XLHuk

Exploring Perspectives of People with XLH:
Insights into Disease Impact, Daily Challenges, and Treatment Views

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Abstract

Background. X-linked hypophosphataemia (XLH) is a genetic disorder causing severe symptoms, with limited effective treatments, leading to a significant disease burden.

Objective. This study aimed to understand the experiences of individuals with XLH, including symptom burden, daily life impact, and perceptions of current therapies.

Design. Cross-sectional study.

Methods. A survey was conducted with input from UK-based individuals living with XLH, encompassing all age groups. The survey collected data on the demographics, symptoms, and health indicators of people with XLH, utilising the EuroQol 5-Dimensions 5-Level (EQ-5D-5L) framework to assess quality of life. Information on disease management was gathered, including opinions on current disease-specific treatments (e.g., burosumab, phosphate, calcitriol, or vitamin D supplements). Statistical analyses were performed to investigate differences in the perceived effectiveness of disease-specific treatments, as well as to assess the potential association between burosumab usage and various health outcomes.

Results. Data were collected from 110 people living with XLH and 19 caregivers. People with XLH were prescribed various disease-specific treatments, which included vitamin D supplements (10.9%), phosphate and calcitriol supplements (31.8%), and burosumab (37.2%). Sixty-one percent of burosumab users considered their treatment to be “extremely effective”, as opposed to 2% of vitamin D/phosphate and calcitriol users. Compared to people with XLH who did not receive burosumab treatment, those that did reported better ability to perform usual activities (OR = 0.28, 95% CI = 0.12 – 0.62), a lower level of pain/discomfort (OR = 0.27, 95% CI = 0.12 – 0.61), reduced anxiety (OR = 0.19, 95% CI = 0.010 – 0.42), and better ability for mobility (OR = 0.45, 95% CI = 0.20 – 0.98) and self-care (OR = 0.70, 95% CI = 0.21 – 0.96).

Conclusion. The use of burosumab was associated with increased satisfaction and improved health scores in this study. However, further research is needed to validate these findings.

Keywords: X-linked hypophosphataemia (XLH); Burosumab; Quality of life.

Background

X-linked hypophosphataemia (XLH) is a dominant genetic disorder caused by mutations to the PHEX gene on the X chromosome. This mutation leads to over-production of fibroblast growth factor 23 (FGF23), resulting in low levels of blood phosphate. Symptoms typically emerge in early childhood, including abnormal bone growth, delayed walking, and a waddling gait. In adults, XLH presents with osteomalacia, muscle weakness, pain, fatigue, and hearing loss (1).

XLH is rare, with an estimated prevalence of 3.9 per 100,000 births, but the exact prevalence remains elusive due to the difficulties diagnosing XLH (2). In the UK, the prevalence has been estimated at 14 cases per million population, equivalent to around 950 people with XLH (3,4). However, due to diagnostic challenges and limited understanding of the disease, many people with XLH lack necessary support from their families and medical professionals for the condition. This uncertainty affects various aspects of life, including education, work, relationships, self-confidence, and mental health (2,5).

Current treatment aims to improve growth, reduce skeletal deformities, and manage pain through vitamin D supplementation and oral phosphate, often with dosing 4 to 6 times a day. However, studies reveal significant disease burden despite treatment, including chronic pain and diminished physical and mental health (6). Widely reported issues such as multiple daily dosing, variable drug efficacy, and side effects further underscore the need for better treatment options (6).

Burosumab (Crysvita®), developed by Kyowa Kirin, is a monoclonal antibody that inhibits excess FGF23 activity. It received marketing authorisation for childhood XLH treatment in 2018. Studies have shown that burosumab is effective in normalising blood phosphate and reducing bone deformities, with most adverse events exhibiting mild to moderate severity (7,8). While the Scottish Medicines Consortium recommends burosumab use in children and adults, based on the available evidence, NICE recommends use for children in their guidance on burosumab for treating X-linked hypophosphataemia in children and young people (October 2018) (9–11).

Some adults in England can access burosumab through the Early Access Programme, but it remains inaccessible for most people with XLH. XLH UK, works to support people with XLH and their families in the UK. They raise awareness through publishing stories depicting the lived experience of people with XLH and contribute to research efforts (12). XLH UK currently collaborates with NICE to incorporate patient perspectives into decision-making processes in NICE's ongoing Single Technology Appraisal.

Despite the challenge of low disease prevalence, XLH UK surveyed 129 people with XLH to gather insights into living with XLH and caring for people with XLH, as well as their experience with burosumab amongst those who received it. The study aims to enhance

understanding of disease burden and burosumab's real-world impact on the satisfaction of people with XLH alongside existing clinical studies.

Methods

A survey was co-designed by XLH UK, Metabolic Support UK—two disease-specific patient organisations—and people living XLH. The goal of the survey was to obtain perspectives of living with XLH, including the burden of symptoms, impact of the disease on day-to-day life, and views on existing treatments.

A small group of people with XLH and their caregivers tested the survey prior to recruitment using the XLH UK and Metabolic Support UK's databases. The survey was also promoted through social media platforms and on the organisations' websites. The survey collected responses from the 2nd of Oct 2022 to the 30th of Oct 2022.

The survey collected demographic information including current age group, age of diagnosis, employment status and country of residence. Information about disease management were also collected, including the professional help sought, current disease-specific medication (e.g. burosumab, Phosphate, calcitriol, or vitamin D supplements) and additional symptom management drugs (e.g. painkillers). Subjective opinions about the effectiveness of current treatments were recorded. Current XLH symptoms (e.g abnormal gait and muscle pain) were also recorded with answers rated on a Likert Scale. To evaluate patient reported outcomes (PROs), two measures were used. People with XLH were asked to rate their overall level of health (from 1-100, worst to best health) and answer the EuroQol 5-Dimensions (EQ-5D-5L) questionnaire. EQ-5D-5L is a validated tool for capturing PROs developed to measure the health of respondents using five questions. These are the current level of mobility, pain/discomfort, anxiety/depression, and level of independence with self-care and performing usual activities. Respondents then score themselves using five levels: no, mild, moderate, severe and extreme (or "unable to" in the case of "mobility" and "self-care"). For example, a person experiencing severe pain will give a score of 4 in the "pain' category, whereas another person who experiences mild pain will give score of 2 in the same category. Responses are combined to form an EQ-5D-5L profile that summarises the respondent's state of health (13).

Research questions

In addition to describing the main characteristics of the surveyed population (survey responder, age, age of diagnosis, place of residence, employment status, disease symptoms, current treatment, hospital type where treated, responses regarding each domain of the EQ-5D and overall health questionnaires, and perception of treatments) the following research questions were addressed based on the information collected in the survey:

- Does attending specialist or teaching hospitals result in people with XLH being more likely to receive burosumab treatment compared to attending general hospitals in the UK?
- Are there significant differences in the perceived effectiveness between burosumab and other disease-specific treatments amongst people with XLH?
- Is there an association between burosumab use among people with XLH and aspects of their well-being measured by the EQ-5D-5L framework or an overall health score? If so, what is the magnitude of this association?

Statistical analysis

To visually examine the survey data prior to statistical tests, demographics, symptoms, and wellbeing characteristics of people with XLH were plotted using frequency distributions and summary statistics. A series of statistical methods—depending on the variable type—were used to address each of the research questions. **Table 1** outlines the variables tested, their types, and the corresponding statistical tests used.

Table 1. List of variables and the statistical methods used.

Goal	Variable type	Outcome variables	Methods used
Assess the potential association between reported burosumab usage and factors such as the type of hospital providing medical care, perceived treatment effectiveness, and health outcome scores.	Continuous	Self-reported health scores	T-test or ANOVA (>2 groups)
	Ordinal	EQ-5D-5L domains	Mann-Whitney U test or Kruskal-Wallis test (>2 groups)
		Perceived treatment effectiveness	
	Categorical	Hospital type	Chi-square of independence
Quantify the potential association between reported burosumab usage and health outcome scores.	Continuous	Self-reported health scores	Linear regression
	Ordinal	EQ-5D-5L	Ordinal logistic regression

A mix of linear regression and ordinal logistic regression were used to quantify the potential association between reported burosumab use and health outcomes. The regression model reports the results as adjusted odds ratio (OR) instead of relative risk (RR), given the cross-sectional nature of the study and the lack of longitudinal follow-up.

The analysis also considered factors which may bias the relationship between burosumab uptake and health. These factors are referred to as confounders and included age and employment status. Age was selected as a confounder as a previous study noted that phosphate level varies with age in people with hypophosphataemia (14). Meanwhile, employment status was selected for its pronounced effect on mental health (15). We considered other variables, such as age of diagnosis and hospital types, as potential confounders, but we did not observe a significant association between these variables and both the dependent and independent variables warranting inclusion in the model as confounders. Additionally, we did not find additional literature to justify their use as confounders.

Results

Study population

The survey was completed by 110 individuals living with XLH and 19 caregivers of people with XLH. Amongst the 129 people with XLH, 15 of them (11.6%) were children below the age of 18, and the biggest age group was 30-40. The mean age of XLH diagnosis was 6.1. Most respondents reported living in England (75.2%), with fewer living in other parts of the UK including Wales (12.4%), Scotland (7%), Northern Ireland (3.1%) and overseas territories (1.6%), with one respondent living in Ireland. Most of the adult respondents reported currently working, either full-time (39.5%) or part-time (23.3%), while a significant proportion of them were on long-term sick leave (8.5%) or had become full-time carers (often for family members suffering from hereditary XLH). **Table 2** summarises the main demographic characteristics of the survey respondents.

Table 2. Main demographic characteristics.

Demographic characteristics	People with XLH (n = 129), n (%)
Survey responder	
People with XLH	110 (85.3)
Parent/Carer of people with XLH	19 (14.7)
Age group	
<18	15 (11.6)

18-30	25 (19.4)
30-40	37 (28.7)
40-60	36 (28.0)
>60	13 (10.1)
Place of residence	
England	97 (75.2)
Wales	16 (12.4)
Scotland	9 (6.98)
Northern Ireland	4 (3.10)
Channel Islands	2 (1.55)
Republic of Ireland	1 (0.78)
Employment status	
Employed full-time	51 (39.5)
Employed part-time	30 (23.3)
Long term sick leave	11 (8.53)
Stay at home / full-time carer	11 (8.53)
Full-time student	9 (6.98)
Retired	9 (6.98)
Self-employed	4 (3.10)
Unemployed	3(2.33)
Prefer not to answer	1 (0.78)
Age of diagnosis, mean (SD)	6.1 (12.2)

Disease management amongst people with XLH

Amongst the 129 respondents, about 55% attended a teaching hospital, while 28.6% visited a specialised hospital and 17% attended a general hospital. Regarding their current disease-specific treatment, 48 of them (37.2%) reported burosumab use at the time of survey, and 55 of them (42.6%) reported the use of phosphate/calcitriol supplements or vitamin D supplements.

Table 3. Demographic characteristics of the respondents.

Demographic characteristics	People with XLH (n = 129), n (%)
Hospital type	
General	19 (17.0)
Specialist	32 (28.6)
Teaching	61 (54.5)
Unknown	17 (13.2)
Current treatment	
Burosumab	48 (37.2)
Phosphate and calcitriol supplements	41 (31.8)
Vitamin D supplements	14 (10.9)
I'm not having any treatment	25 (19.4)

Using chi-square test of independence, we found that people with XLH who are attending specialist and teaching hospitals were more likely to receive burosumab treatment ($p = 0.014$), with its usage observed in 47.5% of respondents attending a teaching hospital, 43.8% attending specialist hospitals, and 10.5% attending general hospitals.

Burden of XLH

The study population reported a range of XLH symptoms ranging from narrowing of the spinal canal (32.3%) to growth delay/short statures (93.8%). **Figure 1** describes the prevalence of XLH symptom severity, ranging from mild, moderate to severe, for each symptom. The prevalence of XLH symptoms in percentages is described in **Appendix Table 1**.

Figure 1. Prevalence of symptoms people with XLH experience

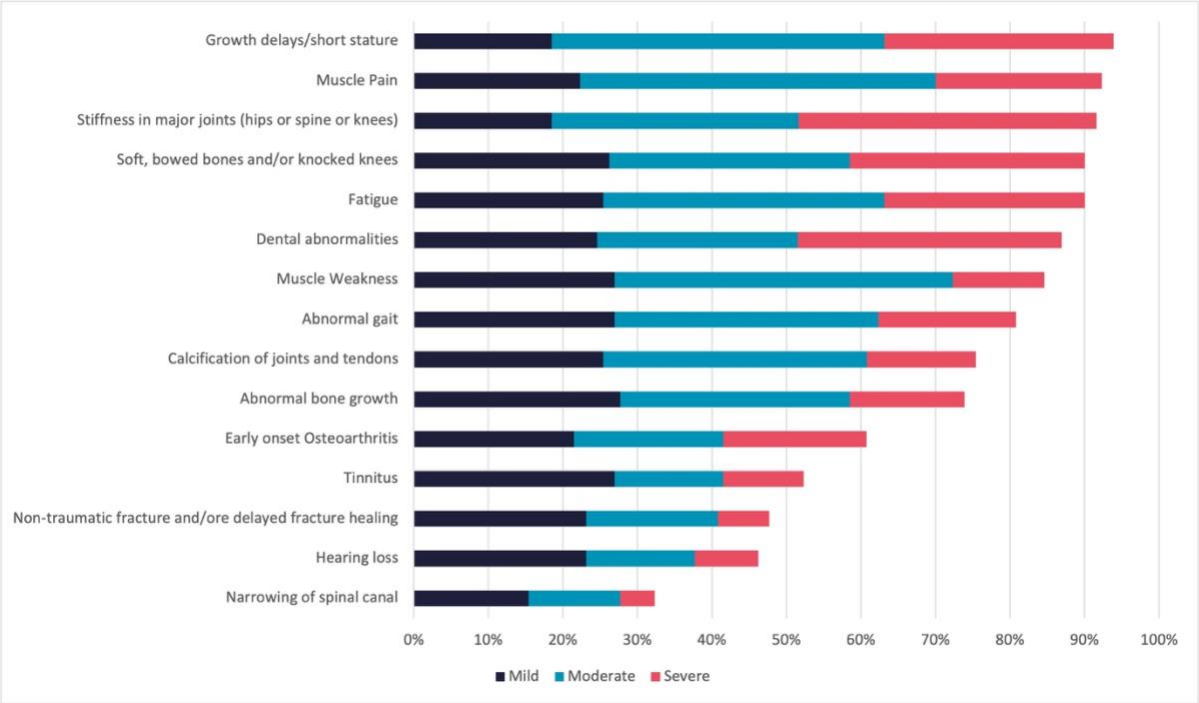

Figure-1.

Perception of disease-specific treatments of people with XLH

A significant disparity was observed in the perceived effectiveness of disease-specific treatments among people with XLH: 96% of respondents using burosumab reported it as "moderately" or "extremely effective" in symptom management, while only 36% of respondents on standard treatments regarded the treatment as "moderately" or "extremely effective" ($p < 0.001$). **Figure 2** shows the perception of treatment effectiveness amongst respondents who report the use of each type of disease-specific treatment.

Figure 2. Perception of disease-specific treatments.

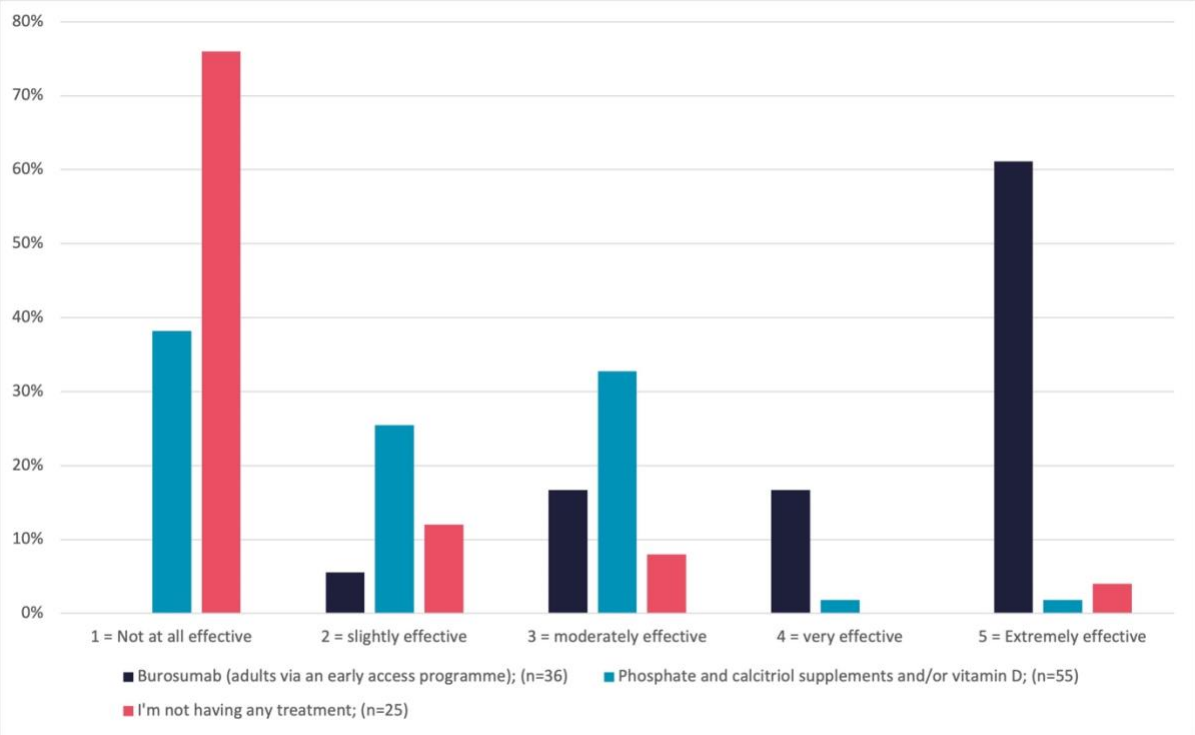

Figure-2.

Quality of life and overall level of health

Responses were collected for each domain of quality of life using the EQ-5D-5L, as well as for the overall health score for all people with XLH surveyed. **Appendix Figures 1 to 5** summarise the findings of the quality of life, presenting the percentage of responses for each questionnaire item in each domain of the EQ-5D-5L. The quality of life of respondents was found to be lower than that of the average for UK adults (16) (see Appendix Figures 1 to 5 for more information). Regarding the overall level of health score, a median value of 60 with an interquartile range between 47 and 75 (on a scale of 0-100) was observed, where 5 and 100 represented the minimum and maximum values obtained, respectively.

Reported burosumab use was significantly correlated with better scores in addressing pain/discomfort (OR = 0.27, 95% CI = 0.12 – 0.61), anxiety/depression (OR = 0.19, 95% CI = 0.010 – 0.42), mobility (OR = 0.45, 95% CI = 0.20 – 0.98), performing usual activities (OR = 0.28, 95% CI = 0.12 – 0.62) and self-care (OR = 0.70, 95% CI = 0.21 – 0.96). In addition, respondents who reported burosumab use, on average, also reported better health by 18.6 points (95% CI = 10.06 – 27.05) on a 100-point scale.

The OR results represent the difference, between the two groups, in terms of the likelihood a respondent may report a worse level of disease-attributable health impact on the five-point ordinal scale used in EQ-5D-5L. For example, compared to respondents reporting the use of standard treatment (or no treatment at all), those who reported burosumab use are, on average, 73% less likely to also report worse health by one point on the five-point scale for pain/discomfort (OR = 0.27).

Table 4. Association between reported use of burosumab and patient-reported outcomes.

EQ-5D-5L dimensions	p-value	Adjusted odds ratio	95% CI
Mobility	**0.006**	0.45	0.20 – 0.98
Self-care	**0.045**	0.70	0.21 – 0.96
Usual activity	**<0.001**	0.28	0.12 – 0.62
Pain/discomfort	**<0.001**	0.27	0.12 – 0.61
Anxiety/depression	**<0.001**	0.19	0.010 – 0.42
Additional outcome	**p-value**	**Coefficient**	**95% CI**
Overall health	**<0.001**	18.6	10.06 – 27.05

Reported disadvantages of disease-specific treatments

All respondents were requested to outline the pros and cons of their current disease-specific treatments. Among respondents receiving standard treatments (such as vitamin D or phosphate and calcitriol supplements), nearly all expressed dissatisfaction. The predominant concerns included ineffective treatment, challenges in adhering to a complex dosing regimen, gastrointestinal discomfort, and other adverse effects. Conversely, respondents receiving burosumab primarily reported satisfaction regarding its effectiveness and ease of administration. However, four respondents noted experiencing restless legs as a side effect.

Discussion

This study used a survey of 129 people with XLH to understand the disease impact as well as the perceived satisfaction regarding the effectiveness of disease-specific treatments. Debilitating symptoms were common, including moderate to severe muscle pain and stiff joints which affected around 70% of all people surveyed. To manage or treat their symptoms, people with XLH reported using various disease-specific medications, including

burosumab and other standard treatments such as vitamin D, phosphate, and calcitriol supplements.

The notable finding that 96% of people with XLH who received burosumab reported it as "moderately" or "extremely effective" in managing their symptoms stands in clear contrast to the 36% effectiveness rating reported for standard treatments. The disparity in perceived effectiveness between burosumab and the other standard treatments among people with XLH underscores the potential impact of this novel therapeutic agent in addressing the unmet needs of people living with this rare genetic disorder. Our analysis also revealed potential associations between burosumab use and key dimensions of PROs. Specifically, individuals who reported using burosumab demonstrated significantly better scores in each of the EQ-5D quality of life domains compared to those who did not use burosumab.

However, it is crucial to acknowledge that these findings can't be interpreted as causal. The cross-sectional design of this study limits our ability to establish cause-and-effect relationships between burosumab use and PROs. While significant associations have been identified between burosumab use and better scores in certain aspects of well-being, the possibility that other unmeasured or unknown factors are contributing to these associations cannot be ruled out. For instance, the presence of selection bias or other residual confounding could not be controlled for and could influence the observed results. Due to the small sample size, only a small number of confounders could be selected to avoid overfitting (17). While the results suggest promising associations between burosumab use and better health scores among people with XLH, further observational studies incorporating robust epidemiological and statistical methodologies are essential to comprehensively assess the real-world implications of this drug in the XLH population.

Another limitation of this study was the absence of data collection on the gender and ethnicity of the surveyed individuals. Understanding how gender and ethnicity intersect with the experience of living with XLH could offer valuable insights into potential disparities in symptom manifestation, treatment outcomes, and overall quality of life. Moving forward, it would be important for future research to incorporate these dimensions to achieve a more thorough understanding of the disease and its impact on the lives of people with XLH.

The distribution of people with XLH seeking care across different types of hospitals in our study population highlights potential disparities in access to burosumab treatment. The findings indicate the likelihood of receiving burosumab varies based on the type of hospital attended, with higher rates observed among people attending specialist and teaching hospitals compared to those attending general hospitals. This suggests that people with XLH who seek care at specialist and teaching hospitals may have better access to burosumab treatment, potentially due to factors such as hospital resources, expertise, and referral patterns amongst other factors. Addressing these disparities in access to care is essential to promote health equity and improve outcomes for all people affected by XLH.

Our study presents several strengths. Firstly, based on estimation of disease prevalence and population data (3,4), there are approximately 938 people with XLH in the UK, meaning the

study sample in the current study represents about 15% of the total XLH population. This participation rate mirrors the result from Rare Disease Europe's 2018 study, which revealed that around 15% of people with rare diseases have participated in quality-of-life research in the past (18). The current study also has a higher coverage rate than the largest XLH quality-of-life study to date, which took a sample mostly from the US (6). The extensive participation from people with XLH ensured respectable sample representativeness and enhanced the external validity of the results. Moreover, the co-design of the survey with people living with XLH ensured the collection of data captures meaningful real-world lived experience. A sound methodological design, including survey development and testing, has been implemented, along with the most appropriate statistical analyses given the sample size and completeness of the variables collected. Lastly, the study findings have the potential to inform decision makers and clinicians about evidence on treatment satisfaction and real-world treatment experiences in people with XLH.

While the results suggest promising associations between burosumab use and better health scores among people with XLH, other studies, preferably randomised and controlled, need to be considered to establish a robust causal relationship and validate the treatment's efficacy.

Conclusion

XLH causes debilitating symptoms, and the lack of effective treatment leaves most people with XLH with substantial disease burden. While burosumab usage was associated with enhanced satisfaction and better health scores in this study, this information should be complemented by other research studies that appropriately determine the efficacy and safety of this treatment to ensure informed decision-making.

Funding

The study was conducted with funding provided by XLH UK. This financial support enabled the execution of the survey, data analysis, and manuscript writing.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgements

The authors would like to express their gratitude to XLH UK and Metabolic Support UK, two disease-specific patient organisations, for their invaluable support and collaboration throughout this study. Additionally, the authors extend their appreciation to the

respondents of the surveys, including individuals living with XLH and carers, whose participation made this research possible.

Ethical considerations

All participants provided informed consent prior to participating in the survey. Participants were assured that their responses would remain anonymous and that their participation would have no negative impact on their current care. Participants were informed that their anonymized responses might be used in other research or for marketing purposes by XLH UK and Metabolic Support UK.

Consent to participate

Informed consent to participate in this study was obtained from all individual participants included in the study. Consent was collected in written form, and participants were informed that their responses would be anonymized and used to present patient and carer perspectives in the evaluation of Burosumab. Participants were assured that their submission would remain anonymous and that the responses provided would have no negative impact on the care they currently receive.

Consent for publication

Consent for publication of anonymized data was obtained from all individual participants included in the study. Participants were informed that their anonymized responses might be used in other research or for marketing purposes by XLH UK and Metabolic Support UK.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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