-rays, physiotherapy, and have to see a private endodontost for dental treatment that is going to cost about £7000. I have not found a NHS dentist who knows about xlh and have had some horrific dental experiences I am waiting to have 8 root filings redone plus crowns. This is all because of XLH. My mental health is very poor and I feel I have no life. I am a 32 year old woman who has never been able to work for more than a few months here and there. This is because of having xlh as an adult. I desperately want to work and have a social life but cannot as I'm in too much pain and so exhausted and weak.
My younger brother is on burosumab and he is reducing his painkillers and has way more energy than I do and his dental issues have settled down. I missed the opportunity to go on burosumab which was not my fault at the time. I'd love to lead a more normal life and want to go out and go to work. Currently I'm at home claiming disability benefits and have little social life and cannot work.
Please approve this medication and enable adults like me to have a chance at less pain, more energy and ability to work and help others instead of me needing help all the time.
The cost of the medication is considerable but compared to a lifetime of no work, many surgeries, much intervention by medical staff on the NHS, poor mental health and feeling like a second class citizen due to disability. There are not many people with xlh who need burosumab. Please reconsider this and give burosumab to adults in the UK.
Thank you for reading.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am writing this on behalf of my thirty-two-year-old son, who has X-Linked Hypophosphatemia (XLH), Cerebral Palsy and Learning Difficulties.

[redacted] is a wheelchair user. He has a curvature of his spine and a barrel chest. He is in increasing pain with his joints and cannot walk independently. [redacted] has suffered hearing loss due to XLH and struggles to cope with constant tinnitus. He is also dealing with discomfort in his kidneys due to calcium build up. He was, in fact, brought to the brink of kidney failure by too much vitamin D – part of his treatment.

[redacted] cannot live independently and requires a carer. If Burosumab represents an opportunity to arrest degeneration or improve pain in XLH patients, then I believe it must be offered.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Not fully. Please see my comments.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Please consider the costs of not providing this treatment because it needs to be thoroughly investigated. If patients are given the medication they will

not be requiring so many other services from the NHS. This needs to be calculated because it would impact the cost effectiveness.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Please reconsider, I have added many comments explaining my reasons for this.

- Committee-discussion - The condition, point 3

I wish so very much that all adults could receive this medication because it is more than a physical condition it's a life long, altering and progressive sentence that causes so much pain and suffering. This condition has been around for such a long time and now it has been researched and treatment found its such a shame for this not to be considered and available. Please reconsider.

- Committee-discussion - XLH is a rare condition, point 3.1

I come from a family where several members have XLH. It has made a huge impact on our lives. I have watched my grandmother deteriorate so much that she was in lots of pain and had very restricted movements.
As I get older myself I also am facing a future where my own mobility will decrease and that is really sad. With each family member growing up then more and more people are being born with this condition.

- Committee-discussion - Effects on quality of life, point 3.1

I have lived with XLH all my life and it has had a negative impact on almost everything. I have not been able to participate in so many things due to fatigue, worry over injury and the impact of how long an injury would take to recover and through my joints just not allowing me to join in. I have spent time in hospitals, I have had fractures and I am in lots of pain.
I cannot do so many things due to XLH.

When I was going through fertility treatment I opted to have any embryos checked to see if they held this gene because I would not have wanted any child of mine to have this condition. Sadly I am not a mother. I had breast cancer and I am convinced that my XLH caused my healing to be prolonged. I would love to foster but my XLH is a massive part of the reason why I am not. This condition has caused me to lose out on a life I so very much wanted. The impact of this condition is devastating.

- Committee-discussion - Effects on quality of life, point 3.2

I also suffer with anxiety and migraines due to the stress of this condition. I work 4 days a week and this has such a toll on me that sometimes at the weekend I am completely exhausted and overwhelmed from trying to keep up and do what others are capable of at my age and it's so frustrating and

takes massive effort. Sometimes the stress of it all is not just physical but mental too.

- Committee-discussion -Treatment population, point 3.4

I score highly on my pain, when you live with constant pain you only realise it until it's gone. I would have loved to have been part of the trial but I was undergoing cancer treatment at the time. I am very grateful that my mother received it and my cousins and their children. I wish with all my heart that my sister could have the opportunity because she has a young son and she will need to be as fit and healthy as possible to take care of him and so that this doesn't effect his life too. I am always worrying about the future

- Committee-discussion - Normalising serum phosphate levels, point 3.7

I have heard such positive things from members of my family who have been able to have this treatment and I am so happy for them.

- Committee-discussion - Modelling excess fracture incidence, point 3.13

Fractures are the biggest worry and cause of pain. Especially as if I get a fracture then it takes a long time to heal and then is forever weakened. I feel like I'm living my life with less and less of a normal working body.

- Committee-discussion - Utility benefit for carers and family members, point 3.17

As I am from a family with XLH I have cared for my late Nanny and I am helpful to my mum and my sister because we all understand what we are dealing with. We are very good at supporting one another but we have our own limitations and that's the most frustrating part of this condition.

I have to rely more and more upon my husband to help me do simple tasks. I feel guilty that he misses out on so many things because of me. He is very supportive and understanding and it impacts on him too because he wants to share experiences with me and show me things but he knows that I am unable to do them.

As we know our limitations we always try and prepare and base our decisions so that we can be as independent as possible but this is not fair or fun. I have to make choices and sacrifices for something that others wouldn't even consider.

Sometimes friends and colleagues do not ask me to do things because they can see me struggling or know that I won't be able to. That's really sad too because I miss out or everyone misses out.

- Committee-discussion – Recommendations, point 3.21

As people get older with XLH they require more and more support and so this cost effectiveness is not clear. From mobility aids, hospital appointments, physio to people being unable to work this causes more strain on lots of vital services.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As a partner of and father to a son who both suffer from XLH I'd like to voice the difficulties I face as a carer and that we all face as a family.

Fortunately, my son has been born at a time when Burosumab is available to him and his treatment was started at the age of one. We have great hope based on current evidence that he will be able live a relatively normal life and isn't affected too greatly by irregular growth issues and the daily pain that my partner endures.

As a result of XLH, my partner has knocked-knees and osteoarthritis which causes her pain on a daily basis and affects her mobility, and ability to look after our son in the way she would like. This of course means I am heavily relied upon to do even basis tasks around our home such as carry our son up and down the stairs, lift him in and out of bed or the car and bathe him.

XLH greatly affects my partners mental health and she is worried about how her physical condition will deteriorate in the future and how she will cope with raising a young child. We would like a second child but we are both incredibly anxious about whether she can physically handle this.

XLH also means my partner requires a lot more rest than myself and sleepless nights with a newborn have been even more of a struggle. I am there to care for my son and take the pressure off her when I can but working a full time job makes this very difficult.

This of course affects my mental health also, as I am overtired, overworked, stressed and anxious.

I worry for my sons future should he not be able to continue taking Burosumab beyond his 18th birthday as I do for my partner should the medicine not be approved.

We have met with a number of XLH patients who have been part of the adult Burosumab trials and have only heard incredibly positive things. Those who were once barely mobile are now able to walk and care for themselves without pain.

I pray a decision is made that will vastly improve the physical and mental well-being of all adult XLH sufferers and their families.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am commenting on this subject as I am a user of the life changing drug burosumab. I was first diagnosed with XLH at the age of 2 and I have been under the continuous care of GOSH and UCLH. Prior to burosumab I spent over 25 years with fractures to my left femur. Now as a user for 5 years I can walk 9 holes of golf and function without pain. Please authorise the drug and do not put my 2 daughters through the pain I have experienced.
Kind regards
[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Mostly. It can be challenging to convey the challenges patients endure with XLH.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I believe the biggest thing to remember is each patient with XLH is an individual, and it is hard to list out what each patient suffers through living with a rare disease and chronic pain.

- Recommendations, point 1.2 “Why the committee made these recommendationsUsual treatment for XLH is oral phosphate and active vitamin D. Burosumab is used in the NHS for treating XLH in people under 18; this evaluation is for treating XLH in adults. Clinical trial evidence shows that burosumab increases the level of phosphate in the blood more effectively than placebo. This evidence also suggests that people having burosumab may have less pain and fatigue, and improved physical functioning compared with placebo in the short term, but this is uncertain. There are uncertainties in the assumptions used in the economic model, particularly about the long-term effects of burosumab on how long people live, fracture rates and the quality of life of people with XLH and their carers. And all of the cost-effectiveness estimates are above the range normally considered an acceptable use of NHS resources. So, burosumab is not recommended.”

This does not highlight what the disease looks like when compared to life on conventional treatment with phosphate and active vitamin D. Without Burosumab the disease continues to progress and deteriorate the skeleton, and due to the use of sodium phosphate at high doses daily to try and achieve a "normal" range of blood phosphate, you develop Nephrocalcinosis, thyroid issues, and lack of mineralization of the bones leading to poor healing of the bones following corrective surgeries and pseudofractures. Burosumab attacks the hormone FGF23 stopping the disease from progressing and allows the skeleton to mineralize and heal properly. The damage is already done in adult patients, but the burden on the healthcare system is so much more as an adult, and this drug could keep patients from needing extensive care and being able to live a better lifestyle slowing down the progression of XLH. Cost of the drug is high but when you look at what it costs patients annually to manage their disease and the impact on the healthcare system and their careers as contributing citizens, i'd think the cost of the drug becomes comparable to that loss.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am the father of a child (now adult) with XLH. Although he received the best care available at that time (high phosphate and alfacalcidol) he is left with a number of issues from the failure of that treatment to completely compensate for the lack of a functioning XLH protein. In particular, he experiences diminished energy levels, increasing bone pain, regular infections of his teeth often leading to root canal surgery and diminished mobility. At present he is a fully contributing member of society but I worry his ability to continue as a worker and tax payer could end sooner rather than later if he is not offered the opportunity to take Burasumab. It is clear from the reports of other XLH patients that this drug has changed their life. I want my son to have that opportunity so the quality of his life can be maintained.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

the costs of not treating patients has not been given enough attention as surely the financial cost of this will outweigh the cost of burosumab making it worthwhile to recommend for treatment

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

there was no consideration of the cost of not treating with burosumab which clearly indicates that in the long run it is the financially more sound option

- Are the recommendations sound and a suitable basis for guidance to the NHS?

no, this leaves many nhs patients abandoned and will increase the amount the NHS must invest into them in the long run. not to mention their experiences in their physical and emotional wellbeing.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am not sure of the law regarding disability discrimination, but the easiest way to ensure that someone is not subject to it, is to ensure that they are minimally disabled in the first place. the evaluation committee have that opportunity. additionally, the gender ratio of the incidence of XLH is 2:1 females to males so this decision will disproportionally affect females. Finally, removing the opportunity for this treatment impacts the opportunity and decisions that a couple may make as the impact on a pregnant persons body is enough without factoring in (preventable) chronic pain and risk of fracture.

- Recommendations, point 1.1 “Burosumab is not recommended, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) in adults.”

Taking me off this now, would have a huge impact upon my physical wellbeing as well as my emotional health as burosumab allows me to get out of the house and work full time and essentially gives me my livelihood. The problems caused by removing it include constant severe chronic pain and a severe deterioration in my physical health.

- Recommendations, point 1.1 “Burosumab is not recommended, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) in adults.”

What is recommended instead? is it not established elsewhere in the report that no viable alternatives exist?

- Recommendations, point 1.2 “This evidence also suggests that people having burosumab may have less pain and fatigue, and improved physical functioning compared with placebo in the short term, but this is uncertain.”

for me personally, as an XLH patient who has been on burosumab for 5 years, I can confirm that my legs are less bowed, resulting in an increase in height by approximately 2 inches and a huge reduction in stiffness and daily chronic joint pain.

- Information-about-burosumab – Price, point 2.2 “Price”

Have the costs of not treating patients been taken into consideration? for example, further medical procedures, clinical treatment investigation, not to mention things such as contribution to tax and the distribution of benefits to those patients who can no longer work.

- Committee-discussion - Effects on quality of life, point 3.2 “likelihood of social deprivation”

Additionally, the questions that get asked to patients who are having phosphate multiple times a day by peers and strangers can cause social anxiety, leading to a reduction of compliance to taking the medicine. I can confirm this to be the case with myself pre-burosumab and refuse to believe I am the only individual to have experienced this.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a 31 year old woman who was diagnosed with XLH at the age of 6 weeks. My mother is a spontaneous case and my sister was also diagnosed.

Traditional treatment of phosphate and calcitrol has been very unsuccessful in helping with the symptoms of my condition.

As a child the bowing in my legs was so severe you could easily fit a football through my legs. I have only grown to the height of 4ft6. My mobility is poor. I suffer from chronic pain all over my body and severe fatigue.

I suffer mentally and physically from this condition. I have tried to take my own life twice because of it and often have to have therapy sessions on the NHS - another significant cost.

I have active metabolic bone disease, arthritis and osteoporosis. I have an MRI scheduled next week because they want to see how arthritic my knee has become - it’s likely it will soon require a replacement. Another cost incurred to the NHS.

I have since gone through 15 operations to try and fix the deformities, none have been fully successful and I will be having another surgery next year. The cost to the NHS must be outstanding!

Speaking of surgery, each time I go under the knife I develop a new allergy to anaesthetics, pain medication and topical treatments like dressings. This

is making it extremely difficult to treat my condition and means I am very limited on medications I can take. My last allergy happened in April during surgery in which I reacted to morphine. I was under the care of ICU and ended up having to suffer taking only one paracetamol and one ibroprofen due to my height and weight. Imagine having major surgery and all you can be offered is that!

Due to my deformities and short stature, having children was also a difficult decision. I have had 2 babies, both via c-section. There have been complications so I am now under the care of a gynaecologist team and have had many expensive tests/treatments.

My skeleton is covered with pseudofractures and resembles that of a car crash victim. Every day of my life is one of pain and difficulty. To have what could potentially ease my symptoms and begin to heal my body taken away before I even got a chance to try it is heartbreaking. I'm not sure how much longer I can bear this strain.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

To Whom It May Concern,

I am writing this in support for my 10 year old daughter, [redacted] [redacted] DOB [redacted], relating to her ongoing treatment with burosumab for X linked hypophosphataemic rickets (XLH) to request NICE considers to continue to approve this therapy for children when they stop growing and become adults.

[redacted] was diagnosed at the age of 6 weeks with inherited XLH and struggled significantly in her early years with severe bone pain, immense fatigue, delayed walking and reduced mobility/ physical ability and difficulties engaging with childhood and schooling activities resulting in her needing DLA and increased staffing ratios at school.

Since commencing the burosumab therapy 5 years ago, the results have been nothing short of astonishing. She is now pain-free, is growing at a reasonable rate with minimal signs of rickettsial bowing and is able to thrive at school with an above average attendance and can now be involved with normal schooling activities such as playing sports and attending school trips, all of which was impossible whilst she was off the treatment.

Irregardless of the moral argument that a child should not be subjected to severe pain or limited opportunities when a highly effective treatment is available, there are numerous pragmatic reasons why continuation of burosumab is a logical decision.

The cost of providing additional SEND funding to a child who now requires no such additional support is high. When my daughter was young, she required 1:1 care due to her physical limitations. The current SEND finding is £6000 per child per year with more money available via possibly more via Top Up funding via an Element 3 funding request (please see the below guidance).

https://www.gov.uk/government/publications/high-needs-funding-arrangements-2023-to-2024/high-needs-funding-2023-to-2024-operational-guide

As a family we no longer need to claim DLA nor a carers allowance given her current good health, again saving the state further money. When she was younger she required significant additional DLA funding and my wife had to suspend her carer to provide near-constant care for her. This is no longer the case, again due to the burosumab treatment. My wife now works full time and we have not claimed DLA or carers allowance since she started treatment.

Cessation of treatment will inevitably result in increased symptoms requiring additional unnecessary medical treatment from primary, secondary or even tertiary health care at an increased cost to the state. There will also be a significant increase in the possibility she may require more invasive or even surgical interventions in future, as individuals with XLH often require correct orthopaedic surgeries, such as osteotomies, and are at increased risk of stress fractures of the long bones as well as degenerative condition of the joints. In addition, the phosphate supplementation she would require should burosumab be discontinued causes [redacted] significant gastrointestinal upset, namely severe diarrhoea, impacting her quality of life and school attendance.

I should also note that stopping burosumab would have a severely detrimental effect upon the quality of life of a young child, one who has had experience of what a more typical life can be like for a number of years due to her treatment.

There are significant costs associated with treatments that she would require if treatment were stopped, several examples of which are listed below:

Examples of costs of treatment – as per the NHS Payment Scheme (NHS Tarriff) 2023-2024 for musculoskeletal complications, ranging from low cost interventions such as Cognitive Behavioural Therapy for pain (code AB112 funded at £453/ year), to spinal epidural injections (AB20Z at £654 per procedure), intra articular therapeutic injections (AB2Z at £704 per

procedure), to surgical interventions ranging from minor foot procedures for trauma (HT35 at £1,364procedure) to very complex hip & knee procedures for non-trauma (HN80A at £25, 049 per procedure).

Give the possibility of chronic pain and limited physical activity if burosumab is discontinued, there are limitations regarding employment opportunities or the ability to remain in full time work; this loss to the Exchequer in terms of income tax (as well as the societal loss of an individual to contribute to their community due to physical ill health) coupled with the costs of additional medical treatment and sick pay starts to make less and less financial sense, especially as the costs of all biologic medications eventually drop after the original patent expires (the patent for Crysvita is expected to expire in a little over 4 years in February 2028) – please see the below reference.

https://www.pmprb-cepmb.gc.ca/CMFiles/VCU/VCU-Crysvita-en.pdf

Finally, as General Practitioner physicians in Primary Care, my wife and I would have to either reduce or indeed stop overall our clinical responsibilities to provide care for our daughter, should NICE decide to discontinue treatment with burosumab. This would also be compounded by the fact that as my wife also has XLH and receives burosumab (with extremely effective results), should my wife's treatment be stopped in 2024 (as the original NICE consultation period ends) I would have to reduce my working commitments as a GP earlier than planned in order not only to provide child care (due to my wife's physical limitations and disabilities/ chronic pain worsening should treatment be stopped) but to provide care for my wife as well. Given the current GP shortages at the time of writing (December 2023) at a time of record primary care demand (the average GP being responsible for 2300 patients, with 35 million appointments being provided in August 23 – please see the below reference), and the fact that NHS waiting lists at the time of writing remain extremely high at 7.7 million, the loss of experienced clinicians will further worsen theses difficulties and will overall cost the state even more money.

https://www.bma.org.uk/advice-and-support/nhs-delivery-and-workforce/pressures/pressures-in-general-practice-data-analysis

https://www.england.nhs.uk/long-read/monthly-operational-statistics-december-2023/

Given my arguments I hope NICE see fit to consider the continuation of burosumab therapy in those with XLH as I believe it will be cost effective in the long term.

[redacted]

[redacted]

Name	[redacted]

Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am [redacted], and I live in the United States. I am in my late sixties and have X-linked hypophosphatemia. I believe you are seriously under-appreciating the daily challenges of XLH adults, especially those related to calcification/enthesopathy and the progressive nature of the condition.

My symptoms were relatively mild until my early forties, when calcification and enthesopathy had manifested throughout my body, in all the major joints and spine, to a degree I could no longer ignore as I'd done for twenty years before that. I was trained as a lawyer, but despite the largely sitting nature of the job, I became disabled from that career by the age of forty. due to the mobility challenges, pain and overwhelming fatigue. I now work part-time as a self-employed fiction writer, and would work more if not for the pain and fatigue caused by my XLH.

I have been on burosumab for seven years, since the age of sixty-one. Prior treatment with vitamin D in my childhood, and phosphorus and calcitriol later, had been completely ineffective, so when I started burosumab, the pain, fatigue, and calcification-related muscle spasms had become debilitating, and were progressing so rapidly from year to year, that I anticipated becoming bedridden within just a year or two. I had only two to four functional hours per day to do everything that needed to be done, from hygiene and housework to work and hobbies and social interactions, but I knew, with a sense of terror, that even that functionality was rapidly shrinking.

Fortunately, while the burosumab was unable to reverse the existing calcification, it did end the spinal spasms, and slowed, if not entirely stopped the progression of the calcification/ethesopathy. I got to the point where I could engage in daily activities for three or even four times as long as I had before burosumab. Over the next several years, it felt like I was aging in reverse, able to do things I couldn't have done a decade before burosumab treatment started. And now, seven years after starting burosumab, I'm still feeling better than I was when I started the treatment, with no noticeable progression of the calcifications/enthesopathy, despite reaching an age where aging takes a toll on all bodies. I can now anticipate a future that allows me some continued mobility and the ability to engage in my writing career and hobbies, such as quilting and (limited) vegetable growing (in containers).

It would, of course, have been better if I'd been on treatment before my spine became entirely calcified so that I cannot turn my head, look up at grocery store shelves above eye level, or twist my torso, before my joints

became largely frozen due to calcification, before I could no longer stand up straight. But there was no effective treatment available for me when it would have been even more useful. There is an effective treatment for adult patients now, and they need it before their symptoms, like calcification/enthesopathy, become irreversible and totally disabling.

Adults with XLH have suffered long enough with no effective treatment, and now that there is an effective treatment that would enable patients to have a relatively normal life, it is unconscionable to deny them that treatment. Please reconsider your decision to deny access to burosumab for treatment of XLH in adults.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Burosumab has changed my life. Without it I would not be able to work full time and therefore lose my ability to support myself, losing my independence at only 23 years old. I can feel my pain, stiffness and fatigue increase when my medication is due, indicating clearly how much of a difference it makes to my daily life.

I am scared of what my future without Burosumab looks like, a future of pain and fatigue, lack of independence and income and lack of social life, loss of my passion for working in childcare due to physical inability to do so and worsening condition leading to potential fractures putting even more of a strain on the NHS.

XLH has such an impact on my daily life, I suffer from extreme fatigue, pain and stiffness on a daily basis. On Burosumab these symptoms are manageable and drastically reduced. I have never before been on a medication that manages my symptoms, this also has a big impact on my mental health, I feel I am able to live a more normal life on Burosumab. In the past being on phosphate has totalled up to countless minutes waiting for medication to dissolve multiple times a day which is highly impractical and interferes with trying to live my life as my day had to be planned around making sure I could get my medication. The phosphate medication is unpalatable, unpleasant and ineffective at managing my day to day symptoms, in addition to being wholly impractical and unconducive to working full time and living a full life as a 23 year old should be able to do.

Name	[redacted]
Role	Not specified

Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Adults and children should be able to have it

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

By the very nature of this medication being witheld - that is discrimination against a group of disabled people - those with XLH

I am a 32 year old woman with XLH.

I was diagnosed when I was 2 and received the old fashioned treatment for this condition when I was growing up. I can say without a doubt that if I had received Burosumab as a child it would have been far more effective and less traumatising than the old alternative/current treatment and I might not have needed surgery at all.I received major reconstructive limb surgery from ages 13-16. About 10/11 surgeries including removal of all metalwork.

I have not been trailed on Bursosumab. Since being an adult (17+) I have not received any care for anything to do with XLH and accessing anything for help has been futile and almost non-existent.

I can’t work, I need help with lots of my daily tasks and need adaptations/aids for things such as cleaning, shopping, driving, cooking, eating, showering going outside for my wellbeing.

I have headaches migraines, joint pain, muscles weakness, muscle pain, bone pain, dental problems, problems with hearing and ear discomfort, tinnitus, hyper mobility, back pain, stiffness, my feet hurt so much I can

barely walk anywhere or do anything anymore, can't travel or go on holidays even in my own country now. I am unable to make friends or form romantic relationships because I am basically not a part of the world due to all of this. Unable to exercise now too.

It goes without saying that this has had and still does have a major impact on my mental health which is almost non existent right now because I do not get to live a life like other people or even close to that. I am suicidal nearly all the time and have had, multiple suicide attempts due to being forced to live like this. I am dehumanised and live without dignity.

The financial impact is truly devastating especially because I can't work and am on benefits. I spend most of my income on health appointments, aids, treatments, adaptations. I live in a part of the country where I can't even access an NHS dentist because of how this condition affects me, let alone a specialist. I have to find my own way across the country at my own expense to pay for private dental care which costs thousands and thousands of pounds. And I have to do the same for umpteen scans, tests, MRI's etc across the country, also at my expense. I have had to been seen privately for physio, orthotics, specialist endodontist, private mental health help, urology. I literally have to somehow pay for the type of healthcare someone who earns a really good salary is on would have if they needed it.
Not to mention what modifications I need to make in my own home with whatever is left over.

I need help with almost everything but my brother and mother are on Burosumab and they have been able to work, meet people, drive, do their food shops, go on holidays/breaks and generally are able to take care of themselves better because they are on it.

I would relish the opportunity to be on Burosumab as my family and other people with XLH are doing much better on it. I have no quality of life because of this condition and for a medication like this to exist which could change my life and has changed so many others to be taken away or denied completely is beyond inhumane, unfair and unethical. There is no doubt in my mind that the 10/11 surgeries I had to go through and all the appointments, tests, scans, blood tests, MRI scans, trips to A&E, mental health crises, has and will continue to cost the NHS more than this medication ever could. Not to mention being on benefits my whole life and what that adds up to. I could be a semi functioning human being with some semblance of a life if I had this treatment. Contributing to society, being a part of something - rather than imprisoned in social housing due to my health - which I cannot help. It is literally life saving.

To put my family members and others on it to then take it away is beyond a gross moral contradiction. It's barbaric and inhumane. They are living human beings - as am I not lab rats. The cost of something like this should never be a reason that people living like me are not allowed to have it - not have it taken from them. We are being penalised for the very nature of this condition - that it is so rare that of course there are not going to be

thousands and thousands of people that need it because there aren't that many of us to use as proof. I am proof, so are my mother and brother and so is everyone else in this country both known and unknown.
I can't imagine what is going on in the mind of someone who could allow children to have this their whole life and then have it taken away from them in adulthood either. That is unbelievably dark and sadistic. And again totally immoral.

I hope you will read this and give this a second and proper consideration. Please try to put yourself in my shoes or imagine if this was your own family. Access to life changing medication is a basic human right - not a privilege. Thank you.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

As a parent of a child with XLH, I believe that crucial evidence on the withdrawal of Burosumab at 18 has not been fully considered and I would urge the committee to reconsider its decision. The decision not to recommend Burosumab for adults with XLH will be devastating for patients and their carers. The consequences of removing this life-changing medication at a crucial stage of development, increasing the pain and fatigue they experience just as they reach adulthood, will be severe and resonate throughout their lives. It will reduce their ability to live independent lives and support themselves, with implications for their mental health, while also increasing their dependence of family members and carers.

- Recommendations, point 1.2

Our child was diagnosed with spontaneous XLH at the age of three and a half and was initially treated with Phosphate Sandos. He began Burosumab as part of a clinical trial shortly before his sixth birthday.

From birth, he experienced severe leg pain which woke him most nights. He has had multiple painful dental abscesses which have resulted in teeth being removed under general anaesthetic and mental caps applied at the age of three. At the time he started being treated with Burosumab, he had severe bowing to his legs and was significantly shorter than his twin brother without XLH.

Oral phosphate was a difficult and unpleasant treatment to live with and its effectiveness appeared to be negligible.

Over the five and a half years that our son has been treated with Burosumab, life has felt much more normal and we have seen a dramatic improvement in his condition. His legs have straightened, his growth has improved, he rarely wakes with pain in the night. While he lacks the energy and stamina of his twin brother and peers, he lives a life that is largely comparable to theirs, participating in football and other sports and activities.

The prospect of Burosumab being withdrawn when our child reaches adolescence is devastating. This is a challenging period in most children's lives. The removal of Burosumab at this stage of life with the risk of increased pain and fatigue could impact on the the rest of our son's life, shaping both his physical and mental health. His potential to live a full, independent adult life is dependent on having continued access to Burosumab.

- Committee-discussion - Utility benefit for carers and family members

I am a mother to three children, one with XLH and two without. The demands on me as a caregiver to a child with XLH are dramatically different to those as a caregiver to children without XLH.

The first few years of my child's life were shaped by periods of severe pain during the day and waking with excruciating pain in the night. He was unable to walk any distance and we took a scooter with us every where we went. I needed to be available to take him to hospital visits, including multiple trips to have teeth removed due to abscesses, to administer the Phosphate Sandos he needed five times a day (including waking him at night for the final dose of the day) and to be available when fatigue meant that he was unable to cope with a full school day. The effects of continuous disrupted sleep due to him waking nightly in pain were felt by all members of the family.

XLH has had a limiting effect on the activities my child has the energy for and can participate in and this has impacted on our entire family. But his life and ours has been dramatically improved by Burosumab. His life is now comparable to that of his twin brother and his friends. He doesn't have their energy or stamina but he is able to participate. He can go to bed expecting to sleep through the night and not be woken by the horrific pain that was such a part of his early childhood experience. His legs are straight and he is a height that - while still shorter than may peers - does not attract unwanted attention at the secondary school he has just started. He can live a mostly normal life and for the first time in his lifetime, I have been able to return to work.

We had never heard of XLH until our child was diagnosed with the condition at the age of three and a half but it has shaped our family's lives over the last 11 years. It is heartbreaking for us to contemplate the implications for

our child if Burosumab stops when he reaches adulthood. His future will never be the same at that of his brothers and friends without XLH but Burosumab could give him a chance to live a full life, to have a career and live independently. We hope that NICE will recognise the limitations their decision not to recommend Burosumab for adults will have on the lives of our children and their families and reverse their decision.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Physical Health - My physical health is definitely declining. I'm 35 and have osteoarthritis in my hip, I have knocked knees, horrid knee pain and lower back pain. I ache and get very stiff in my knees, back and hips. I get extremely tired. I'm am a mum to a 1 year old and I struggle to play with him, carry him up and down stairs, and just generally move him around like in and out of the car and in and out of the pram

Mental Health - I've had to have counselling as I am deeply sad about the way my legs look. There is not a day that goes by that the way they look doesn't affect me. I get very depressed due to low confidence and low self esteem. I'm also very anxious that my knees are going to bend more and that my hips are going to give in. I also get very sad with the physical challenges that I have with my child, I want to be able to play with him without stiffness and be able to carry him comfortably. With this I get very anxious about my future, I'm terrified that this disease will prevent me from being the mum I want to be.

Support - I need constant support due to my mental health as I have frequent break downs. I rely on my partner to lift /carry especially our son. He runs errands for me and does quite a lot of the house work. He always baths our son as lifting him in and out of the bath is difficult. I also have to have a lot of support form my family to help with the house and my son as I get so tired and physically drained.

Hospital - I've recently had x-rays and MIR scans due to the pain in my knees, hips and lower back. I have an appointment with my doctor this month to discuss. I'm not on any medication currently. I was taking

Phosphate Sandoz but it was causing unpleasant side effects; bad stomach, vomiting and worst of all stiff joints. It would actually be more painful to walk when taking it so I decided it wasn't worth it even though my body needs it.

Over all my future scares me, I'm anxious that my body is going to give in and that I will be very limited physically. I love to be as active as possible and to be an interactive mum. I do not want this taken away from me. If anything, I believe having access to Burosumab could significantly improve my physical health. People that have this disease were born with it and will die with it, I think its only fair we have access to this new medication that targets the problem head on. It drastically increases phosphate levels and people that I have spoken with involved in Burosumab trials say their aches and pains have gone. They can walk further and have a much better quality of life. Please make the right and fair decision, it could change so many lives. Thank you

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Recommendation, point 1.1

I have never been offered Burosumab for my condition - X Linked hypophosphataemia. The oral phosphate and active vitamin D is intolerable affecting normal everyday activities

- Information-about-burosumab – Price, point 2.3

I would like to know how these figures compares to the endless orthopaedic procedures I have undergone. Operations, MRI, CT, Xrays etc and are on going for life.

- Committee-discussion - XLH is a rare condition, point 3.1

This is indeed a progressive condition. As I have aged my related health problems have increased. This makes me very anxious as I have passed it on to my daughter

- Committee-discussion - Committee-discussion - XLH is a rare condition, point 3.2

My symptoms started in childhood, however the emotional and mental side effects of the condition are immense. You are never free from the endless and complicated related problems. Teeth, hearing, bones, activities, stiffening, restricted movement. I have had to give up work and take early retirement. Buy a bungalow and buy an automatic car to help cope with life.

- Committee-discussion – Treatment pathway, point 3.3

Taking oral phosphates and active vitamin D is not living a normal daily life. Constant diarrhoea and stomach cramps means it is not an option for any length of time. It makes you a recluse as you can not attend everyday work place and eating out is not an option.

- Committee-discussion - Utility benefit for carers and family members, point 3,17

Over time I am definitely going to need care. At the moment my husband helps with every day activities I can not manage. This is a constant worry for my future as I don't want to progressively end up with more and more care. However if no further treatment is available this is inevitable which is a scary thought. Every month that goes by with no treatment is a month lost to this condition.

- Committee-discussion - Equality, point 3,19

I would not have taken early retirement if I had received treatment which meant I could still enjoy going to work. It is very important for me to keep socially involved with work/hobbies. Its a shame this condition affects the ability to work normally - therefore deprivation of being socially active is a main problem.

- Committee-discussion - Recommendations – 3.21

Surely the cost of burosumab per individual is nothing compared to the orthopaedic operations/scans/x-rays etc ongoing for life. This is a cost calculated but there is no cost given to the emotional and mental health side.

Name	[redacted]
Role	Not Specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

I do not feel the lived experience of those with XLH has been taken into account. Anecdotally across the XLH community, those adults who have been taking Burosumab have had excellent outcomes and the progressive nature of the disease has been paused. There needs to be further consideration of the lived experience from patients to co-design the future optimal treatment. Patients need Burosumab for XLH which is a disease with minimal understanding across society. Further consideration needs to be given to the conventional treatment which is not tolerated by the majority of patients, resulting in it not being taken and being ineffective.

After a specific time period will the cost of the medication reduce (when the patent expires)? This could result in reduced costs for administration resulting in a more cost effective successful treatment.

Please can we understand why this has not gone via the 'Highly Specialised Technology' (HST) route. It should be explicit why it was approved via the HST route for paediatrics but not for adults. What is the evidence that this is not HST?

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The XLH population is small and patients suffer awful progressive symptoms. As a sufferer of XLH I feel let down by a system that puts cost before health and wellbeing in a country that prides itself on its welfare state. Would the decision have been different if Burosumab had been assessed via the HST route like it was done in paediatrics?

I do not feel the clinical effectiveness has been recognised through this review. Adult patients have had excellent outcomes by taking Burosumab and these have not been reflected through the guidance.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I do no believe the recommendations are of a sound and suitable basis for NHS guidance. They do not recognise the terrible impact which XLH can have on individuals. This is a rare disease and not well understood by the majority. The clinical experts recommend Burosumab and the patients are benefiting from it. Therefore, it should be available as a treatment option for

Consultants to prescribe if necessary. Not all patients will require the treatment but some individuals are deteriorating at an alarming rate physically, socially and mentally. Further understanding needs to be gained on how Burosumab has improved the lives of those who take it. It is not acceptable to just stop treatment at 18 years old based on age and not clinical requirement or need.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am particular interested in inequalities relating to age and location.

Age being a protected characteristic should mean there should be no discrimination however, it according to this draft guidance Burosumab will be withdrawn at the age of 18. Firstly treatment should not be withdrawn based on age when skeletal maturity may not have been met. Secondly, XLH is a deteriorating condition which can be prevented through the use of continued treatment (current conventional treatment is not tolerated by individuals). Treatment should not be blocked just because of an age bracket. The need for a 25 year old with XLH to receive Burosumab might be more than a 12 year old with extremely mild symptoms.

It is acknowledged that Burosumab has been approved in Scotland. If it is not approved for adults in England then we are creating an inequality across the UK.

- Recommendation – point 1.1

Having been on Burosumab since the clinical trials started in the UK I can absolutely confirm the medication has changed my life. I am the fittest and healthiest I have been. It has given me hope that my children (grown up) will not suffer with the deterioration that I have done as an adult. XLH didn't impact me much until I was in my 30's. It was only then that I started to suffer from pain, stiffness, weakness and fatigue. Since starting Burosumab these symptoms have reduced and I am far happier.

This inherited bone condition can impact on quality of life and mortality on a similar scale to someone who has diabetes; however, there is less understanding and no adequate treatment available (apart from Burosumab). This causes an inequality for something we have no control over. Diabetes may be self inflicted and the patient will receive adequate treatment whilst XLH is inherited and we receive no effective treatment.

- Recommendation – point 1.2, There are uncertainties in the assumptions used in the economic model, particularly about the long-term effects of burosumab on how long people live, fracture rates and the quality of life of people with XLH and their carers. And all of

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

Burosumab has prevented much additional input from both primary and secondary care. Since starting Burosumab the treatment and input required has significantly reduced. Less x-rays, less Consultant appointments, less blood tests, less transport costs, less GP visits, less pharmacy input, less physiotherapy, less medication costs for secondary factors (such as anti-depressants), no requirements for renal input and ultrasound scans, no additional MRI scans etc.

My quality of life has improved and I no longer have to worry about taking oral medications that make me sick. I can socialise with friends, volunteer in the local primary school (I'm retired). I can now go on holiday without worrying about sickness associated with oral medications. I'm physically stronger which allows me to participate fully independently with my activities of daily living. Previously my husband and grown up children would have to help me with shopping. Now I can do this independently. I was worried my husband would have increased carer burden as I age, however, now he no longer needs to care for me.

- information-about-burosumab - Marketing authorisation indication point 2.1

By stopping medication when an individual reaches 18, creates an inequality and discrimination against the protected characteristic of age. If the clinical specialists and Consultants believe this medication is the correct treatment for an individual they should be able to administer this without being restricted by age. An individual at 25 years old (with significant symptoms and high rate of deterioration) may benefit from Burosumab more than an individual at 13 years old (with mild symptoms). When looking at the XLH community, many patients start to deteriorate in the 30's which is when the costs of input will skyrocket and quality of life will deteriorate (preventable with Burosumab).

- information-about-burosumab - Marketing authorisation indication point 2.1

My son did not develop as quick as his peers and did not stop growing until in his 20's. The children's services continued his care past 18 years old for this reason and he was taking up to 16 k-phos 2 tables per day. In current times this would mean his optimal treatment (Burosumab) would stop at 18 years old, despite being so effective as his body matures.

Due to not receiving Burosumab as a child, my son had extensive reconstructive surgery. Without Burosumab, he now runs the risk of his deformity returning and needing further extensive surgery. Think of the impact this has on his mental, physical and social health, knowing it is preventable.

- committee-discussion - Effects on quality of life point 3.2

Before starting Burosumab I suffered from excessive pain, stiffness and fatigue on a daily basis. Although I have been able to work through my adult life, my XLH symptoms have prevented me from achieving my potential through my career. I have never been able to progress due to the progressive fatigue, pain and stiffness experienced on a daily basis. Although now retired, these symptoms have virtually resolved since taking Burosumab. I still get some stiffness which has developed since the age of 30 but it is much improved since taking Burosumab.

I started taking Burosumab before I retired. If it wasn't for Burosumab I would have needed early retirement which I could not afford. This was a scary situation when supporting a family and having a medical condition through no fault of my own. The relief of symptoms that Burosumab brought allowed me to continue working and actually enjoying my final working years. Now I am able to volunteer due to Burosumab keeping my symptoms at bay.

- committee-discussion - Effects on quality of life point 3.2. For adults, symptoms include osteomalacia (soft, weak bones), bone pain, fractures, pseudofractures, joint stiffness, restricted movement, neurological complications, hearing impairments, spinal cord compression, dental problems, muscle weakness and fatigue.

This is a vast range of symptoms which unfortunately I have developed as my disease has progressed. It is a lot to deal with when there is little understanding and empathy for the condition. I am now in my late 60's. Since taking Burosumab these symptoms have reduced and my quality of life has dramatically improved. Despite friends of the same age starting to have reduced mobility, mine has recently improved and my pain levels have decreased to zero. My stiff joints have eased and I can now exercise in a gym on a daily basis. Prior to Burosumab I lived a very sedentary lifestyle. As a consequence, my mental health and social health have improved.

My hearing is much better since starting Burosumab and I can now engage in conversations with friends when the room is loud. Previously I couldn't hear conversations properly so didn't participate in some activities.

My teeth had also deteriorated as my XLH progressed. I have had many teeth removed resulting in the need for dentures. I did not want dentures but couldn't have any alternative treatment because my bones were not strong enough for implants. After taking Burosumab for a certain time, my dentist has now fitted me with implants due to the increased bone strength and adequate healing. Despite having to pay for this dentistry work privately the results have been outstanding. I would not have been able to achieve these results without Burosumab.

However, it has to be noted that my deteriorating teeth occurred over the period of my life without Burosumab and I have had to pay privately for the

dental implants. Other sufferers of XLH will have deteriorating teeth if not taking Burosumab and may not be able to afford dental implants which causes inequality. Burosumab could prevent this inequality. It is also worth noting, that the incidence rate of dental abscesses since starting Burosumab has significantly reduced for my son.

- committee-discussion - Disutility for incident fractures point 3.16.

Prior to taking Burosumab I suffered from spontaneous fractures which wouldn't heal and contributed to my progressive pain and stiffness. Now on Burosumab I don't fracture and my previous fractures have healed. I no longer require frequent x-rays or MRI scans.

Due to historic deformity causing deterioration of my knee joints, I have recently had 2 total knee replacements. Previously, the orthopaedic department were concerned about operating due to my bone health and healing rate. Since being on Burosumab I have had my knee replacements with no complications and excellent healing. My bones feel strong and I am excelling compared to peers who have had knee replacements at the same time. This has been noted by other clinical staff such as physiotherapists. The Consultants are extremely happy with my progress. Without Burosumab I would not have achieved the same excellent outcomes from my knee replacements. I am sure that if my son is to remain on Burosumab through adulthood, he will not require the knee replacements like I have.

- committee-discussion - Utility benefit for carers and family members point 3.17.

Since starting on Burosumab the carer burden on my family has reduced. My husband and sons were having increasing demands put on them to support me through daily life. Simple tasks such as shopping, washing clothes, making the bed were becoming increasingly effortful and tiring. The pain, stiffness and fatigue would prevent me from doing these tasks and I was worried this would exacerbate so I then needed support washing, bathing and dressing. I had already started having difficulties getting dressed and putting shoes on. This caused a detrimental impact to my social health as I did not want to burden family by asking them to help me get ready to see friends and consequently my mental health. Since starting Burosumab, the support needed by my sons and my husband has reduced. 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. I now enjoy these activities whilst previously they filled me with dread.

Me, my husband and my sons are now much happier as we can spend quality, enjoyable time together rather than just helping me with jobs and chores.

Name	[redacted]
Role	Not Specified

Other role	Not Specified
Organisation	Not Specified
Location	Not Specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No I don't I don't think that the evidence has clearly taken into account the decline in economic productivity that XLH individuals will have if their burosumab treatment is stopped. Also the quality of life impact on those involved.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Cost effectiveness a difficult thing to measure but no I do not think this is a reasonable interpretation. As an example, I am a professional who, since receiving treatment with burosumab, I have been able to return to work full time. I am fully independent now, have a school age child and am off all benefits. I contribute well to soceity and support others in my role as a GP. Should this treatment be removed, I will return to being unable to work fully because of the pain, mobility issues and numerous other problems. This will be the same for my daughter when her treatment is discontinued. In the long run this will cost more to the economy than giving us the treatment and enabling us to work. Then on top of it, there is the huge improvement in quality of life which should not be underestimated.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the information being collated has not been able to be followed up for long enough due to the limited time to collect data. We do not know yet about all the long term benefits and the the problems that will occur on stopping treatment. My 9 year old has been on treatment since the age of 5. On starting it, she needed additional support and a 1:1 a lot of the time for mobility issues and marked disability. Now she is able to play hockey for the school. It has been that transformational. Prior to treatment she cried and had pain when standing for even 10 minutes - the thought of this coming back when she stops is quite honestly terrifying. In addition the fact that treatment has been agreed in Scotland for longer to reassess tells us that longer term data is simply not available yet so as a bare minimum, England should do the same.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I strongly believe that stopping this treatment after commencing it in children and adults is discrimination against individuals with disabilities. There is an effective treatment available which will get cheaper over time and it will be denied to people who desperately need it.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I feel that there is an age discrimination in that children who have been on burosumab and have all done so well are being denied it once they transition from paediatric clinic to adult clinic. This usually happens between ages 16 -18 whereas the stages of skeletal maturity can be as late as 21 years of age, or even older.
As young people will often be ‘filling out’ weight-wise at this stage this will put extra strain on bones and joints and therefore bowing and other skeletal abnormalities that have healed may deteriorate thereby negating the excellent effects that burosumab has been shown to have on children.
Therefore I feel that burosumab should be approved for all adults where shown to be clinically appropriate but feel very strongly that it should be approved for all children when transitioning to adult care.

Name	[redacted]
Role	Not specified
Other role	Not Specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

No, see letter pasted below - you have not taken into account anything other than immediate costs. What about the delayed costs related to disablility and people's inability to work, please see below.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, please see below. You agree that clinically it is an effective treatment (and there are no other suitable replacements) but cost effectiveness is based on a year of life in a young person (eg 16) being worth the same as someone in their 90's.
Stopping this treatment will mean that people in their teens and onwards may cease to be able to hold down jobs and remain economically active into adulthood. This has not been included.

Also I cannot see it has taken into account that Burosumab comes of patent in 4 years so the relative cost should then drop significantly.

• Are the recommendations sound and a suitable basis for guidance to the NHS?

No, as mentioned below.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. I believe that you are discriminating against young people with chronic illnesses who would other be given a chance of a good quality of life so discrimination against age.

To Whom It May Concern,

I am writing this in support:
1) For my 10 year old daughter, [redacted] [redacted] DOB [redacted], relating to her ongoing treatment with burosumab for X linked hypophosphataemic rickets (XLH) to request NICE considers to continue to approve this therapy for children when they stop growing and become adults.
2) For myself to be allowed to continue to receive burosumab as an adult for X linked hypohosphataemic rickets as an adult who is currently already receiving treatment.

[redacted] was diagnosed at the age of 6 weeks with inherited XLH and struggled significantly in her early years with severe bone pain, immense fatigue, delayed walking and reduced mobility/ physical ability and difficulties engaging with childhood and schooling activities resulting in her needing DLA and increased staffing ratios at school. She also had chronic diarrhoea on the phosphate Sandoz alternative meaning she struggled to attain faecal continence. Frequent accidents caused much distress. She

woke frequently at night due to pain, could not keep up with her friends, was chronically tired and quite honestly did not have a good quality of life. Her legs were also becoming progressively bowed.

Since commencing the burosumab therapy 5 years ago, the results have been nothing short of astonishing. She is now pain-free, is growing at a reasonable rate with minimal signs of rickettsial bowing, and is able to thrive ats school with an above average attendance and is able to be involved with normal schooling activities such as playing sports and attending school trips, all of which was impossible whilst she was off the treatment. She loves dance, competes in sports teams and quite honestly has been described by her school as a new child. She no longer has any additional support in any area. She calls it her magic medicine.

There is also very much a moral argument that a child should not be subjected to severe pain or limited opportunities when a highly effective treatment is available, there are numerous pragmatic reasons why continuation of burosumab is a logical decision. Currently, we have been told, that when she stops growing, burosumab will be discontinued.
The cost of providing additional SEND funding to a child who now requires no such additional support is high. When my daughter was young, she required 1:1 care due to her physical limitations. The current SEND finding is £6000 per child per year with more money available via possibly more via Top Up funding via an Element 3 funding request (please see the below guidance).

https://www.gov.uk/government/publications/high-needs-funding-arrangements-2023-to-2024/high-needs-funding-2023-to-2024-operational-guide

As a family we no longer need to claim DLA nor a carers allowance given her current good health, again saving the state further money. When she was younger she required significant additional DLA funding and we were in the process of applying for mobility allowance. I had to stop my career as a GP to provide near-constant care for her as she was so fatigued she could only manage half days at school and was ill very frequently. This is no longer the case, again due to the burosumab treatment. My wife now works full time and we have not claimed DLA or carers allowance since she started treatment. [redacted] now has above normal school attendance. Cessation of treatment will inevitably result in increased, requiring additional unnecessary medical treatment from primary, secondary or even tertiary health care at an increased cost to the state. There will also be a significant increase in the possibility she may require more invasive or even surgical interventions in future, as individuals with XLH often require correct orthopaedic surgeries, such as osteotomies, and are at increased risk of stress fractures of the long bones as well as degenerative condition of the joints. This does not even take into account quality of life for a child who has been shown what a good quality of life can be like for a number of years. She is also likely to develop numerous stress fractures which is what I did before commencing treatment. [redacted] is a clever child and wants to be a

doctor or a vet when she grows up. Given the degree of frailty she had before starting treatment (and the fact that her symptoms have since started to come back when her doses needed to be adjusted) tells me that the stopping of burosumab for her as a young adult will cost her her future career too. This of course would have an economic impact too and this is similar for other children too.

There are also significant costs associated with treatments that she would require if treatment were stopped, several examples of which are listed below:

Examples of costs of treatment – as per the NHS Payment Scheme (NHS Tarriff) 2023-2024 for musculoskeletal complications, ranging from low cost interventions such as Cognitive Behavioural Therapy for pain (code AB112 funded at £453/ year), to spinal epidural injections (AB20Z at £654 per procedure), intra articular therapeutic injections (AB2Z at £704 per procedure), to surgical interventions ranging from minor foot procedures for trauma (HT35 at £1,364procedure) to very complex hip & knee procedures for non-trauma (HN80A at £25, 049 per procedure). This does not take into account increased GP and other healthcare appointments.
Give the almost certainty of chronic pain and limited physical activity if burosumab is discontinued, there are limitations regarding employment opportunities or the ability to remain in full time work; this loss to the Exchequer in terms of income tax (as well as the societal loss of an individual to contribute to their community due to physical ill health) coupled with the costs of additional medical treatment and sick pay starts to make less and less financial sense, especially a the costs of all biologic medications eventually drop after the original patent expires (the patent for Crysvita is expected to expire in a little over 4 years in February 2028) – please see the below reference.
https://www.pmprb-cepmb.gc.ca/CMFiles/VCU/VCU-Crysvita-en.pdf

Finally, as General Practitioner physicians in Primary Care, I would have to either reduce or indeed stop overall our clinical responsibilities to provide care for [redacted] daughter, should NICE decide to discontinue treatment with burosumab. Given the current GP shortages at the time of writing (December 2023) at a time of record primary care demand (the average GP being responsible for 2300 patients, with 35 million appointments being provided in August 23 – please see the below reference), and the fact that NHS waiting lists at the time of writing remain extremely high at 7.7 million, the loss of experienced clinicians will further worsen theses difficulties and will overall cost the state even more money.
https://www.bma.org.uk/advice-and-support/nhs-delivery-and-workforce/pressures/pressures-in-general-practice-data-analysis
https://www.england.nhs.uk/long-read/monthly-operational-statistics-december-2023/

Myself, [redacted]
Stopping Burosumab for adults will result in myself having to end treatment. Before I commenced burosumab, my working ability had dropped hugely

and I struggled with immense fatigue, bone pain, especially at night causing broken sleep. Recurrent stress fractures and growing numbers of stress fractures.

I had to stop working at one point because of my own symptoms and then return at massively reduced hours (8 hours a week). Since commencing burosumab:

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. As a result I can sleep and function and as mentioned I am able to work full time. Incredibly, 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. I could not work effectively.

Since getting burosumab, the pain and fatigue are so much better and it will honestly be life destroying stopping this treatment. I will need someone to help care for me and my daughter meaning my husband's ability to work will be compromised too.The NHS will in effect lose two full time GPs as well as a child who wants to do the same. Given that the meds are not long to come off patent. I strongly believe this is an unethical decision.

Our family sadly lost our daughter [redacted] (unaffected by XLH) to cancer at the age of 4 several years ago. There was no treatment that was effective for her cancer type (a malignant tumour). It was devastating but we understood that everything that could be done was.
To now be faced with there being an effective treatment available for our other daughter [redacted] and myself but it to be denied on cost when it will have a huge impact on quality of life and future for us all just seems incredibly wrong and unethical. For my daughter also to have lost her sister to cancer, then to watch first how stopping treatment for me affects me and to know that she will come next is unthinkable given all we have gone through.

As a GP, I completely understand the issue of cost but what you are currently looking at is immediate costs, not the long-term costs economically as a whole in terms of losing productive working people to the economy. My husband and I have given our lives to the NHS and continue to want to do so. It seems incredibly wrong that all this will be taken away.
Given my arguments I hope NICE see fit to consider the continuation of Burosumab therapy in those with XLH as I believe it will be cost effective in the long term.
Thank you for your time and I would be grateful to see you reverse your draft decision.

Kind regards,
[redacted]

Name	[redacted]
Role	Not Specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I was born in 1971 and after dislocating my shoulder at the age of three, a specialist paediatrician at Leighton Hospital viewed my x-rays, completely by chance and noticed abnormal structure of the bone. He diagnosed me as having renal rickets. This condition is nowadays known as XLH, (X-Linked Hypophosphatemia, a disorder characterised by low levels of phosphate in the blood. Phosphate levels are low because phosphate is abnormally processed in the kidneys, which causes a loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets). My XLH was a spontaneous case, so I am the only member of my family to have it.

Very little was known about the condition at that stage, and I was prescribed Vitamin D, Calcitriol and Sandoz Phosphate soluble tablets. I spent a lot of time in hospital with related monitoring of the relevant levels and once, was in critical care following a coma like episode which turned out to be Hypercalcemia, an excess of calcium.

I was short in stature, (I am only 5’2” now) and my legs started to bow at around age 5. I also had lots of dental abscesses some of which required hospital surgery, (it was only much later in life I found out this was because of XLH. My walking gait became very affected by my bowed legs.

I lead a fairly normal life, the main effect being different to my friends and suffering some taunts etc. At age 19 in 1991 I accepted the offer of having my left femur bowing corrected by a very big orthopaedic surgery at the Royal Hallamshire hospital in Sheffield which involved cutting my femur in two places and fitting a ‘nail’ (a long rod) all the way down the middle of my femur with screws to hold it in place. I had the same procedure done on my right femur in 1993.

The surgery improved my gait and increased my height slightly. However, after the first operation my hip began to lock and it was discovered that the nail they had put in my femur was too long, (they didn’t have the correct size available at the time) and was catching and hooking on my muscles which was extremely painful and debilitating. They had to remove the nail and fit the correct size nail.

The next issue I had was severe pain in my feet which left me unable to walk. After many years trying to find help it was thought to be that the pain was just due to the abnormal, and changed, biomechanics of my legs.

Throughout this time, I was still suffering with dental abscesses and despite countless root canal treatments the roots of my teeth were dying (due to XLH) and I started to have to have lots of teeth removed.

I also started to suffer from hearing loss, vertigo and tinnitus in my right ear, which led to violent ‘drop’ attacks of nausea and vomiting which necessitated bedrest. which was eventually diagnosed as Meniere’s Disease, again, probably caused by XLH. I had several surgeries, injections etc to try and ease the symptoms but to little avail.

In the year 1999 I began surgery to straighten my lower legs. The technology had progressed, and this procedure was done by fitting an Ilizarov, (an external cage), to my realigned tibia and fibula. This was done at The Royal Liverpool Hospital by Mr Nyagam and his team. Although living with the frames on my legs for 9 months per leg was extremely difficult and painful, the surgery was successful and again improved my gait and height. Unfortunately, at this stage of technology, it was inevitable that patients living with this external cage would get very severe bone infections, of which I suffered several, sometimes resulting in hospital stays. I believe that it may have been these infections that triggered my next and ongoing additional health issues. Over a period of years I began to suffer extreme fatigue, cognitive impairment, increased pain and a general decline in wellbeing. I was eventually diagnosed with ME/CFS, (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome).

Although the XLH and related operations made life very difficult I managed to lead a reasonably normal life. I began working for my families very successful engine remanufacturing business in 1988 and did vocational day release and night school education for seven years eventually becoming highly qualified and experienced and all aspects of the business including automotive technician, advanced automotive machining, office management, accounting, sales, marketing etc. I eventually became a director in the business, and worked very hard at my role, aiming to improve sales and customer service to the best of my abilities. I married and we had two boys, [redacted] in 1997 and [redacted] in 2000. IHowever, the worsening ME/CFS symptoms unfortunately meant I had to take time off work and was eventually too poorly to work from around the year 2005. I worked extremely hard at trying a myriad of treatments to find improvements for my ME/CFS eventually spending three months as in inpatient in a specialist ME/CFS clinic in Romford, Essex. Sadly, I could not find anything that improved my symptoms. My poor health contributed to my divorce from my wife in 2010. At this point I was living alone, completely unable to work and bedbound for a lot of the time.

In around 2017, although I had always suffered with bone/muscle/joint pain, these symptoms worsened over a period of years, and I was diagnosed with Osteoarthritis. Over these years, and to the present day, the pain in my hands, elbows, neck, shoulders, hips, femurs, knees and feet increased and the mixture of all these symptoms has left me with a mainly bedbound poor quality of life where I am in constant pain. I can only lie, sit or stand for

limited amounts of time so my life is spent managing my pain. This has taken a toll on my mental health, and I suffer from anxiety and depression. One of my biggest regrets is that I've missed out on a lot of my boy's lives and activities.

My right knee is completely worn out, it is bone on bone and needs replacing. However, the orthopaedic team at Liverpool have said they wouldn't replace the knee before a surgery to restraighten my right femur, (the result of the original surgery is not great). I have been given a date for my preoperative assessment, but I really don't feel that I'm well enough to undergo this surgery. I was desperate for Burosumab to receive funding as this would give me a chance at improving some of my symptoms and then hopefully feel well enough to have the surgery. It's particularly frustrating because my XLH doctor at Sheffield Northern General Metabolic unit have said they already prescribe Burosumab to eligible patients and have seen fantastic results.

Through being involved with the wonderful charity XLHUK, (they commissioned a short film about my story which can be seen here https://www.youtube.com/watch?v=Nvts9QeqdAU I have heard many other suffers similar and worse stories and also the life changing benefits of Burosumab. I would beg you to approve funding of this potentially life changing treatment to at least give me and my fellow sufferers a chance at improving our poor qualities of life.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a male with XLH in my late twenties. I work an office job. I have never had access to Burosumab. XLH has impacted all areas of my life. I suffer from chronic bone pain, stiffness, fatigue, depression, and regular dental infections. XLH has prevented me from living a full life, consistently inhibiting my attempts to progress in my career, fitness, & social life. Every day is a struggle, I have often contemplated suicide.

Being able to access this medicine was my hope for a better future. I have met others with XLH at patient support events and seen first-hand how severely those with the disease decline with age. Without this medicine I expect I will not be able to work later in life, and will transition from being a high earning taxpayer to being dependant on state support to survive well before retirement age. Those I have met with XLH who have been able to access Burosumab on the early trial have described it as life changing.

I feel deeply let down by this decision, the committee has rejected the treatment for adults based on cost-effectiveness, but accepts this treatment is both clinically effective and that there is no effective alternative treatment. While the treatment is expensive per individual it is both affordable due to the very low number of people affected, and necessary due to the severity of the disease and lack of alternative treatments. This treatment should be offered to adults with XLH as part of The Highly Specialised Technologies Programme as it meets all four routing criteria defined by NICE. The assessment of the committee that there are close to 1,000 affected adults in England is a gross overestimate.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am a sixty two year old woman who was diagnosed with a spontaneous case of XLH (X-Linked Hypophosphatemia) at birth.

Every year until the age of fourteen, I had my legs broken and straightened. I slipped in and out of comas induced by vitamin D and twice suffered cardiac arrest on the operating table.
I have severe osteoarthritis. I wake up crying out in pain as my knee dislocates. I have a permanent headache because my degrading vertebrae are causing pressure on my spinal cord. I have tinnitus because XLH is a bone condition, and you hear using your bones.
I have passed XLH on to my two children, both of whom are wheelchair users. I am a carer for my son who has cerebral palsy and learning difficulties and my daughter became disabled in 2011 when her illness became much more aggressive. My children will not grow up to look after me in my old age. They will not even be able to look after one another when I am gone. They cannot care for themselves or live independently.
I suffered a hairline hip fracture in my twenties and fractured my ribs in my forties. Even when the break is surgical, as with having both of my femurs broken and straightened in my fifties, the healing time is prolonged for someone with XLH. My left femur has never fully healed, it still troubles me and I have nerve damage from the operation.
My pain is becoming increasingly difficult to deal with and there is no let up. XLH is degenerative so my joints will only get worse. It is becoming

increasingly difficult for me to drive. I've been reliant on a vehicle with an automatic transmission for some time but even that is becoming a struggle. Burosumab has shown positive effects which can only improve quality of life and reduce the need for expensive orthopaedic surgeries for adults with XLH.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

Review of Burosumab for XLH Rickets
From [redacted], patient at UCLH Hospital

I am a 60 year old patient at the Metabolic Department at UCLH with XLH Rickets and have had monthly injections of Burosumab for the past 3 years. I have had mobility and pain issues from the condition from a very young age and operations for this, including left and right bilateral osteotomies, 2 cervical with metalwork and and 1 thoracic full laminectomies and left and right hip and knee replacements, steroid injections in both hands to help with pain.

As a result of these operations I now have other medical issues - 2 DVT's, a damaged autonomic nervous system and nerve damage in my neck and shoulder that is hyper sensitive and causes relentless pain.
My pain levels have not lessened from going on Burosumab, as I already have/had many issues with the condition including pain, mobility, stiffness, inability of work, my social and personal relations are very afffected and as a by-product of all of this my moods and mental health are greatly affected too.

However, since taking Burosumbab, my MRI, bone scan and X-ray reports show that I have had no further deterioration or new issues in my condition since taking the drug, which is wonderful and is being attributed to taking the injections.

Given the extent of how the condition has affected me, I cannot imagine what would happen to me physically should the injections be stopped. 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.

This condition affected my grandmother, father and uncle and I watched them all deteriorate, have restricted movement and suffer continual pain and surgeries for their whole lives, that prospect haunts me daily.
Over the years I have had to give so many things up and almost everything I can still do comes with a payback price of pain, stiffness or lack of mobility and this has a very great affect on my mental wellbeing.
I am a very social person but have become very stressed about going to places I don't know and even small gatherings make me very anxious about going and on edge when there.

My husband is an amazing man and works his working life around me. He has had to take over most household chores now and it causes me great stress and upset that he has to do or assist me with so much, both physically and socially.

Everything I do ends up being calculated, measured and stressful and this takes the enjoyment out of nearly everything - I have to measure every activity with deciding if the during and/or after price is worth it. Some things are just no longer possible for me at all and I have had to try and come to terms with them as they happen. However, having just become a Grandmother, not being able to help my daughter and granddaughter in most physical ways is really affecting me greatly, as I cannot be left alone with the baby because I cannot physically do the necessary things. I feel angry, guilty and very miserable about this.

My sister, her two sons and my daughter also have XLH and all have been affected to some extent so far. However my nephew, [redacted] 23 years old is most affected and also a patient at UCLH on Burosumab for the past couple of years. He has noticed remarkable improvement in his mobility and pain levels since then. He even turned down a job abroad because it would mean he could no longer get the medication if he went and he considered that too high a price for him.

It is hard to put into one review how important controlling this condition is to me and no doubt others, who are now suffering the affects of it. This drug brings hope to me and anyone else who endures its effects.
I am trying to contact my nephew to submit his own feedback and hope I can do this in time, as there have been issues logging the data, which I hope has not affected the number of people logging their reviews.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

I do not believe all the patient evidence and stories have been considered. This disease significantly impacts the lives of those suffering with it and close relatives and families.

Have we been able to demonstrate that those younger adult patients on Burosumab have shown less deterioration than those not taking Burosumab?

Have we been able to account for the cost of disease progression if Burosumab is not taken. Eg. significant life long input included carer burden. (There is a workforce shortage within the NHS and social care.)

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not believe they are as not all evidence has been truly considered. Objective data from clinical trials has been utilised but qualitative data from patient experience needs further exploration. XLH is not widely understood and I do not wish for a decision to be made now that NICE will regret in future. Scotland has approved Burosumab in adults therefore, the same decision should be followed to prevent inequalities across the UK.

It is known that many other countries follow the decisions of NICE in the UK so this decision has to be correct otherwise it will negatively impact patients across the globe.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not believe they are. They go against what patients and clinical experts believe is the best care. The guidelines do not promote clinical excellence which is ironic for NICE.

Being a young adult who takes Burosumab I can confirm it has completely changed my life. I now have no pain, stiffness or fatigue. My physical, social and mental health has been positively transformed.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Particularly age. There is discrimination if we are to stop medication at the age of 18 when clinical experts agree it will still benefit adults. The skeletal system does not reach maturity until after 18 and continues to deteriorate as XLH patients progress through life. It is important to appreciate only those

living with XLH can truly understand this therefore, further exploration of XLH experience is needed.

- Recommendation – point 1.1, Burosumab is not recommended, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) in adults.

There is ethical issues with stopping treatment for those patients who receiving Burosumab as a child when they enter adulthood. Humans do not reach skeletal maturity until further into adulthood and XLH is a progressive deteriorating condition meaning Burosumab is required for longer periods that just childhood. Preventing patients of certain age groups from receiving a drug could be seen as an inequality due to age being a protected characteristic.

- Recommendation – point 1.2, This evidence also suggests that people having burosumab may have less pain and fatigue, and improved physical functioning compared with placebo in the short term, but this is uncertain.

Having lived with XLH throughout my life and receiving optimal care through a Metabolic Bone Centre I can confirm Burosumab does indeed reduce pain and fatigue whilst boosting physical and mental health. Despite receiving extensive treatment (phosphate, active vitamin D and many surgeries) I have not been as well as I am on Burosumab. Daily pain levels in my achilles tendons have reduced from 8/10 to 0/10 when all previous treatment failed.

- Recommendation – point 1.2, all of the cost-effectiveness estimates are above the range normally considered an acceptable use of NHS resources. So, burosumab is not recommended.

The XLH population is considered to be very small. Previous literature has suggested the incidence rate is 1 in 20,000 but more recent literature states 1 in 100,000 meaning there are less patients that would need funding for Burosumab. The inability of utilising economies of scale should not impact this life changing disease. (Especially when considering Burosumab is already funded for paediatrics and within Scotland. This means the additional adults requiring this medication is actually a small number.)

- information-about-burosumab – Price, point 2.3, The list prices per vial of solution for injection are £2,992 for 10 mg/1 ml, £5,984 for 20 mg/1 ml, and £8,976 for 30 mg/1 ml (excluding VAT; BNF online accessed November 2023).

Previously when taking vitamin D and phosphate supplements I would require frequent scans including MRI, x-rays, bone density, 6 month hospital appointments with my Endocrinologist, 3 monthly blood tests, regular physiotherapy (privately funded for, which is a recognised healthcare inequality), annual kidney scans plus annual appointments with a

Consultant urologist, 3 monthly visits to the GP and pharmacy to source K-Phos 2 (notoriously difficult to access with local pharmacists disagreeing with hospital pharmacists on safe alternatives). Previously I have also undergone extensive orthopaedic surgery requiring regular input (ranging from weekly to 6 monthly) over a period of 10 years. During this time I was requiring 8 X-rays at every appointment.

Since taking Burosumab I now have 1 telephone appointment with my endocrinologist and blood tests in primary care every 9 months. We have agreed that this could be moved to longer and I have suggested a Patient Initiated Follow Up pathway as I do not require any regular input or investigations.

This demonstrates a balance cost efficiency, resource efficiency and good quality care meaning the NHS resource can be used to treat those who need additional input.

The impact on my work has also been significant. Taking time off work for appointments and investigations has significantly reduced which reduces the impact of healthcare inequalities. We know that some public members do not receive treatment because they cannot afford time off work.

- committee-discussion - Normalising serum phosphate levels, point 3.7, The clinical and patient experts noted that pain experienced by adults with XLH who stop burosumab treatment from childhood would differ to pain experienced by someone who has lived with it for their whole life because of ineffective conventional treatment

Being an adult who previously didn't take Burosumab as a child I can confirm that my pain, stiffness and fatigue has been eliminated since starting Burosumab. This has been with no side effects whatsoever. (When taking vitamin D and Phosphate I regularly had intolerable side effects including diarrhoea which meant I had to skip doses to live in current society.)

- committee-discussion - Modelling excess mortality risk from XLH, point 3.10.

An inequality which often goes un-noticed with XLH is the awareness that it does increase mortality. I struggle to source travel insurance, life insurance, and private healthcare insurance due to XLH being known to increase mortality but not being a recognised condition on databases. An example was when I had to consult directly with the Medical Director at HSBC life insurance to persuade them to offer me appropriate cover.

- committee-discussion - Modelling excess mortality risk from XLH, point 3.11, long-term effects such as kidney damage

As an individual receiving conventional care for XLH I struggle mentally and and struggle to accept that I had kidney damage from my mid 20's. The

thought of returning to conventional treatment which negatively impacts organs is worrying. I do not think I will take the conventional medication if Burosumab is stopped. Having a medical condition which requires treatment that puts my at higher mortality risks through no fault of my own depresses me.

- committee-discussion - Modelling excess mortality risk from XLH, point 3.11, The committee was aware that XLH may affect a person's ability to do paid work because of both the condition itself and caring for family members, however the extent of social deprivation associated with XLH and its link to mortality rates remained unclear.

I currently work within healthcare and previously required reasonable adjustments plus removal from the on-call rota. Since taking Burosumab and stopping conventional treatment all reasonable adjustments have been stopped and I no longer require any changes to my on-call duties. I previously did not think I could continue working in the NHS due to the progressive nature of XLH but since taking Burosumab I now have no worry about a life long career within the NHS and doing what I love - Improving the lives of other patients.

- committee-discussion - Modelling excess fracture incidence. Point 3.13, The committee concluded that real-world evidence is needed to support the assumption and exploring different morbidity benefits from a reduction in excess fracture incidence with burosumab is appropriate.

I have been lucky to receive Burosumab as a young adult. My peers have not been in this fortunate position. Since taking Burosumab, my peers have developed fractures and use crutches to mobilise. I have developed no fractures, use no walking aids and I'm able to participate in sports/exercise every evening. Without Burosumab I would be following the same route as my peers have done on their conventional treatment.

My Mother who has XLH deteriorated significantly in her late 20's/30's and beyond including fractures) and I have not done so whilst taking Burosumab.

- committee-discussion - Utility benefit for carers and family members, point 3.17, The committee suggested that any exploration of the potential benefit of burosumab on carer utility should only include carers without XLH, to avoid potentially double-counting the utility benefits of burosumab.

This feels unfair as I with XLH also care for my Mother. The carer burden for me (with XLH and my Bother (does not have XLH) and Father (does not have XLH) has been significantly reduced since my Mother started receiving Burosumab.

I will currently not start a family of my own due to risk of my children having XLH. Knowing the impact the disease has on my Mother and how much I have been required to support her prevents me from bringing children into the world. It is not ethical for me to have children and rely on them to care for me and my XLH as I deteriorate. It is also not ethical for me to bring children into this work who may have XLH, be treated with Burosumab until 18 years of age and then have a life of deterioration when Burosumab is stopped.

If Burosumab is approved in adults I will feel more confident to have children as I will not deteriorate and they will not have their treatment stopped in adulthood.

To confirm, since taking Burosumab my Mother has needed less support performing activities of daily living. She is able to go shopping on her own, catch buses into town to meet friends and has even joined a local gym. Despite being in retirement, her activity levels, health and independence is improving whilst her friends are deteriorating.

- committee-discussion – Equality, point 3.19, This is because XLH affects the ability of people with XLH and their carers across generations to do paid work. Because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not an equality issue.

I have noted that if I was not on Burosumab I would not be able to continue my work long term within the NHS. This would negatively impact my career progression compared to peers. If Burosumab is continued I will be able to continue working within the NHS.

- committee-discussion – recommendations, 3.20.

Considering the importance of individuals self managing their own healthcare needs this decision is very disappointing. Without Burosumab I cause a significant burden on the primary and secondary care services which utilises valuable capacity that is needed for others.

The positive change in my physical, social and mental health since moving from conventional treatment to Burosumab has been unexpected and outstanding.

If Burosumab is not recommended in adults it will also significantly negatively impact the transitional period between paediatric and adult services which is a priority for the NHS.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified

Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I would really appreciate it if you reconsider the decision to make burosumab available for people with xhl to give us a better and healthier future.

At the moment I am 38 years old and struggling with walking, I need a new hip and my back is so stiff I cannot bent over to tie my shoe laces.

The pain in the hip and back are getting worse by the week it feels, it is hard for me to get in and out of a car because of the back being so soar and stiff. I walk like a 90 year old and if I drop something on the floor someone else need to bend down to pick it up.

I have a big crack in my Femur bone that doesn't heal proper and a lot of small stress fractures in other bones of my body. It is just a matter of time until something breaks completely. As you can imagine it brings a lot of pain and discomfort.

I hope you can help us to give us a brighter and more mobile pain free future.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Dont think so. XLh needs help.

We just found months ago about XLH. He is luckily a UK citizen. He needs this medication as an adult, we truly wish you can help him. Thats why we came here. Please help.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified

Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

• Has all of the relevant evidence been taken into account?

As parents of a child with XLH, we believe that not all the evidence on the withdrawal of Burosumab at 18 has been considered, and would like the committee to reconsider its decision to not recommend Burosumab for adults. The impact of this decision on both carers and patients will be devastating. Reverting to phosphate treatment, a far less effective treatment, for those accustomed to Burosumab will increase pain and suffering for patients at a vulnerable time in their life. Has the committee considered a recomendation aboutnot removing Burosumab from those that have started treatment already?

• Are the recommendations sound and a suitable basis for guidance to the NHS?

We dont believe they are, has the committee given enough consideration to the Psychological and Social impacts of stopping Burosumab on children at an extremely vulnerable point in their life for their psychological and social development?

- committee-discussion - Normalising serum phosphate levels, point 3.7.

our child is currently aged 11 and has been on Burosumab since the age of 5. He was diagnosed with spontaneous XLH when he was 3yrs old. So he was on Phosphate treatment for 18 months. We have noticed an transformative difference in his mobility and general health since being on Burosumab. He plays football and, whilst he still gets tired, and is shorter than other children, his movement and enjoyment of life is generally similar to that of his twin brother, who does not have XLH.

Since being on Burosumab we have noticed he gets less pain in the evenings, and we need to give him Ibuprofen far less regularly than when he was on Phosphate Sandoz. We are concerned that increased exposure to pain at, what is for most adolescents, a challenging stage of life will result in a significant decline in his mental health and limit his chances at enjoying a full and rewarding life in the future. The result of the withdrawl of Bursomab is as yet unknown, but the costs in terms of mental health, pain reduction therapy and treatment, dentistry over his life could be significant. To continue to benefit from the effects of Burosumab in childhood, we believe that Buros should be continued into adulthood for those that have started. To take the treatment away abruptly would mean that [redacted] would have to deal with increased and unknown pain at a what is, for non-XLH children, an academically and socially difficult stage of life. The risk we see is that all of the good things that Burosumab has enabled [redacted] to do; Play

football, hang out with friends, develop interests get suddenly stopped because he has to deal with a lot more pain and fatigue than during his childhood. In effect, by not allowing him to continue with the Burosumab, Pain will be inflicted on him and his life could be radically impacted.

- committee-discussion - Utility benefit for carers and family members, point 3.17.

With Burosumab our child has a normal life. We are both able to work and support our three children. It is unknown what the impact would be for children who have been accustomed to Burosumab during childhood suddenly having the medication withdraw. But what is known is that adults on phosphate treatment suffer from increased risk of; fractures, dental health problems and problems with kidneys and other parts of the endocrine system. The impact on the family caring for a child with XLH is unknown. With Burosumab both adults in our family have been able to return to work, this has meant that the whole family has benefitted from stability. The removal of Burosumab will likely mean that someone in the family will need to spend large amounts of time caring for [redacted], more frequent hospital visits, increased dental problems and surgery, increased psychological support and counselling. Burosumab currently reduces the burden on society, because everyone in the family can contribute. As a result of the removal of Burosumab, it could mean other family members having to give up work or education in order to support [redacted]. This will be likely to add to the psychological impacts of XLH on [redacted] that have already documented. [redacted] is a very bright and generally happy boy, but he does already need psychological support from his teachers at school because of XLH. An increase in the use of opiods, or increased feeling of dependency when he is just becoming more independent will be likely to have devestating effects for his whole life. It may limit his life choices and trigger other forms of dependency such as opioid or alcohol dependency. We note that figures for increased treatments in psychological counselling, alcohol and drug dependency are not included in the cost benefit analysis.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am a thirty five year old woman with X-Linked Hypophosphatemia (XLH), a degenerative bone condition. The older I get, the thinner my bones become, the more the cartilage in my joints disintegrates, the weaker my muscles become, the more the integrity of the enamel on my teeth breaks down. Some people with this condition have their spinal cords compressed, lose their hearing and have their ligaments stiffen to hardtack.

I lost my twenties to chronic illness because my body simply ran out of the energy it needed to function. I was a capable, intelligent, high-achieving student whose peers turned to her for advice and academic support. Since 2011, I have been unable to care for myself. I use a wheelchair, battle a tidal wave of symptoms every day and have to rely on my aging parents to take care of me and my brother who has both XLH and Cerebral Palsy. Every day I am fatigued to the point that my body has to make critical decisions about functionality. Cognitive function, unlike heart and lung function, is not essential to life so that's something my body will willingly sacrifice, along with digestion. I slur my words and struggle to find them. I double over with cramps and sleep for hours, like a cat, wherever I can curl up. And, when I wake, I feel neither refreshed or renewed.
The quality of my sleep is poor because if I stay still for too long, my joints lock and will try to dislocate when I move. If I stand for any period of time it begins to feel as though my heel bones will rupture through the soles of my feet. I walk as though I have been riding a horse for forty-eight hours; unfortunately, I don't have the hip mobility to mount a bike, never mind a horse.

My childhood was radically better than my mother's because there was a new medication on offer: Phosphate Sandoz. Taking that medication, however, caused my parathyroids to become overactive, flooding my body with calcium and leaving me extremely ill between the ages of eleven and thirteen. At thirteen I had three and a half parathyroids removed. A procedure which has proved to be disastrous for my long-term health. Now, as I empathise with seventy-three-year-old father over the skeletal and cognitive symptoms we share, and struggle with increasing pain, there has been another breakthrough in mediation which might curtail my pain and slow the degeneration of my musculoskeletal system.
My quality of life is poor. I pay for every activity I undertake, from making a phone call to leaving the house. The nausea, pain and fatigue are crippling. I am a talented sculptor and writer who would like to contribute in so many ways but I am hamstrung by my health.

I have regressed from promising young woman to child who, on my worst days, has to submit to being washed, pass my cutlery to my parents because I am shaking so badly I cannot cut my own food, and come to terms with being housebound.

My joints are deteriorating at a more rapid pace since turning thirty, forcing me to return to Phosphate Sandoz which makes me feel wretchedly unwell. People with XLH also suffer from UTIs, kidney stones - due to the build-up

of calcium in the kidneys - and from spontaneous abscesses which require root canal treatment and, very often in my case, the prescribing of morphine.

I know there aren't many of us with XLH but for those living with the condition every day, the impact can be catastrophic. I am tough, I have had to be, but I would like to have a chance at a better quality of life. As the positive impact of Burosumab in adults with XLH has been recognised, in think it would serve the NHS in terms of long-term cost effectiveness for NICE to approve the treatment. Any beneficial treatment has knock on effects. Less pain means greater mobility means improved muscle strength means better joints support means a lowered risk of accidents and fractures. The cumulative effect of this across the population of adults with XLH can only save the National Health Service money in the long term.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Have they understood the long term impact on individuals physical and mental health. Also the longer term costs of not providing the treatment as other medications are not effective

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don't believe that the study takes in to account the whole life costs of not providing the treatment based on the longer term medical and care costs if this treatment is not provided. Also ongoing costs and impact on quality of life to the individual and mental impacts on family and carers.
Also its not clear what deal the NHS would get if they committed to it across the UK rather than just Scotland

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No as I don't believe they take in to account quality of life for the individual and families impacted by this condition and how it impacts on day to day life with pain, trying to do day to day things with children and family.

Name	[redacted]

Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I'm a friend and carer for [redacted], 60, an adult with XLH, who has received vietually no treatment for XLH over her whole life. (Just one dhort time on phosphate and calcitriol which made her feel a lot worse and affected her blood calcium levels negatively.

Since being on burosumab, [redacted] has had less immobility, had no falls, and can stand and walk a lot easier and with more confidence. She previously had fractures and pseudo fractures and has had none since being on burosumab. Unfortunately [redacted] has not been treated for XLH her whole life and has issues from not receiving any treatment. However in spite of this, since starting burosumab she has had no falls but was falling frequently previously up to 3 times a week. She has had no further fractures, having sustained two just before starting treatment. She was taking painkillers including opiates prior to treatment. She can now walk with more confidence and not feeling she has to take care with every step. Her energy levels have improved and after her up coming hip replacement surgery, she will be able and willing to return to working as a registered nurse.

I help [redacted] with the usual household chores and DIY around the house that she herself cannot manage. I also provide emotional and support for her.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

Dear Sir/Madam,

Due to the recent XLH meeting regarding the future treatment with Burosumab I would like to share with you how XLH has defined my life.

I was born with XLH in the late fifties, my late mother and my two sisters also have XLH, as do most of their children.

As a child I had surgery on both legs at age 6 and throughout my childhood I suffered many fractures, spending many months in and out of plaster. When I was only 18 years old I started married life and a career, I began having more fractures and spent a whole year in plaster, during that time I lost my job.

For the next 30 years I have had so many operations including internal fixations in both Tibias (right leg was operated on twice) and in the left thigh. I have spent so many hours, days and weeks of my adult life in hospitals, undergoing complex operations, physio and so many other clinic appointments.

I feel sad that I lost out on my chosen career and lost various job opportunities due to XLH affecting my mobility. I also know my daughters have lost out as well due to their XLH.
Every day has to be planned around how far I could walk or how tired and fatigued I became. I tried my very best to bring up my family and when I look back I know it was so hard keeping up with everything and everyone else while coping with day to day pain and suffering.

In May 2021 I started my treatment with Burosumab. It has made such a huge difference to my life, my wellbeing and even my mental health. Within a few months I felt so well and strong, something I have never felt until now! I have even named the medication my " Super Hero Drug"
I never knew what my body had been missing until then.
When you are born with a medical condition you don't know any different, but I do now! It's wonderful to feel normal, to be able to do day to day activities and not feel any pain, tired and worn out. I can now go out all day, no planning needed and still have energy the next day without stiffness and painful aching legs. I can stay at an event longer and don't have to worry about getting home because I'll be fatigued the next day.
I now only need to go to clinic appointments once a year and have regular blood tests. My life is no longer tied around hospitals and my close friends cannot believe the change in me.

As a child and most of my adult life living with XLH I now know the impact that Burosumab has had. It has transformed my life and the thought of not being able to access this treatment in the future is so deeply worrying. It is so upsetting I do not want to go back to the way I was before, it would be devastating for me and the whole family. I am also concerned that as I get older and as I already have arthritis and other age related ailments occur, how will I be affected if I'm no longer taking Burosumab to treat the XLH? I want and hope to be as fit as possible for as long as possible. My late mother suffered so much in her last 25 years. In her 50s she could not stand at all for more than a few minutes, was reliant on a walker in her 60s (inside her bungalow too), she then became wheelchair bound and completely unable to stand due to multiple fracture in both legs, eventually she needed to be cared for 2 paid carers, four times a day. It's important to note that this is entirely due to her mobility and inability to move, dress

herself. I dearly hope that in the future this will not be necessary for people with XLH.
I feel very lucky and grateful to have a close family and husband who have given me so much support and have given up so much of their own lives, also my dear lifelong close friends who are always there for me.
I wish for my now adult children who have XLH to have the same access to this drug for their future health as they have seen the remarkable changes within me.
I hope you find this insight to my life living with XLH and what it was like prior to and what it's like now having The Super Hero drug Burosumab.

Kind regards,
[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Dear committee, I am a 62 year old woman with XLH that was passed on to me by my mother, I have 2 older sisters.I have 2 grown up children who also have XLH and a grandchild that has not inherited the gene. I have had several operation from the age of 16 having my legs straightened as they were extremely bowed to having fractures in my femur that needed to have a rod put in place, I have had two operations on my knee as there were bits of loss bone that caused the knee to lock and I would be unable to walk without pain, a few years ago I had a complex hip replacement and another rod in the other femur.

Before burosumab I worked part-time as a special needs teacher because I couldn't manage working more due to the throbbing bone pain and how tired I got during and after each class. It was agreed that my hours were reduced so that I could have extra time to recover from each morning. This obviously took a large financial pressure on us through loss of earnings.

I always felt less than as in not reaching my full potential not just in work but all other areas, socially not having the energy to go out feeling uncomfortable whilst out because of pain and not being able to move freely as a would become stiff in my hips and back and would need help to move about which in turn made me anxious that also would get knocked into in larger settings so I avoided them.
I could not stand to cook dinner or go out shopping so my husband took care of all of this, including hanging the washing and keeping the garden tidy.
The strain this puts on a relationship has been tremendous as it feels I am a constant burden and felt conscious that others do not fully understand.

When I was 56 I was disabled and felt my future was bleak. I would constantly need pain relief during the day and night so that I could at least sleep with the bone and muscle pain.

Since being on burosumab my whole life has changed! I have zero no pain, stiffness or tiredness. I have been able to delay my other hip replacement for another year as there is no pain. After 6 months of being on burosumab, I went full-time at a larger school, doing what I love. I am always shocked with how it's changed me as I am on my feet constantly, and do not need to worry about what I am doing later that day.

I cook meals and do so much more that was originally left for my husband. I also go food shopping and have lately been cutting the grass in the summer. We have been going out together socially and I feel that I can genuinely join in more with our friends. My emotional side has also improved as I can cope with the day ahead and do not need any pain relief. I even managed a hike for the first time up a mountain in Wales!

I also have not had any tooth abscesses and only get minor leg cramps from overdoing it as I think my body is not used to the extra exercise.

I fear greatly for my future if I had to stop burosumab, as I expect to go straight back to being in severe bone and muscle pain, reducing my hours at work, and taking a reduction in income. I may even need surgery right away. I don't even want to think about the surgery recovery time as it is always incredibly difficult with XLH. My outlook will again be bleak and would deteriorate physically, emotionally and socially, so much so that I feel I have been given a sort of life sentence of disability. I really do feel this could be all avoided if I continued burosumab.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
I cannot emphasise enough the positive effect that Burosumab has had on my daughter's life over the last 4 years. Whilst she still gets pain it is manageable and allows her to work and live a relatively normal life. This would not have been possible had she still been on her previous medication due to the fact that it merely kept her levels balanced but did not manage the symptoms she experiences. She does still experience pain and fatigue but, through our experience of her taking Burosumab compared to her previous medication, I am absolutely convinced that this would be increased tenfold. Burosumab has given her, and our family, a quality of life that would otherwise have not been possible due to the pain and tiredness that she would be experiencing. I implore you to reconsider your initial guidance	

and give her and other adults the opportunity to live the fullest lives they can. I appreciate that Burosumab is not cheap, nothing worth having ever is. However, please consider this against the benefits it provides and the lessened impact it will have on the public purse overall.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

Re: Burosumab
I am a life long sufferer of XLH. My mobility has been severely impacted because of this. XLH caused my bones in my legs to deform, I also sustained fractures. My confidence was very low, and it effected my self esteem. Five years ago I could only walk using walking aids. We had to sell our family home, and down size to a ground floor flat as I could no long manage to climb the stairs. I was being prescribed phosphates and calcium, which I took for years, but it had very little effect on my condition. In 2020 I was given the opportunity to go on the trial for Burosumab. The results have been amazing. I no longer need walking aids, I don't feel fatigued, I can now climb a flight of stairs, my mobility is so much improved and I feel more confident and positive. I also have a much lower need for pain relief.

In 2021 I had limb correction surgery on my left tibia and fibula and had a Taylor Spatial frame fitted while the bones healed. In January this year I had a steel rod fitted into my right femur to correct a deformity, I recovered well from both surgeries.
I urge you to please consider allowing the continued use of Burosumab for adults with XLH. For me it has been positively life changing.
[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

Life with XLH is a life lived on the outside looking in. It excludes a lot of activity which most people manage on a daily basis. As an adult born in 1962 I now face daily pain, decreased mobility and stiffness all of which are

increasing with age. Fatigue is now impacting greatly on a daily basis as anything physical needs to be done in the morning because as afternoon approaches the fatigue sets in to the point of feeling sick. Evenings are spent resting or sleeping which excludes most social activities. Getting used to declining anything social particularly which is physical means its out of the question.

Employment choices are restricted more often than not needing desk based/sitting occupation which in turn needs to increased stiffness when the need to move happens. With XLH sufferers need the freedom to sit/stand/walk as needed to avoid some of the pain and stiffness.
XLH means risk of stress fractures during life. I have had many in the bones of my feet and a tibial stress fracture causing decreased mobility for the duration of healing. They cannot be operated on. At one time I had 2 stress fractures on each foot and it was during the treatment of these with ultrasound (which was not helping) that I started on Burosumab. Within a month CT scan showed fractures uniting and within 2 months, healed allowing me to walk again. This was my first insight to how this medication can be of vital help to adults.

Another very reassuring factor is that my phosphate levels are now within the normal range which has never been the case for my entire life. To me this proves that Burosumab is enabling normal function of my kidneys and in itself is most definitely worthy of continuation.
XLH requires plenty of physical help with everyday tasks such as housework and personal care. Difficulties dressing as joints and ligaments seize up with calcification which restricts movements required for washing and dressing oneself. Public transport travel is off the agenda as stairs are not possible, walking between platforms ie., tube stations and getting on and off trains with gaps between platform and train step are highly dangerous.

This condition is degenerative and progressive and adulthood requires more surgery for joint replacements at the time of life when we are faced with slower recovery, anxiety about the surgery itself, any complications which occur as our joints are not "standard". Life lived on the outside looking in necessitates stoicism and strength of character, whether or not your personality allies to these, the condition forces you to become so.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
• Has all of the relevant evidence been taken into account?	

I can see from the comprehensive report that much evidence has been gathered and I appreciate that trying to develop objective evidence based on familial experiences is extremely difficult. I would therefore suggest that there is more evidence to be considered through a deeper understanding of the impact that XLH has on adults, their families and support networks.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The statement that the treatment is not cost effectiveness is not reasonable. The accumulation of the impact of XLH is huge, greater than the sum of the parts. The full cost benefit brought about by burosomab is under-estimated in the interpretation of the evidence.

• Are the recommendations sound and a suitable basis for guidance to the NHS?

No, they are not because it has not taken full account of the accumulation of the challenges and quality of life of XLH in adults. The pervasive nature of XLH symptoms impact every aspect of life and the accumulation of the challenges is greater than the sum of the parts. Physical, social and mental wellbeing are all significantly impaired. Medical Research had come up with a rare game changing medication, this is what research is for. This is so important for many people.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Not in an objective sense. Burosomab is already approved for use in children. There must be an inherent discrimination when the individual turns 18 years old and are treated differently. Everyone is different and just because society has drawn a line at 18 does not create a clear boundary between adult and childhood.

- committee-discussion - Effects on quality of life, point 3.2.

In my experience as dad of two children with XLH who are now in their mid 30s, I have seen and experienced the impact of this condition. I can clearly support the notion that XLH has a large impact of quality of life of the sufferer. It has a huge impact on carers. For us as a family it was extremely difficult having to deal with the physical impact with the children and the psychological impact on them. Perhaps the less easy to understand is the emotional impact felt by sufferers and carers. Society does not treat individuals with physical deformity like this well at all. The emotional impact is huge, which worsens as they grow older, becoming increasingly introvert. This covers everything from not being able to engage in normal activities,

restricted access to society in general, being ridiculed in the street by the ignorant. Finding a partner in life is very challenging indeed. I have made more relevant comments in the free comments section.

- committee-discussion - Treatment pathway, point 3.3.

The conventional treatment, whilst greatly appreciated at the time, is also a challenge. Both by children took oral phosphate and alpha-cidol. Despite that they endured, and continue to endure, multiple surgeries. Dealing with the medication, the testing and the surgery was a major part of their lives. Anything that can remove the need for that surgery is with its weight in gold. Its no normal life and it is not confined to children, the impact in them as adults is similar.

- committee-discussion - Modelling excess mortality risk from XLH, point 3.11.

The modelling here is clearly highly complex and comprehensive and, as a layman, can only really restate my points about living and ageing with XLH. It is clearly different in each patient but the physical symptoms lead to patients withdrawing from areas of society that most of us take for granted. This permeates all aspects, from getting and keeping a job, self confidence, access to sport and social groups. It is huge. All the factors accumulate, leading to many mental health challenges. The real world is not a forgiving place and can, in many cases, be very cruel.

- committee-discussion - Utility benefit for carers and family members, point 3.17.

I think perhaps the role of the carer and family members is very difficult to account for in such a model. As a father of two adults with XLH, I am not there day to day with them to help manage situations but we spend a lot of time, effort and emotion supporting through lifes challenges. The day we took my son to university, aged 18, with his legs in lazirov fixators was one of the hardest thing I had to do. He spent his first year virtually confined to his tiny room. How different that would have been if he had been on burosomab with the improvements evidenced today. Supporting our children through this is very difficult. My daughter also a real challenging time at university, she had only been there a couple of weeks when, after a short fall, had fractured her leg. Because she had XLH she was in a wheelchair for a year. Supporting her through this was so difficult. If she had burosomab, she would still perhaps fractured her leg but the recovery would have been weeks, not a year.

- committee-discussion - Cost-effectiveness estimates, point 3.18.

This is such a complex thing to model. The only area I feel I would comment on is as follows: As previously stated my two children have XLH, inherited from my wife with XLH and her mother with XLH. In the immediate family I have witnessed the impact of XLH on 14 people over 4 generations. Not a

month has gone by without hearing of one of them enduring a fracture and are awaiting surgery of some description, a screw, a plate. The fractures seem to occur more in adults.

- committee-discussion – Recommendation, point 3.21.

Firstly, I would thank NICE for the amazing effort that has gone into this evaluation, I come from a world of financial and business modelling, I know it is not easy.

As a parent of two adult XLH sufferers where we have seen the benefits of burosomab, I am unlikely to ever agree with this conclusion. To us, the benefits have been enormous. Game changer benefits. The cost of the medication is clearly a very important factor but the cost of not having the medication is immense, although much harder to measure. Like I said in earlier comments, I have seen the impact of XLH in 14 people over 4 generations covering 50 + years, up very close and personal. It is a lifelong devastating condition. Over the years the medical intentions have improved. My mother in law spent a year in a hospital bed with her legs clamped straight, the benefit lasted about a year as far as I am aware. My wife endured tibial osteotomies on more than one occasion as well as pins and screws as an adult. My children went through hell as children with all the interventions but benefits were there, though not so significant. Now, there is a gamechanger. Now for a very emotional, but very relevant, bit. When my son was at primary school, 30 years ago on school sports day he insisted on taking part in the running race. He, like all of us, knew he could not run, but he insisted. He took twice as long as anyone else to get the 80yards down the track. He ran as best he could, and he finished. He took part, everyone was applauding and in tears. That was the last time I saw him take part in any sporting activity. So, skip forward to the last couple of years since taking burosomab. He had been taking burosomab for about 4 months and we were visiting him. He said look at this, and he actually jumped in the air, albeit only a foot perhaps. That was the first time he has ever been able to do anything like that since being 8 years old. Not that we all go around jumping but that was really something amazing. His mobility has increased dramatically, he walks straighter, in less overall pain, he can get around, to and from work much easier and his mental health is much improved from where it had been, he even is able to go swimming. The impact of the improvement across the whole family is very very clear. On another point, as a young man just out of university, he could never develop a personal relationship. I recall a day he said to me, well, I git my degree, I got a job, I just need to find someone to share that with. he got there in the end but what most people take for granted, took him 10 years or more, really difficult from a mental health perspective.

My daughter had to come off burosomab as she was pregnant but hopefully will be able to return to taking it. Enabling her mobility and improve her engagement with her daughter and indeed her place of work. She has suffered with many fractures over the years, we cannot go back to that.

This is what medical research is for. To withdraw it for adults would sentence my children to a life of increasing mobility issues, pain, arthritis leading to a very much impaired quality of life and increasing mental health issues. Their engagement with the workplace would reduce and the whole family would be impacted by that.

Even thinking about having a child with XLH, on burosomab and having that withdrawn at 18 and then sending them off to university. my two had a really hard time with XLH at university, let's not allow that to continue when we can do something about it.

The pervasive impact that XLH has on lives profound, it creates issues every avenue of life. When taken together it is enormous. bigger than the sum of the parts. Please re consider your recommendation.
This drug is not just effective, it is an absolute game changer and our family bears witness to that.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I wished to submit my thoughts as an adult living with XLH who is not currently accessing Burosumab. My XLH was expertly managed in childhood and adolescence but, despite careful lifelong adherence to current treatment and receiving all relevant monitoring and support, my symptoms have noticeably deteriorated in adulthood, and I'm currently only 32.

I have always experienced stiffness which was only occasionally accompanied by pain, but my pain is now daily and at times requires painkillers to complete routine activities. In the last 6 years I have also required two surgeries to address spontaneous stress fractures (one in each femur) which my body wasn’t able to heal, the second of which was known to be there for at least 4 years. In addition, the impact of my XLH is such that my femurs are deformed and misshaped and this has massively impacted the success of both procedures – the first took significantly longer than expected to the extent that I had to stay in hospital for 13 nights instead of 2, I required a blood transfusion, was unable to walk fully independently for 7 months, and required physio for 10 months. During my second surgery the plate again couldn’t be fitted as planned because of the shape of the bone and its position is now causing pain and impacting my ability to walk, so that I am now severely limited in activity compare to pre-surgery we are planning a further surgery for it to be removed. Once again, I have required extensive physiotherapy both before and after that procedure

as well as the accompanying X-Rays, MRI, CT scans, and appointments that are needed for investigations. At all times I have followed my standard treatment rigorously, taken all medical advice, maintained a healthy weight and managed my general health, but it simply is not enough.

As demonstrated in my own experience, it cannot be over-stated that even a simple stress fracture for a person with XLH is just not comparable to that in a person without XLH. Not only are my fractures more likely, but my body is unable to heal them the treatment options are both limited and complicated by the condition, with unpredictable and extensive impact to both me and the NHS. Because of the strain of XLH, each time I experience a fracture and surgery the toll that it takes means that I lose a little bit more range of movement, mobility, independence, and I live with new pain, and require more medical care. In each case and based on the evidence currently available, myself and my medical team have strong reason to believe that these procedures would have been avoidable had I had access to Burosumab.

The impact of XLH in my life now is unfortunately even wider than these procedures. The steady increase in pain and complications has meant that I am no longer able to do the things I loved to do in the way I was previously able to, such as travelling, exercising, even seeing friends. I have always been an active, happy, sociable person but the constancy of the pain and stiffness means that I now also experience fatigue, migraines, and brain fog and I have been forced to make a concerted effort to change the way I plan and spend my time to try and limit and cope with my symptoms. This has also meant changing my working pattern to allow for rest days and again, that is not a decision I expected to face at 32. The life that I knew is slowly being eroded and my future taken away not only due to the impact of surgery, but simply the general progression of XLH in adulthood, and it is relentless. As one friend recently said; “it feels as though as soon as you’ve recovered from one thing you have to undergo something else”.
When I met my partner 4 years ago I was open about my XLH but I was more active, had more energy, and had hoped to avoid further surgery but since then he has had to adapt to taking on more and more of our domestic duties, provided care for me and taken time out of work when I was unable to move, wash, or dress independently after surgery, has supported me through the emotional fall-out of my procedures and as my pain has become worse, and adapted plans, including our honeymoon, while we try to better understand my symptoms and what I need. It is one of the worst things for me to know that the burden I now unexpectedly live with I have also passed to him, and that my XLH jeopardises the future we imagined. I’m sure you can also appreciate the toll this takes on mental health, and I now regularly see a counsellor to help me process the generalised anxiety, stress, and increasing fear for my future that now accompanies living with XLH.

The reason I wished to share all this was not to be doom and gloom and in fact, if you met me you would meet an outwardly happy, determined person and I do all that I can to maintain my treatment and current health. The

reason I have shared this is to bring to life for you the reality of XLH as an adult, even with the best care in childhood and the best effort now; it is constant, it is insidious, it is draining, it is only getting worse, and when procedures are required, they are massive. Of course I understand that the cost of Burosumab must be reasonable, and that resources are not only precious but scarce. That is why I wish to demonstrate the cost that not having it, even in one person, has already and continues to generate. Having Burosumab for adults would not be a 'nice to have', it would not just make things a little bit better or simply take the edge off; the extent to which it has been proven to reduce pain, allow the body the resources it needs to function and heal properly, would be literally life changing for me and others like me and I believe, provide greater financial value that the regular, extensive, and multi-factor care I currently have to access.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Living with XLH is a constant battle as the condition is degenerative and is a whole-body condition. The challenges I experience daily are constant and debilitating pain, fatigue, joint stiffness, mobility restrictions, inability to maintain employment, psychosocial issues and depression.
Fractures began in my early teen years and continued into my 50's. These fractures never heal correctly and generally require surgical intervention. Recovery from surgery is a long process and requires long rehabilitation sessions to become mobile again.

Compared to traditional treatment, the new treatment has helped immensely with the fracture/surgery healing process. The level of care since starting the new treatment has changed with less depression, better mobility, increased energy and more independence.
XLH requires a lot of support psychologically, financially and from family & friends.

The new treatment has been life-changing for me, and I encourage this medication to be available for the whole XLH population.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified

Conflict	No
Notes	
Comments on the DG:	

Since starting Burosumab in 2020 our daughter's life has changed dramatically, and as a result our family life has too. She was able to graduate and work a demanding, fulltime job. Of course she still has pain and is very aware of when she is due her next injection but the relief that it provides is unbelievable, both for pain and fatigue. But, the pain is much more managaeable, mostly with OTC medication. As a parent, it is simply awful to witness your child in pain, whatever their age. But, when something comes along that significantly changes that level of pain and fatigue, it is glorious and we are so thankful and grateful for it. Bursosumab has given us hope for her future and the thought of not having it is quite frankly terrifying.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

As a husband of a wife with XLH and a father of a son with XLH, I have seen the effect that this condition has had on their lives. My son has been affected throughout his life, having a number of operations on his legs from primary school age to his mid twenties. My wife has had four operations on her legs starting when she was 13, with further surgery in her thirties and early sixties. The amount of time they have spent in hospital and attending appointments at various other hospitals(Orthopedic,Nephrology,Dental,ENT) has been extremely challenging for us as a family.

This has continued over many years for both of them and this has had an effect on family life, school, education, and employment opportunities for both of them and me.

They are currently taking Calcitriol and Phosphate for their symptoms of pain and fatigue and they both have experienced difficulty maintaining the required daily level without gastro intestinal problems.
It is very difficult to see family members with this level of pain and fatigue when there is a more effective and tolerable treatment available.
This condition has had a major impact on our quality of life.

If you are unable to provide this new treatment due to lack of data and the cost analysis ratio I would like to see further trials undertaken to allow a more informed evaluation to be considered.

As you acknowledge that Burosumab is more effective and understand the limitations and difficulties of the existing medications I urge you to reconsider your decision.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

XLH has impacted my life from the age of three. In my early years, I had bone problems, numerous hospital visits and various treatments.
At age thirteen I had my first operation on my leg (osteotomy) with a prolonged recovery period and unfortunately the outcome did not prove to be successful. In my thirties due to the pain I was experiencing and the effect the condition was having on me, I opted to have further surgery (osteotomies) on both legs. The recovery was prolonged and painful. My most recent surgery was at age sixty one. This was a more complex operation on my leg and had a longer than expected recovery period. I have had associated problems with hearing loss and back pain. Pain and fatigue are ever present and these symptoms have increased through adulthood and into older age.

I wasn't diagnosed with xlh until age thirty four (after I was diagnosed in my second son). He had to endure numerous hospital visits and to date has had five operations on his legs. He is now in his thirties and experiencing similar progressive problems (pain, stiffness, dental issues etc) as I did. The condition also effects my family. They have had to accommodate the impact of the condition while providing increased support due to the progressive nature of the condition in adulthood.
At this age I can confidently say that this condition has many implications. Throughout my life, at school, finding employment, in social situations and it continues to do so today. Dealing with it over a long period of time is exhausting and difficult. This requires energy which unfortunately is something we don't have.

I feel the current treatment available is not effective due to the difficulty tolerating the required daily amount of phosphate.

Due to the effects of xlh on myself, my son and my family, I was disappointed with the current decision not to approve Burosumab for adult use, especially as it has been approved for use in Scotland. I hope that you will reconsider your decision and give those with xlh the opportunity to try a treatment which could have a positive effect on their symptoms and daily living as they have had the vision to do in Scotland.

If you are unable to approve this treatment, I would hope that you would conduct further trials to enable you to gather and monitor the data you require to make a more informed decision.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am the mother of a young man, born in 1994, with a spontaneous case of XLH. My son had a challenging childhood on oral phosphate, but was generally well cared for with minimal surgery until 18, when he was discharged from paediatric care. He missed an invitation to the Early Access Program to trial burosumab as an adult because he was working abroad.

I want to relate to you some of the invisible costs of his XLH – to him and his family – because I feel these have been inadequately recognised in your Quality of Life assessment.

My son's ability to maintain his employment as a financial analyst is impacted. He had to resign from one job, because the long hours – considered normal for young men in the City – could not be maintained and he was reluctant to admit a health barrier for fear of discrimination. In addition, the numerous dental interventions (several root canals) have cost him dear in time and dental fees.

My son's ability to participate in his chosen sports is also significantly impacted by his XLH, both because his energy levels fluctuate and even small bumps and sprains become major barriers to mobility. When he has to stop exercising this negatively impacts his mood and he is prone to depression. Fear of the future also has a significant impact on his mental health – I overheard him asking his grandmother about her arthritis, as he worries this will be his burden soon.

I strongly feel that burosumab will be important for my son as he continues to age, and that his quality of life and our burden of care as parents will be significantly improved if it is available when needed.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified

Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

• Has all of the relevant evidence been taken into account?

I am not sure that the consequent costs of making multiple people (inc. carers) economically inactive have been fully factored in.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not believe so. In our case, the value of £20-30k per QALY does not come close to the potential loss of income, tax paid, benefits required and general loss of economic activity / output.

• Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not believe so. The decision leaves XLH patients with no effective treatment and it will be a step backwards in terms of NHS treatment.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am not sure of the law regarding disability discrimination, but the easiest way to ensure that someone is not subject to it, is to ensure that they are not disabled in the first place. The evaluation committee have that opportunity.

The gender ratio of the incidence of XLH is 2:1 females to male so this decision will disproportionately disadvantage women.

- Recommendation – Recommendation, point 1.1, Burosumab is not recommended, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) in adults.

What is recommended instead? It is established elsewhere in the report that no viable alternative exists.

- Recommendation – Recommendation, point 1.1, This evidence also suggests that people having burosumab may have less pain and fatigue, and improved physical functioning compared with placebo in the short term, but this is uncertain.

My daughter has been on burosumab for 5 years as part of a trial. The improvement to her clinical condition means she is almost unrecognisable from the person she was when she started the treatment. Her pain levels and mobility, and her ability to exercise, work and generally exist means she can now live independently and productively. She is currently studying a sport science degree and training to be a coach and early years sport teacher. This would not be possible without burosumab and it is unlikely that she will be able to see this through without it.

- Recommendation – recommendation point 1.2, There are uncertainties in the assumptions used in the economic model, particularly about the long-term effects of burosumab on how long people live, fracture rates and the quality of life of people with XLH and their carers

Should those for whom this clearly works be denied it because of statistical uncertainties? Wouldn't it be better to maintain treatment of those for whom there's no uncertainty whilst those uncertainties are investigated?

- information-about-burosumab – price, point 2.2,

Have all the costs of NOT treating this patients been considered (noting that the report acknowledges that there is no effective alternative). This does not just include consequent healthcare costs for the patient themselves, but lack of economic activity for the patient and any care-givers required, including both tax income lost, spending power curtailed and benefits needed to be paid.

- committee-discussion - Treatment pathway, point 3.3, Both patient experts were having burosumab and said that it had been a 'game changer' for them,

It is worth noting that the situation for patient experts from XLH families is actually better than for those with do novo mutations. XLH families have often developed expertise and approaches that mitigate the disease effects, particularly in early years, potentially reducing the long term effects. De novo mutations are normally picked up later in life (given the condition's rarity and unfamiliarity to most physicians) by which time significant, avoidable and permanent damage has been done.

- Committee-discussion - Cost-effectiveness estimates, point 3.18, £20,000 to £30,000.

This seems very low given the severity of the impact of XLH. In the case of my daughter, it is likely to take her from someone earning well in excess of this (and the economic benefit that entails) to someone requiring benefits herself and for her carer (who is likely to be a currently high-earning and tax-paying professional).

The basic sums for that alone would justify the NHS paying a lot more per year to avoid this happening, quite apart from the direct NHA costs of standard 'treatments' and the health effects.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

My son has taken Burosumab since age 6. He is now aged 11 and the improvements for him have been literally life changing. Despite 4 hourly oral phosphate day and night, before Burosumab, he had extremely bowed legs, couldn't walk down the road due to pain and fatigue and kept falling over and banging his head. He was also teased at school. Since taking Burosumab his legs are now completely straight and strong and he has caught up with his peers with height. He has no restrictions to walking and now loves football and swimming. Unless you were in the know (he still has slight craniosynostosis) he now looks like a perfectly healthy child. We are very concerned that the Burosumab will be taken away from him when he stops growing and he will go back to having oral phosphate which did not work for him and he will be at risk of bone deformities again such as fractures and pain. This will also impact his mental health and employment opportunites.

I also take Burosumab as an adult with XLH. Before this I was very stiff and in pain and worried that I would have fractures. Having Burosumab has reduced the stiffness and enables me to continue working as an NHS Clinical Nurse Specialist. On Burosumab I have now normal bone profile blood results. Without it I am also very concerned about my future as I am aware that XLH is a progressive disease. I have another 20 years work ahead of me, which I do not wish to risk stopping due to my condition.

Please can you reconsider your decision and grant access to adults as we know that Burosumab treatment the only way for people with XLH to have a chance of living normal lives and stay in employment without relying on significant support from the NHS services. Thank you.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No

Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

As a member of a family with multiple XLHers my parents knew to watch for the signs of bowing in my legs. I was diagnosed early and started conventional treatment. Unfortunately,,,, this did not prevent my bones from becoming weak and my legs bowing. At age thirteen I underwent bilateral osteotomies with one being a very traumatic experience which I still have PTSD of hospitals today. After my osteotomies the treatment was stopped due to my disease being a "childhood disease". I stumbled through life with ups and downs until I was in my thirties when the downs were more common than the ups. By my late thirties I was in severe pain unable to shop for groceries, limited with myself care, my social life with friends and family were nonexistent due to not being able to participate in social events, and my pain was so severe I could not work my full-time job. I was struggling physically with extreme bone pain (9/10), stiffness of joints, hearing loss, and extreme fatigue. Financially I struggled with being able to pay my bills due to not being able to work full time and depleting my savings trying to pay for high medical bills like over 13 medications each month, x-rays and labs, hearing aids, and nonstop dental issues. Mentally I was struggling with not being able to live a normal life of someone in their 30's and dealing with physical struggles and financial issues. I suffered with major depression and honestly didn't want to live any longer. However, in 2016 I found out about the clinical trials for Burosumab. I joined the study and within the year began taking the medication. After three months of being on treatment my stiffness began to subside and my pain level was dropping. Now 6 1/2 years of being on Burosumab my bone pain very minimum (2/10), stiffness only bothers me if I'm standing for hours at a time, my mental status is much improved, and I feel like Burosumab gave me my life back. XLH is NOT just a childhood disease, it is a whole-body whole life disease and should be treated accordingly.

As a child the only symptoms that I experienced were bowing of my legs, bone pain in my legs, dental abscess, and mild fatigue. When I reached adulthood (twenties) I was very active and had mild bone pain and some fatigue . However, when I reached my thirties, I began to notice an increased progression of XLH symptoms. My bone pain became more severe, stiffness of my joints caused mobility issues, I started experiencing hearing loss which is now moderate in the right ear and mild in the left requiring hearing aids that I cannot afford $5000, continued dental issues, extreme fatigue, extreme mental issues, and spinal stenosis so severe that I had to undergo cervical surgery to prevent from being paralyzed from the neck down. Some of my symptoms have improved since I started taking Burosumab like bone pain, joint stiffness, and my mental status . However, due to not being treated my whole adult life this has caused progression of many XLH symptoms that are not reversible.

At age 42 I had lost my father, the only person that I could speak with about XLH that understood the struggles I faced. I was in severe pain and honestly didn't know if I wanted to continue to live. My mental health was an emotional wreck. My Dad had taught me to be determined growing up with a disease that would not determine who I was. As I remembered his words one day, I googled XLH. We had only found out the actual name after my Dad had become paralyzed from his severe spinal stenosis caused by XLH. That day I found a patient advocacy/support group. Through this group I found others with the same disease but most importantly I found out about the clinic trials for Burosumab here in the US. I have heard several people in the XLH community call this a miracle drug. It is easy to see the difference it makes in the lives of children. It is so amazing to think those kids will not face the traumatic orthopedic surgeries my generation faced. However, what isn't easy to see are the stories like mine. I am now able go to the grocery store to buy my groceries, cook meals for my family, and live a life with minimum pain and fatigue. What you also can't see is that I am not mentally struggling now to hold on for others when I didn't want to hold on for myself. Burosumab gave me my life back!!! Why should anyone struggle if it isn't necessary? The cost of the drug is very minimal compared to the life you can give someone.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost of the drug is very minimal compared to the life you can give someone.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I personally feel if Burosumab is not recommended for use of adults then this is a great injustice for a community of rare disease patients and promoting the use of opioids and narcotics for pain relief.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Since XLH is a whole body whole life disease how can it not be considered discrimination against the adult XLH population to withhold a proven treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified

Conflict	No
Notes	
Comments on the DG:	

XLH has had a significant impact on my life since birth. Pain and mobility issues have become increasingly painful as I'm aging and the physical toil I feel everyday is exhausting. The current medication makes little or no difference and I am relying on pain relief daily. Burosomab was a chance for me to have a chance of some potential changes in my everyday life but this decision has robbed me of the opportunity of even some improvement. Dental pain is daily as is the pain from my shoulders to my ankles, the deteriorating nature of this disease is frightening and having an effect on my mental health. What is most worrying is the fact that my two daughters that are having Burosomab treatment have seen almost miraculous improvement. It's a wonder drug for them and I have seen the disease become physically invisible and I'm not hearing reports of pain from them. When they become adults the fact that the treatment will stop and the deteriorating nature of the disease will tak le over is a massive worry and is unfair. I understand the costs of the drug are high but the improvement it makes to people's lives is astonishing

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am a 67 year old with XLH
2nd generation in a family of 4 generations with this disease.
I have had a lifetime of pain, fatigue ,stiffness and 8 surgeries to straighten my legs as a child , knee Arthroscopy in my 40s and both hips replaced in my 50s. this has had a huge impact on my day to day living, on my employment opportunities ie being passed over for promotions because of the way I look I am just 4 ft 4 in tall have bowed legs and arms and walk with a distinct gait. my condition deteriorated as I got older. I was also bullied and discriminated on in many ways

Having always lived with pain and for many years not realising that this isn't the way everyone else feels I suffered many fractures without realising just carrying on the best I could surviving on pain medication and lots of days in bed. Only when having x rays and scans over the years were lots of badly healed fractures revealed.

I have also had fractures that were quickly diagnosed having fractured my ribs on 3 occasions and theses taking 6 months to heal each time.

I was also involved in a car accident in my early 20s suffering multiple fractures to my arm ,jaw ,cheek bone s it took over a year to fully heal . My hip replacements took over a year to heal

I was very lucky to have been able to take part in the early adult trials for Burosumab and have been on this drug for 6.5 years.
initially I took part to provide data to help my grandchildren who were also in in trials not expecting any benefits for me, I was completely amazed that the drug was life changing for me.

before I started on burosumab I could only walk very slowly a short distance and was surviving on strong pain medication including opioids.
I could only plan one activity like going to the shops and then have to recover in bed for a few days being in pain and exhausted, this had a terrible impact on my relationships in my personal and family and friendships my social life was very limited , I felt very depressed and a burden to those close to me .

My husband had to take care of me and our home , my adult children 2/3 have XLH had to take me to hospital appointments help with shopping and every day care.

I have difficulty in putting on socks and shoes , I have to pay for private podiatry and massage to care for me.

Now I am on Burosumab the change is amazing I am able to walk much further my energy levels are so much higher, I sleep well , I can make plans and go out for days go on holidays and enjoy all of these things .
My relationship with my husband is now so wonderful, my friends are in awe of the new me ! I have built a successful small business from home, we moved home and took on a successful renovation I would not have even had the energy to think of before, we have travelled to wonderful countries on holiday and I have been able to enjoy all of this because of Burosumab.
I am looking forward to our retirement now.If this drug is no longer available to me than the future looks very bleak ,I will not go back to the pain and fatigue and living life in the fog of pain meds. most importantly I cannot bear that my children and grandchildren who have xlh will suffer so much the burden to me will be too much to bear
having passed on this disease there is a lot of guilt on my side , I also worry for my daughter who doesn't have XLH that she will end up the carer for all the other s who do .

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

I don't believe that the rare nature of the condition has been fully evaluated for XLH patients that are spontaneous. Moving to burosumab treatment has enabled my daughter to feel less isolated in her experiences and the pain and fatigue reduction has also helped to build her confidence. She is able to participate in team sports which has increased her ability to make friends and feel more included.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The evidence does not assess the earning potential of physically capable individuals to contribute to society and pay tax and NI. You have also not assessed with sufficient weight, the mental impact on patients and their families. If my daughter is not on Burosumab, she will need to return to living at home, will lose her independence and I will no longer be able to earn as I will be her carer - both physically and mentally. I am currently a higher rate tax payer but would need to move to taking a carers allowance to support my family.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't believe that the recommendations to not fund this treatment are sounds as there are no effective alternatives. If my daughter is denied burosumab she will be facing a life of pain and increased social isolation which will be highly significant to both her and all of her family.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The easiest way to ensure that someone is not subject to disability discrimination is to avoid them becoming more severely disabled in the first place. Please consider this when making the final decision.
In addition, XLH effects females to males in the ration of 2:1 and therefore removing this treatment disproportionately disadvantages women.
Finally, I do not believe that my daughter will be able to endure the additional strains on her body that pregnancy will bring if her burosomab treatment is removed.

- Recommendation – Recommendation point, 1.1, Burosumab is not recommended, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) in adults.

What is the alternative? Is it possible to reduce the price so that these patients are not abandoned?

- Recommendation – Recommendation point, 1.2, There are uncertainties in the assumptions used in the economic model, particularly about the long-term effects of burosumab on how long people live, fracture rates and the quality of life of people with XLH and their carers. And all of the cost-effectiveness estimates are above the range normally considered an acceptable use of NHS resources. So, burosumab is not recommended.

Do the uncertainties warrant further investigation before a valid, clinically sound decision can be made? Is more evidence required to fully evaluate the impact of removing the only effective treatment?

- information-about-burosumab – price, point 2.4, The company has a commercial arrangement. This makes burosumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

Please can the company revisit the discount applied to the NHS so that these patients are not deprived access to the only effective treatment.

- committee-discussion - Effects on quality of life, point 3.2, Symptoms generally start in childhood. For adults, symptoms include osteomalacia (soft, weak bones), bone pain, fractures, pseudofractures, joint stiffness, restricted movement, neurological complications, hearing impairments, spinal cord compression, dental problems, muscle weakness and fatigue. A clinical expert added that people may develop hyperparathyroidism, which can lead to cardiovascular and kidney complications. The patient experts said that pain is a large part of living with XLH and managing the excruciating, radiating bone pain often involves using opioids. They explained that in attempt to avoid pain, people with XLH will restrict their movement, which causes their muscles to stiffen up, reducing mobility. Reduced mobility can make it more difficult to manage weight. The patient experts added that because XLH is a genetic condition, people with XLH may also be a carer for family members who may have more severe symptoms. The carers may have to stop work to do this. The company highlighted that XLH may be associated with an increased likelihood of social deprivation for people with the condition. This is because of the limitations on ability to work, and for their carers who may also have XLH. The committee concluded that XLH has a large impact on quality of life and the ability to do day to day activities and work.

XLH can also be spontaneous with no other family members effected and in our experience was very difficult to diagnose. This created a feeling of loneliness, isolation and fear.

The daily slog through the pain, stiffness and fatigue, which is being managed with pain killers, also means there is a tendency to withdraw from activities and social events.
These restrictions also limit the range of employment opportunities that can be undertaken.

- committee-discussion - Treatment pathway, point 3.3, The clinical experts explained that the aim of using oral phosphate is not to normalise serum phosphate levels. This is because the doses needed for normalisation are generally intolerable, with side effects including diarrhoea, which substantially affects people's ability to do day to day activities, and hyperparathyroidism, which can cause permanent kidney damage.

Nephrocalcinosis is already present from oral phosphate treatment prior to taking burosumab. Returning to this treatment would surely progress this further and lead to more kidney complications. The return to stomach pain and diarrhoea would have a massive impact on her daily life.

- committee-discussion - Treatment pathway, point 3.3, Both patient experts were having burosumab and said that it had been a 'game changer' for them, reducing pain and resulting in a positive behavioural cycle of being able to move more and feel less stiff, with accompanying weight loss.

It also gave my daughter the confidence to try sports that she wouldn't have previously. Through this she has gained confidence and friendships benefitting both her physical and mental health.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

• Has all of the relevant evidence been taken into account?

No. As Burosumab has only been made available to a (relatively) small amount of people with XLH, it is not fair to make an assumption on it's effectiveness.

Of the people who have had access to this treatment, the vast majority of them are extremely positive and upbeat about it's impact on their lives and the effect it has on their ability to manage their condition and help reduce pain & improve mobility.

XLH is a condition which affects all aspects of daily life. Small trivial tasks such as putting on a pair of socks or bending down to pick up an object off of the floor are extremely difficult (speaking from my own personal experience of living with the condition) & can cause severe pain, discomfort & embarrassment. My own personal opinion is that when living with XLH it is easier to accept that certain things in life are going to be virtually impossible (running, playing physically demanding sports, etc) but the real frustration and difficulties come in the every day things that most people are fortunate enough to be able to take for granted. Things such as coming down a flight of stairs, getting in & out of a vehicle or even just walking along a flat surface during winter months (when the ground may be slippery) can cause severe stress/worry/concern and I would strongly welcome any treatment that could assist with managing pain & improving mobility and thus increases the quality of life of XLH patients. Whilst I personally do everything I can to minimise the impact XLH has on my life & try to live my life to the fullest, it is impossible to ignore that this condition has a very noticeable impact on virtually all aspects of my life every single day. I would urge that every consideration is given to the use of Burosumab in adults so as those who suffer with the condition can be given a chance to live their lives without such worries every day & future generations can be given hope that their condition can be managed in a much more effective way.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. As mentioned above, this summary has been concluded after Burosumab has been trialed with only a small amount of patients. The nature of XLH is that sufferers can experience varying degrees of pain/mobility issues & overall impact on their life. As a lifelong XLH patient (now 36 years old) I find it incredibly frustrating & annoying that such conclusions can be derived when many patients (myself included) haven't ever been offered the opportunity to trial the treatment. It is acknowledged within the report that current treatments aren't sufficient for managing the condition (and can also have very unpleasant side effects) & I would beg that NICE reconsider their decision and look to roll this out to a wider range of patients with XLH to suitably determine its effectiveness as a treatment. I have had over 30 years on the current recommended medication and still suffer a very significant level of pain & discomfort on a daily basis. I have noticeable mobility issues and feel that it is incredibly frustrating & demoralising to know that there is a new treatment out there which could very well help improve my quality of life but I am (at present) unable to access it. I would plead with NICE to reconsider this decision and give a fair chance to all XLH patients.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Again I would point to the responses above and argue that a fair conclusion has not been drawn from the research conducted so far. I also find it very frustrating given my home is in Carlisle (and only around 8 miles from the Scottish border) that adults in Scotland are able to access this treatment to manage living with XLH and yet sufferers of the condition in England appear to be being told that they are going to be asked to continue with current treatments (which are acknowledged in the report as being inadequate) and denied access to Burosumab (which has had virtually entirely positive feedback from those fortunate to have had access to it in the trial). Having lived with this condition for over 30 years now I would plead that every consideration is given to the use of Burosumab so as young adults suffering with this condition can be given a chance to experience a greater quality of life than I & other patients have had for much of our lives.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

N/A

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am [redacted], and I live in the United States. I am 39 years old and have X-Linked Hypophosphatemia or XLH.

I have been on Burosumab for 4.5 years. Prior to this I had not taken the old treatments of Phosphorus and active Vitamin D since age 14. Ive had 5 leg surgeries to correct the bowing during high school.

I became totally disabled due to the severity of my XLH symptoms progressing so badly that I could no longer be a reliable worker at only 27. I have pain almost daily, and prior to Burosumab being available in the US I had lost all quality of life. I had 6 stress fractures in my legs at the time I started Burosumab, I could barely stand or walk with severe pain & I frequently fell from my legs being weak and giving out on me. I had become extremely depressed being unable to work or have social interactions with

friends. I had lost hope at having any quality of lif.e ever again until Burosumab changed my life. It has helped my bones heal and I do not suffer from constant fractures and bone pain anymore. I have been able to walk and become more active little by little. It helps with the fatigue that also comes with XLH. Struggling with sleep from the pain then makes the fatigue worse & it can go into cycles that are impossible to get out of. This medicine is allowing adults to keep working and being active members of society for longer than before with the old or no treatments in adulthood. Please consider allowing Burosumab for adults as well as children. When we become adults our XLH does not go away, so adults who had burosumab as a child will then go from getting treatment to not having it and that feels almost worse than never having it to not know what u have lost. I can not imagine ever having to live without Burosumab now that I have experienced how it feels to just stand up and walk without the fear my legs will give out or severe pain with weightbearing.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No it has not there is evidence it has made an impact on adults and as you know for children.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. They are not.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This is discriminatory in relation to equalities act and human rights because it seems a lot of basis for not considering licensing on nhs is based on money

I am the first family member known of who grew up with xlh. I was born in 1973 and diagnosed at 7 years old due to my Valgus knees or knock knees as they were referred to. I spent many periods in Hospital trying to get a

diagnosis and then having bilateral femoral osteomoties carried out when I was 11. My experiences were traumatic. I was on phosphate sandoz and cod liver oil. My legs continued to bend after surgery which was not done properly.

The mental impact all my life and embarrassment of legs I can't impress upon you as to how this has affected me. I also was in a lot of pain and had a lot of fatigue which I never understood.
I sought corrective surgery when I was in 20's only to be scorned by orthopeadic surgeons who didn't want to touch them as they were so misaligned and the surgery I had when a child was not done properly. I finally saw a surgeon who was willing to do corrective surgery, osteotomy with IM nails. All on nhs. I had 12 months offf work. I had one leg done and then the other 6 months later.
In my 40's I had to work part time due to pain and flare up in many joints and started having more surgery this time to upper limbs due to early onset arthritis, osteophytes, soft tissue calcification and chronic pain. I had much time off work. I had to recently retire from work on ill health grounds at age of 50 yrs due to pain and impact on my daily living for which I need help and assistance. I also suffer from Depression , anxiety and complex trauma/ptsd all associated with xlh and how I was treated from beginning and my health. To not license this drug for adults is so unfair especially as it seems based on money. To stop this being given when someone turns 18 will not be cost effective to nhs as it will mean that the surgeries people will need, early onset of other bone conditions related to condition, having to retire from work early and use of mental health services will all have extra burden. Moreover the burden of the person with the condition . It's horrible . I have wanted to be dead so many times due to this. If I had been a child when burosomab was about it would of been great but to be a teenager knowing it would be stopped when I reached adult hood; that would be awful .
Please consider us. We are human beings and need this medication which is a huge advancement for people living with this condition. Not licensing it on nhs for adults will create more burden and cost for nhs , social services and dwp in long run. If I could be on this drug which does have known benefits for adults then I could live a life with less pain and fatigue and it would slow down the arthritis developing and also help healing when I need any further surgery which I may do due to secondary arthritis .

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
My position is I have a daughter age 60 and a female granddaughter age 32 and one grandson age 29.	

Daughter with XLH on burosumab
Grandson " " "
Grand daughter no treatment for XLH

The 2 family members on burosumb have more energy, less pain, walk more steadily with less fear of falling, hearing impairment improved and tinnitus ceased, less problem with teeth particularly abscesses, less pseudo fractures and fractures. There are mental health benefits, they are able to work and socialise. They have to be selective about the work they can do as they are unable to stand for long periods.
My Grand-daughter is not on burosuamb and suffers considerably.
At present she has permanent feet, hand, arm, back and leg pain. Her life is punctuated by mental breakdown, very little help from the heath service and so little understanding of her underlying problem.
At the age of 13 she had both her lower and upper legs straightened. This was successful as far as appearance. However going through the number of operations was extremely hard for her - she wanted to go to school and was continually bullied by pupils and lack of care and understanding by teachers.

Her pain is so severs that she has been prescribed additive drugs, unable to work, can't enjoy any social life and lives alone which is extremely hard.

All my family have needed dental care in spite of always paying attention to cleaning etc. Nobody within normal dentistry has any understanding of XLH and the bills are enormous as it necessitates paying for the treatment. She lives in Devon and travels up to Hampshire where we have found an understanding dentist of XLH and the impact on teeth. The cost is very large!
Bristol Dental Hospital as no specialist endodontist
She cant work inspite of being a highly intelligent young woman.

Both my grandchildren have made the decision not to have children - so sad!

I have been Grandmother to the family since the children were born - 32 years ago and have been continued support as needed. I am now 84 and find I cannot do the same so WHO WILL HELP THEM! I also have a limited amount of money for them to have private care.
I sincerely hope they will be able to continue on burosumab. I dread to think how they will be if it is taken away.
So many health problems!!

I've seen how burosumb has helped my daughter and grandson and sincerely hope this can continue. Their lives are not brilliant but I dread to think

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External Assessment Group (EAG) Critique of the Company's Response to the Draft Guidance (DG)

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

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Date completed	11/01/2024

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined.

Table of Contents

1 Overview of the Company's response to the DG 2

2 Critique of the company's response to the DG 2

2.1 Issue 1: Adjusting utilities for placebo effect (DG point 3.15) 2

2.2 Issue 2: Utility benefit for carers and family members (DG point 3.17) 3

2.3 Issue 3: Disutility of incident fractures (DG point 3.16) 4

2.4 Issue 4: Source of utility values (DG point 3.14) 5

2.5 Issue 5: Age and weight distribution of population (DG point 3.6) 6

2.6 Issue 6: Excess fracture incidence (DG point 3.13) 6

2.7 Issue 7: Mortality benefit of burosumab (DG point 3.12) 7

2.8 Issue 8: Stopping criterion and discontinuation (DG point 3.9) 8

2.9 Issue 9: Excess XLH mortality risk (DG point 3.11) 9

2.10 Issue 10: Tapering of treatment effect (DG point 3.10) 10

1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE DG

The EAG provides a summary of the key issues covered in the company's response to the Draft Guidance (DG). The following key issues are covered:

Issue 1: Adjusting utilities for placebo effect (DG point 3.15);

Issue 2: Utility benefit for carers and family members (DG point 3.17);

Issue 3: Disutility of incident fractures (DG point 3.16);

Issue 4: Source of utility values (DG point 3.14);

Issue 5: Age and weight distribution of population (DG point 3.6);

Issue 6: Excess fracture incidence (DG point 3.13);

Issue 7: Mortality benefit of burosumab (DG point 3.12);

Issue 8: Stopping criterion and discontinuation (DG point 3.9);

Issue 9: Excess XLH mortality risk (DG point 3.11); and

Issue 10: Tapering of treatment effect (DG point 3.10).

The company have not updated their base case assumptions.

Within the short timelines available to the EAG (a few working days), the EAG provides a critical evaluation of the company's response to the key issues. The EAG critique should be read in conjunction with the company's response document to the DG and the EAG report.

2 CRITIQUE OF THE COMPANY'S RESPONSE TO THE DG

2.1 Issue 1: Adjusting utilities for placebo effect (DG point 3.15)

The company provides no new evidence or information to support issue 1. The two points emphasised by the company were previously reported in the company submission:

- Any placebo effect on utility appears to be short-lived: placebo arm utilities in the CL303 trial showed an initial improvement at 12 weeks, followed by a return to near baseline levels at 24 weeks.
- WOMAC outcomes following burosumab interruption between finishing study CL303 and starting study BUR02 (reported in Kamenicky [2023])1 show that patients returned to baseline WOMAC scores following withdrawal of treatment. This suggests that there is minimal regression to the mean. If there were significant regression to the mean, there would be a residual treatment effect following treatment interruption. The company acknowledges that the number of patients in this analysis is small, but nevertheless it supports the evidence.

The EAG acknowledged the limited 24-week placebo-controlled trial period but highlighted that not adjusting the utilities for placebo effects adds important uncertainty because the cost-effectiveness results are very sensitive to the utility values, so any small placebo effect can have a large impact on the cost effectiveness of burosumab.

The EAG notes (see Section 4.2.8.3 of EAR) that the study by Kamenicky et al (2023), which is a post-hoc analysis exploring outcomes in participants who discontinued burosumab treatment between the 96-week CL303 study and the 48-week open-label extension of BUR02 (a total of 7 participants), indicates that the benefits of burosumab on improvements in WOMAC stiffness and physical function scores and BPI-SF worst pain scores returned to a *similar level* to baseline (i.e. the study does not state that patients returned to exactly baseline WOMAC scores) and the time to return to baseline is not reported. The EAG notes that out of these 7 participants, four restarted burosumab within 8 months of discontinuation and the other three participants within 13 to 16 months, which suggests that the return to similar levels of baseline utility is likely to be within one year of treatment discontinuation.

The EAG does not consider this issue resolved, but agrees with the committee that it is best practice to use placebo-adjusted values.

2.2 Issue 2: Utility benefit for carers and family members (DG point 3.17)

The company strongly disagrees with the committee's observation that inclusion of utility benefit for one carer may overestimate carer utility benefit associated with burosumab. The company also emphasises that the company base case is for two family members, not necessarily two carers, and that this may include:

- Children with and without XLH will benefit from improvements in the condition of their parent (with XLH) arising from treatment with burosumab.
- Partners without XLH will benefit from improvements in the condition of their partner (with XLH) arising from treatment with burosumab.
- And wider family members, both with and without XLH, stand to benefit from the adults with XLH being treated with burosumab.

The EAG believes that the committee's use of the term 'carer' was referring to 'informal caregivers and/or family members' as per the company's description above.

The company states that the only case where "double counting" might conceivably occur would be where two or more adults within the same family with XLH received burosumab in the CL303 trial,

and some of the improvement in WOMAC score observed in these adults was indirectly due to improvements in the other adult rather than due to burosumab treatment.

The EAG does not consider it appropriate to include informal caregivers and/or family members **with XLH** in the analysis because the spillover effect is **added** to the patient utility benefit with burosumab in the model, which is likely to include double counting of treatment benefits if family members with XLH (in an informal caregiving role) are likely to receive burosumab treatment themselves in the NHS (or, in the case of children with XLH, currently receive it), i.e., the benefits of treatment are double counted when family members with XLH in a caregiving role also stand to benefit from the patient benefit associated with burosumab treatment itself. The fact that there are limited other treatment options available for adults with XLH (beyond vitamin D analogues and phosphate supplementation) suggests that family members with XLH are likely to also be considered suitable for burosumab treatment.

2.3 Issue 3: Disutility of incident fractures (DG point 3.16)

The committee concluded that a disutility for incident fractures is appropriate to include but the duration of disutility in the model would vary depending on the type of fracture included. It also concluded that it would welcome more information on the length of time that fractures in different bones would affect quality of life.

The company response emphasises that impaired bone mineralisation in XLH means that fractures are likely to be slow-healing (without appropriate treatment) and therefore likely to be associated with a long-term health-related quality of life (HRQoL) impact, which the company states is supported by the CL303 trial, where there was no fracture healing between week 12 and 24 in the placebo arm. Furthermore, the burden of disease survey published by Skrinar et al. found that pain ratings were higher for adults who reported a history of fracture (at any time) compared with those who did not. The EAG notes that assuming a lifetime disutility for incident fractures to the tibia, fibula, femur, pelvis, foot or spinal vertebrae (i) does not reflect the likelihood of fracture healing over time, which could lead to improvements in HRQoL rather than assuming a constant lifetime disutility after the event (post-year 1); (ii) because mortality and morbidities are modelled independently, the duration of lifetime disutility associated with fracture events is not adjusting for fracture-specific mortality; and (iii) the disutilities associated with fractures in addition to the treatment-specific utilities may represent some double counting of morbidity effects because the treatment-specific utility values are extrapolated over a lifetime in the model.

The company undertook a search for evidence on the long-term impact of fractures of different bones on utility, focusing on fracture impact in populations with, or at risk of, impaired bone function (patients with osteoporosis, or at risk of fragility fracture) because XLH-specific data are not

available. Three papers were identified and summarised in the company's response (Adachi 2010; Griffin 2015; Borhan 2019):

- Adachi 2010 examined the impact of prevalent fractures on quality of life from the global longitudinal study of osteoporosis in women. The study showed that spine, hip, and upper leg fractures resulted in the largest reductions in quality of life (EQ-5D scores, 0.62, 0.64, and 0.61, respectively, vs 0.79 without prior fracture) compared to no fractures. The EAG notes that the study does not examine the duration of time that fractures in different bones affect quality of life, as requested by the committee, as the follow-up period for each fracture site is not stated in the article.
- Griffin 2015 is based on a study from a single trauma centre in England examining the recovery of HRQoL for a hip fracture, up to one year of follow-up. The EAG notes that the study does not examine the impact post-1 year and the only type of fracture considered is hip fracture; therefore, the study provides no relevant information to address the committee's concern regarding disutility for incident fractures after the first year of the event.
- Borhan 2019 examined the impact of incident fragility fractures (at spine, hip, rib, shoulder, pelvis, or forearm) on the HRQoL among people aged 50 years and older, using 10-year prospective data from the Canadian Multicentre Osteoporosis Study. The study showed that incident spine and hip fractures were associated with significant negative impact on the Health Utilities Index (HUI) scores. Hip and spine fractures were associated with negative impact on mobility, self-care, and ambulation, while fractures that occurred closer to the follow-up assessment were associated with significant impact on HRQoL compared to fractures occurring a long time before it, except for hip fracture where the negative impact lasted 5 years or longer. Women with a hip fracture never recovered to their pre-fracture level score (OR = 0.41; 95% confidence interval [CI], 0.19 to 0.98).

Out of the three studies identified, the EAG considers Borhan 2019 to be the only relevant study to partly address the committee's concerns. This study suggests that hip fractures are associated with a negative long-term impact on HRQoL. However, the study also showed that fractures that occurred closer to the follow-up assessment were associated with significant impact on HRQoL compared to fractures occurring a long time before it, suggesting that the impact on HRQoL over a lifetime horizon in the company's base case analysis is unlikely to be appropriate.

2.4 Issue 4: Source of utility values (DG point 3.14)

The company provides no new evidence or information to support issue 4. The committee noted that post-week 96 data used in the asymptotic model was highly uncertain, and that the modelled utility lies above the observed utility for the burosumab arm, which is then extrapolated over the lifetime

time horizon of the economic model. The committee suggested that the company explore fitting a hierarchical model, a smoother on the data beyond week 96, or both. The company responded that the development and validation of such models was not feasible within the time available and it is not clear that more highly parameterised models would provide increased clarity given the limited empirical data available and limited scope for informative elicitation in a rare XLH disease.

2.5 Issue 5: Age and weight distribution of population (DG point 3.6)

The committee considered the age and weight distribution from the early access programme (EAP) to be more appropriate than the CL303 trial because it better reflects the eligible population in NHS clinical practice. The company responded by showing weight changes recorded up to 3 months after treatment start, at month 6 (±3 months), month 12 (±3 months), and at month 18 (±3 months). Based on these observations, mean weight of the cohort falls below 70kg after start of burosumab treatment. Therefore, the company maintains that using European patients from CL303 with a mean calculated weight of 67.2 kg is a better representation of the weight of the treated XLH population in the long term than the baseline weight obtained from the EAP.

The EAG notes that there is variability in the weight changes recorded up to 3 months after treatment start in the EAP, with a similar to baseline mean weight at 6 months after treatment start (mean weight, 72 kg). The mean weight of 65.6 kg recorded at month 18 is based on 10 patients only compared to 133 patients at baseline (mean baseline weight, 73.6 kg). Therefore, the EAG does not consider the company's response as sufficient to address the issue about the age and weight distribution of the NHS population.

2.6 Issue 6: Excess fracture incidence (DG point 3.13)

The committee noted the high level of uncertainty in assuming a 100% reduction in excess fracture incidence rates with burosumab, upon achieving serum phosphate normalisation. The committee concluded that real-world evidence is needed to support the assumption and exploring different morbidity benefits from a reduction in excess fracture incidence with burosumab is appropriate. The company's response highlights that only one new fracture was identified in the burosumab arm of the CL303 trial during a 48 week observation period (68 patients*48 weeks = 62.7692 patient-years of observation) and one new fracture found in the placebo -> burosumab group between weeks 24 and 48 while participants were taking burosumab (66 patients*24 weeks = 30.4615 patient-years of observation). Therefore, the estimated annual fracture rate based on the CL303 trial is 0.02145 (2 fractures over 90.2308 patient-years), which is lower than the general population fracture rate applied in the model for 18-year-olds of 0.024 and increasing to above 0.050 by the end of the modelled time period.

The EAG notes that while very few new fractures were identified within the short follow-up period of CL303, the EMA assessment report for burosumab clearly states that normalisation of the bone may take months or even years to heal (supported by evidence from CL304 that showed that bone structure was not completely normalised at week 48 in bone biopsies), which could contribute to a continued incidence of new fractures despite burosumab treatment. The EAG also notes that the only data available to support the effects of burosumab on fractures is a post-hoc exploratory analysis of healing of active bone fractures or pseudofracture in CL303. At week 24, 43% (28 out of 65 fractures) of active fractures or pseudofractures had fully healed in the burosumab arm compared with 7.7% (7 out of 91 fractures) in the placebo arm, while 24.6% (16 out of 65 fractures) were partially healed in the burosumab arm but 27.5% (25 out of 91 fractures) were also partially healed in the placebo arm. Therefore, the exploratory outcomes in CL303 show only a trend towards greater healing of active fractures or pseudofractures with burosumab compared with placebo and no evidence to support a reduction in the incidence of new fractures.

The company also highlights that real-world evidence from the EAP shows that no fractures have been reported as adverse events over 389 patient-years of burosumab treatment. In addition, BUR02 with mean burosumab exposure time of 116 weeks shows no new fractures, and BUR03 based on 34 patients receiving burosumab at a single centre in Germany shows no fractures reported as adverse events. Therefore, the company maintains that their approach to modelling a 100% reduction in excess fracture incidence risk is conservative, as supported by trial evidence, the EAP, and expert elicitation on the anticipated effects of burosumab treatment on preventing future fractures (Seefried et al, 2023).

The EAG considers that while it may be clinically plausible that burosumab would lead to a reduction in fractures with improvement in serum phosphate within normal levels the assumption on the long-term effect on preventing future fractures remains uncertain, particularly the assumption that it would lead to a 100% reduction in excess fracture risk, equal to the general population.

2.7 Issue 7: Mortality benefit of burosumab (DG point 3.12)

The committee suggested that evidence on the following may inform the company's arbitrary assumption of a 50% reduction in the excess XLH mortality risk for burosumab:

- The relationship between XLH and the factors proposed to increase mortality risk in XLH (opioid use, effects on mental health, social deprivation, side effects of currently available treatments and consequences of reduced mobility).
- The mortality risk associated with factors proposed to increase mortality risk.
- The extent that burosumab may reduce any mortality risk.

The company's response draws on the potential multi-system effects of hypophosphataemia and intersectional factors that may drive increased mortality in XLH (see Table in company's response to DG) but the potential effects of burosumab treatment on this excess mortality is not known. The company assumes that by addressing the root cause of XLH (i.e. normalising phosphate homeostasis) and mitigating the ongoing, multi-system effects of hypophosphataemia that may drive increased mortality, treatment with burosumab will extend life expectancy. The company provides some details on the association between factors proposed to increase mortality risk and mortality, but none of this external evidence is used in the model to quantify how burosumab could potentially reduce the excess XLH mortality risk. Therefore, the EAG considers the extent of any mortality reduction remains unknown.

2.8 Issue 8: Stopping criterion and discontinuation (DG point 3.9)

The committee considered uncertainty on the stopping criteria and noted that the EAP does not include a stopping rule. It noted that it was unclear how a stopping rule would be implemented in clinical practice. The committee also noted the additional benefits of burosumab, such as reduced side effects and opioid use, that adults with XLH may benefit from despite their WOMAC total score not meeting the improvement threshold. Therefore, the committee preferred not to include a stopping rule in the model.

The company's response refers to the draft recommendations for the management of XLH in adults in the NHS (Mohsin et al., 2022), which states, "Review Burosumab therapy annually within an MDT and consider stopping burosumab after 12 months if average pain over the last week has not improved AND there has not been a reduction in analgesic use from baseline." Based on this draft recommendation, the company have provided a new scenario based on the requirement of improvement in pain at one year. The company states that in the CL303 trial, 43 participants fulfilled the pain criteria at 48 weeks, i.e. their reported BPI score improved compared to baseline, leading to 65.15% patients continuing treatment after one year.

The EAG have a number of concerns related to this scenario. First, it is unclear whether the criteria for continuation of burosumab in the scenario is based only on an improvement in pain at 12 months after starting treatment, or whether it also includes the requirement of reaching serum phosphate levels above LLN at 24 weeks (noting that the criteria used in the company's base case is continuation of treatment based on a requirement of reaching serum phosphate levels above LLN at 24 weeks AND an improvement in WOMAC total score at 12 months after starting treatment). Second, the pain criteria based on observed improvement in BPI score over 48 weeks from CL303 is not the same criteria as discussed in the draft recommendations for the management of XLH in the NHS and may only be considered a proxy for "average pain over the last week has not improved and there has not

been a reduction in analgesic use from baseline". Third, the new scenario leads to a larger proportion of patients discontinuing burosumab treatment at one year, i.e., 34.85% compared to 16.9% in the company's base case analysis, despite the concern of the committee that it is more likely that no stopping criteria is used; in the absence of alternative treatments available and the patient has reached the target of serum phosphate normalisation after week 24, it may not seem reasonable to impose an additional hurdle because of the potential to experience a reduction in morbidities and mortality with phosphate levels maintained and the other benefits of burosumab such as a reduction in opioid use for pain management and reduced side effects. Fourth, the mean change from baseline in utility mapped from WOMAC for the subset of patients fulfilling the pain criteria is substantially higher than the utility values used in the company's base case analysis (0.240 [under pain criteria] vs. 0.215 [base case criteria] from year 3 onwards), which substantially reduces the company's base case ICER from [redacted] to [redacted], but the EAG notes that there were some imbalances in baseline characteristics between the arms of CL303, including greater pain intensity in the burosumab arm compared to the placebo arm, indicating potentially greater pain burden in the burosumab arm at baseline that would lead to a greater reduction in pain and changes in WOMAC scores from baseline.

2.9 Issue 9: Excess XLH mortality risk (DG point 3.11)

The company assumed a hazard ratio of 2.88 (95% confidence interval [CI]: 1.18 to 7.00) for the excess mortality risk associated with XLH compared with the general population to inform the survival of patients on conventional care, while the EAG preferred to use a hazard ratio of 2.33 (95% CI: 1.16 to 4.67) based on the larger and more recent sample of data from the UK CRPD GOLD and CPRD AURUM databases between 1995 and 2022. However, the extent of social deprivation associated with XLH and its link to mortality rates remained unclear. The committee agreed that if such a link did exist, an analysis adjusting for deprivation would be preferred.

The company confirmed that its confirmatory study (preferred by the EAG) does control for deprivation, as the Index of Multiple Deprivation (IMD) was one of the matching variables. Ten non-XLH controls of the same age, gender, IMD and ethnicity were matched to each XLH case. The resulting HR for overall survival between the likely or highly likely XLH population and the matched cohort was 2.33 (95% CI, 1.16 to 4.67), which is approximately a 30% lower risk than the HR of 2.88 (95% CI, 1.18 to 7.00) from Hawley et al used in the company's base case analysis. The company have provided a new analysis of its confirmatory study with IMD quintile added as a factor covariate within the Cox PH model (allowing it to have four dummy categories). The company states that the resulting hazard ratio for mortality from this analysis is 2.49 (95% CI, 1.23 – 5.02), compared with 2.33 (95% CI, 1.16 – 4.67) from the original analysis. The EAG does not have access to the model or data and cannot confirm the company's additional analysis. The EAG notes that the company have

not provided revised base case cost-effectiveness results with the new hazard ratio of 2.49 (95% CI, 1.23 – 5.02).

2.10 Issue 10: Tapering of treatment effect (DG point 3.10)

The company provides no new evidence or information to support issue 10. In the company's base case results different tapering assumptions are assumed for mortality and morbidity when stopping burosumab. The committee concluded that the assumptions were arbitrary but agreed with the EAG's approach to using the same assumptions for both morbidity and mortality treatment effect tapering. The two points emphasised by the company in their response were previously reported in the company submission:

- Morbidity (i.e. fractures) and utilities change quickly, and the tapering should therefore happen in a shorter period of time. The company model therefore assumed an immediate impact on fractures (note, there were no new fractures reported in CL303 after 24 weeks, no fractures in BUR02 and no fractures in the EAP), and a within one-year disappearance of the impact.
- The impact on mortality, however, is more complex. Over time, burosumab treatment is expected to increase physical activity levels, reduce opioid use, reduce obesity and improve mental health. These effects take time, so the experts suggested a longer time period of tapering: both a delay in the positive impacts at the start of treatment as well as a delay in the loss of benefits after treatment discontinuation.

The EAG notes that the tapering of treatment effect assumptions have the least impact on the cost-effectiveness results (see Scenarios 12 – 14 of the EAR) compared to the other key assumptions related to utility values in the model, incidence of fractures, and reduction in excess XLH mortality risk.