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ORIGINAL RESEARCH

Real-World Effectiveness of Burosumab in Adults with X-Linked Hypophosphataemia (XLH) in the UK

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Abstract

X-linked hypophosphataemia (XLH) is a genetic phosphate-wasting disorder caused by excess fibroblast growth factor 23 (FGF23), which leads to skeletal morbidities, pain, stiffness, and impairments in physical function and health-related quality of life. Burosumab inhibits excess circulating FGF23, restoring bone biochemistry. Here we report real-world data from adults with debilitating XLH symptoms who started treatment with burosumab through a UK early access programme. Change from baseline was assessed for bone biochemistry and patient-reported outcomes (PROs) collected from patients' medical records from September 2019 to December 2022. The proportion of patients ($n = 136$; 66% female, median age 44.0 years [range 18–83]) with normal serum phosphate increased from 5% (6/126) at baseline to 63% (52/82) after 6 months' burosumab treatment; mean serum phosphate increased significantly from baseline. Significant improvements from baseline were observed in Brief Pain Inventory short-form Worst Pain, Pain Severity and Pain Interference scores (mean [SD] improvement at 6 months: 1.8 [2.3], 1.6 [2.1] and 1.9 [2.2] points, respectively). Western Ontario and McMaster Universities Arthritis Index Stiffness, Pain, Physical Function and total scores improved significantly at 6 months (15.9 [29.7], 11.4 [24.3], 15.7 [19.7] and 15.4 [18.3], respectively), as did EuroQol five-dimension five-level (EQ-5D-5L) utility and visual analogue scale (VAS) scores (0.16 [0.22] and 17.0 [21.6]). Most improvements were clinically meaningful (where benchmarks exist). This study demonstrates the effectiveness of burosumab in real-world practice, supporting findings from clinical trials, and provides new evidence that burosumab treatment substantially improves EQ-5D-5L utility and VAS scores in adults with XLH.

Keywords X-linked hypophosphataemia (XLH) · Burosumab · Real-world · Early access programme · FGF23

Introduction

X-linked hypophosphataemia (XLH) is a rare, genetic, progressive, phosphate-wasting disorder. It is caused by inactivating mutations in the *PHEX* (phosphate-regulating endopeptidase homologue, X-linked) gene, leading to increased production and activity of fibroblast growth factor 23 (FGF23) and reduced activation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [1]. Excess FGF23 activity increases renal phosphate excretion and reduces intestinal phosphate absorption [2]. The resultant hypophosphataemia in children can lead to rickets, lower limb deformities, disproportionate short stature and poor mineralisation of the teeth [1, 3]. XLH in adults is characterised by persistence of hypophosphataemia, leading to osteomalacia, the accumulation of further skeletal morbidities (such as fractures,

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pseudofractures, osteoarthritis with osteophytes, enthesopathy, spinal stenosis) and decreased muscle strength and function [4, 5]. Patients with XLH also experience musculoskeletal pain and stiffness, impaired physical function [6], reduced health-related quality of life (HRQL) and impaired psychological and emotional wellbeing, which includes negative social experiences, low self-esteem, frustration, depression and anxiety about the future [6–10].

Before burosumab became available, treatment for XLH consisted of oral phosphate supplementation and active vitamin D therapy (calcitriol or alfacalcidol). However, this treatment does not address the underlying cause of XLH, the phosphate supplements frequently cause gastrointestinal side effects and may lead to hyperparathyroidism, and active vitamin D therapy risks hypercalcaemia and hypercalciuria and their sequelae [11].

Burosumab is a fully human monoclonal antibody that inhibits the activity of FGF23, thereby directly targeting the pathological mechanism of XLH [12]. Inhibition of FGF23 restores renal phosphate reabsorption and increases the activation of 25-hydroxyvitamin D, which in turn enhances intestinal absorption of phosphate. In clinical trials in children, burosumab treatment (without phosphate supplements or active vitamin D) was associated with improvements in serum phosphate concentration and healing of rickets [13, 14]. Similarly, in clinical trials in adults, burosumab treatment was associated with improvements in serum phosphate concentration, improvement in osteomalacia (shown by histomorphometry on bone biopsy) and healing of fractures [15–17]. Adults treated with burosumab also had statistically significant improvements in patient-reported stiffness, pain, fatigue and physical function at 48 and/or 96 weeks of treatment, with selected scores in all measures also achieving clinically meaningful change [6]. These improvements were maintained with long-term treatment (up to 144 weeks) [18].

Burosumab is approved for the treatment of XLH in adults in the USA [19], Canada [20] (both 2018), Japan (2019) [21] and Europe [22] (2022). In 2018, the UK National Institute for Health and Care Excellence (NICE) recommended use of burosumab within the National Health Service (NHS) for children aged ≥ 1 year with radiographic evidence of bone disease and in young people with growing bones. Use in adults was recommended in 2024 [23].

An early access programme (EAP) was set up in the UK in 2019 to enable adults who had persistent XLH symptoms despite treatment with phosphate supplements/active vitamin D therapy to receive burosumab until it became available through NHS funding following the appraisal by NICE. EAPs provide an important means for patients with life-threatening or seriously debilitating conditions to access new medicines ahead of marketing authorisation or reimbursement where there is a clear unmet medical need. Such schemes also promote early engagement between manufacturers and key stakeholders (such as the Medicines and Healthcare products Regulatory Agency and NICE in the UK) to facilitate patient access to new treatments [24].

The UK EAP provides an opportunity to evaluate the effectiveness of burosumab in real-world clinical practice. Real-world data (RWD) are increasingly valued by regulators and payers to understand the natural history of rare diseases and to confirm that the efficacy outcomes seen in clinical trials are observed in the broader range of patients encountered in routine clinical practice, including patients who may not be eligible for clinical trials, such as older patients and patients with comorbidities [25]. RWD are particularly useful in rare diseases when clinical trials are, by necessity, often small. However, as yet, little RWD on the effectiveness of burosumab in adults or in European populations have been published.

The current study explored the impact of burosumab on markers of bone biochemistry and patient-reported outcomes (PROs) in burosumab-naïve adults with XLH using RWD collected during the EAP. The primary objective was to determine the proportion of patients who achieved serum phosphate concentration above the lower limit of normal (LLN; according to local reference ranges) after 6 months' burosumab treatment. Secondary objectives were to assess change from baseline in biochemistry markers and PROs (pain, stiffness, physical function, HRQL) during burosumab treatment, as well as characterising the patient population at baseline.

Methods

Study Design

This was a retrospective, longitudinal RWD collection study involving adults in the UK with XLH who received treatment with burosumab in routine clinical practice through the EAP at specialist centres experienced in the management of patients with rare metabolic bone diseases.

Patients

Patients eligible for the EAP were adults (age ≥ 18 years) with a confirmed diagnosis of XLH (based on family history or identified *PHEX* mutation) and persistent symptoms despite prior treatment with oral phosphate and/or active vitamin D at any time, as recorded in the patient's medical records, and who consented to stop treatment with oral phosphate and active vitamin D before starting burosumab. Persistent symptoms were defined as one or more of: non-healing or slow-healing fractures or pseudofractures; moderate or severe pain, stiffness and/or fatigue that, in the view of the treating physician, is attributable to XLH and compromises

HRQL; or impending orthopaedic or dental surgery. The full eligibility criteria are provided in Supplementary Table S1. Patients who had received at least one dose of burosumab through the EAP were eligible for RWD collection.

All patients receiving burosumab treatment through the EAP were invited by their treating physician to participate in the RWD collection. Patients were approached at routine clinic visits or by the care team in their usual way. Eligible patients were given a letter explaining the study and were offered the opportunity to opt out of data collection. Patients who had opted out of data collection within the NHS were not approached.

Patients received their usual treatment and clinical care during the study period (which could include native vitamin D supplementation) and no interventions or changes to patient care were made as a direct result of the study. No specific data recording was mandated.

Data Collection

The data collection period was from 1 September 2019 to 31 December 2022. Pseudonymised data at baseline and at subsequent clinic visits were collected from patients' records for this period. Only data available in the patients' medical records were included, and were transcribed by the patient's direct care team into a bespoke electronic case report form in the IBM Clinical Development electronic data capture database.

Data collected only at baseline included demographics, anthropometric measurements, previous treatment and XLH diagnosis. Biochemistry data, PRO measures and use of pain medication recorded in case notes were captured at baseline and during the data collection period for the current analysis. Biochemistry measures included serum phosphate, alkaline phosphatase (ALP), vitamin D (measured as 25-hydroxyvitamin D) and calcium, and plasma or serum parathyroid hormone (PTH) concentrations. PROs included the Brief Pain Inventory short-form (BPI-SF) Worst Pain, Pain Severity and Pain Interference; Western Ontario and the McMaster Universities Osteoarthritis Index (WOMAC) Pain, Stiffness, Physical Function and total score, and EuroQol 5-dimension 5-level (EQ-5D-5L) utility score and visual analogue scale (EQ-VAS) score. Information about these PRO measures is provided in Table 1. Safety events for the full analysis set (FAS) were reported via the established pharmacovigilance reporting system for the duration of data collection.

Ethical Considerations

The study protocol and supporting documents were approved by the East Midlands – Leicester South Research Ethics Committee (ref 23/EM/0078) and the NHS Health Research Authority and Health Research Wales (IRAS project ID 321609; 9 May 2023). Informed consent was not collected from patients as no identifiable data were accessed outside the direct care team. Only pseudonymised data were used in the analysis. A secure web-based study-specific database was used. The study fulfils the requirements of the Directive 2001/83 EC, Module VIII of Guidelines on Good Pharmacovigilance Practices, the UK General Data Protection Regulation, and the Declaration of Helsinki, and was conducted in accordance with the relevant standard operating procedures of Kyowa Kirin.

Statistical Methods

Baseline was defined as the last non-missing value (including scheduled and unscheduled assessments) before the patient received their first dose of burosumab within the EAP. To allow for variation in the timing of follow-up clinic visits, the window for data analysis was every 6 ± 3 months, based on the time between first burosumab treatment and follow-up visits. Data were analysed for the first three time points after baseline (up to 18 ± 3 months), after which patient numbers were too small for meaningful interpretation. Incomplete dates were set as the midpoint of the missing interval (missing day set to 15th; missing month set to June). Any other missing data were not imputed. Study duration was calculated as the number of days from the first burosumab treatment to the last data collection (last date within the data collection period or early study withdrawal/treatment discontinuation, whichever occurred first).

Baseline characteristics, biochemistry and PRO data at baseline and during burosumab treatment are reported for burosumab-naïve patients only, referring to patients who received their first dose of burosumab within the EAP. These outcomes were also compared between patients who were and were not taking phosphate supplements and/or active vitamin D immediately before starting burosumab treatment on entering the EAP. Continuous baseline variables are reported as the number of non-missing observations (n) and mean $\pm$ standard deviation (SD). Categorical variables are reported as the number and percentage of participants. Safety data are reported for the FAS, comprising all patients who received at least one dose of burosumab during the EAP.

The number and proportion of patients with serum phosphate concentration above the LLN (as reported by the laboratory based on local reference ranges) at 6 months is reported (primary objective). For biochemistry variables, mean change from baseline is assessed using paired t-tests (5% level of significance).

PRO scores were determined according to the published guides for WOMAC [26], BPI-SF [27] and EQ-5D-5L [28]. The England utilities value set was used for the EQ-5D-5L [29]. For all PROs, mean change from baseline was

Table 1 Patient characteristics, medical history biochemistry and PRO scores at baseline

Characteristic	Value ($N=136$)
Demographics	
Age (years), mean ± SD	44.1 ± 14.3
Female/male, *n* (%)	90/46 (66%/34%)
Ethnicity, *n* (%)	
Asian	3 (2%)
Black	6 (4%)
White	105 (77%)
Mixed	3 (2%)
Not stated	19 (14%)
Height (cm), mean ± SD ($n=109$)	154.9 ± 9.4
Weight (kg), mean ± SD ($n=128$)	73.5 ± 16.7
BMI (kg/m^2), mean ± SD ($n=108$)	31.6 ± 6.5
Medical history	
Age at diagnosis, years, mean ± SD ($n=70$)	11.2 ± 18.4
Conventional therapy immediately before starting burosumab treatment in the EAP, *n* (%)	
No	75 (55%)
Yes	51 (38%)
Not reported	10 (7%)
Conventional therapy received (n = 51), *n* (%)	
Oral phosphate and active vitamin D	30 (59%)
Active vitamin D alone	15 (29%)
Oral phosphate alone	4 (8%)
Unknown/not reported	2 (4%)
Pain medication at baseline, *n* (%)	
No	30 (22%)
Yes	77 (57%)
Not known/reported or missing	29 (21%)
Serum biochemistry values, mean ± SD	
Phosphate (mmol/L)	0.61 ± 0.16
Alkaline phosphatase (IU/L)	131.1 ± 53.0
Parathyroid hormone[a] (pmol/L)	8.20 ± 4.764
Calcium (mmol/L)	2.39 ± 0.12
Vitamin D[b] (nmol/L)	52.5 ± 23.0
PRO scores, mean ± SD	
BPI-SF	
Worst Pain ($n=101$)	6.9 ± 2.1
Pain Severity ($n=100$)	5.5 ± 2.1
Pain Interference ($n=101$)	5.7 ± 2.5
WOMAC	
Pain ($n=97$)	51.2 ± 21.0
Stiffness ($n=97$)	65.1 ± 23.9
Physical Function ($n=97$)	50.5 ± 23.8
Total score ($n=97$)	52.0 ± 22.3
EQ-5D-5L	
Index score ($n=108$)	0.51 ± 0.3
EQ-VAS ($n=103$)	54.2 ± 20.5

[a]Measured in plasma at one centre

[b]Measured as 25-hydroxyvitamin D

The BPI-SF uses a numerical rating scale from 0 (no pain) to 10 (maximum pain/pain severity/pain interference) [27]. Worst Pain, Pain Severity and Pain Interference comprise one, four and seven items, respectively. The reference period is 24 h. WOMAC comprises 24 items (5 for pain; 2 for stiffness; 17 for Physi-

Table 1 (continued)

cal Function) and a total score [27]. Each item is scored on a 5-point scale (none, mild, moderate, severe, extreme). The reference period is 48 h. The EQ-5D-5L comprises five domain scores (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), which are used to determine a utility score [28]. Current health status is scored on a 0–100 visual analogue scale (the EQ-VAS). The reference period is today

BMI body mass index, *BPI-SF* Brief Pain Inventory short-form, *EAP* early access programme, *EQ-5D-5L* EuroQol five-dimension, five-level, *EQ-VAS* EuroQol visual analogue scale, *PHEX* phosphate regulating endopeptidase X-linked gene, *PRO* patient-reported outcome, *SD* standard deviation, *WOMAC* Western Ontario McMaster Universities Osteoarthritis Index

assessed using paired *t*-tests (5% level of significance). The number and proportion of patients with score changes greater than the minimum clinically important difference (MCID) were also determined (where MCIDs in XLH have been determined) [30, 31].

Change from baseline in biochemistry and PROs in patients who were and were not taking phosphate supplements and/or active vitamin D before starting burosumab in the EAP were compared using unpaired *t*-tests.

The duration of burosumab treatment refers to treatment within the EAP. Time to treatment discontinuation is determined using Kaplan–Meier survival analysis.

Results

Data were collected for the 142 patients enrolled in the EAP (the FAS) and were analysed for the 136 who were burosumab-naïve at baseline.

Patient Characteristics and Medical History

Characteristics, treatment and medical history for the burosumab-naïve patients are summarised in Table 1, and for the FAS in Supplementary Table S2. The median age of the burosumab-naïve patients was 44.0 years (range 18–83; mean 44.1 [SD 14.3] years) and approximately two-thirds (66%) were women. The mean age at XLH diagnosis was 11.2 (SD 18.4) years and the mean time from diagnosis to first dose of burosumab was 31.5 (SD 18.2) years in the 70 burosumab-naïve patients for whom this was reported. Fewer than half of the burosumab-naïve patients (51/136; 38%) were taking phosphate supplements and/or active vitamin D immediately before starting burosumab treatment in the EAP; 59% (30/51) of these patients were taking both. Baseline characteristics were similar in those who were and were not taking phosphate supplements and/or active vitamin D before starting burosumab on EAP entry. More than half of patients (77/134; 58%) were taking pain medication at baseline.

Biochemistry

The proportion of burosumab-naïve patients with serum phosphate ≥ LLN increased from 5% (6/126) at baseline to 63% (52/82) after 6 months' burosumab treatment (primary objective). Serum phosphate concentrations > LLN were reported in 50% of patients (28/56) after 12 months' treatment and in 41% of patients (21/51) after 18 months (Fig. 1). To assess the potential impact of attrition bias, outcomes were also assessed for a subsample of 20 patients for whom data were recorded at all time points from baseline to 18 months. Results for these patients were comparable to those for the overall cohort (Supplementary Table S3).

Biochemistry values at baseline are reported in Table 1 and changes during treatment are shown in Figure 2. Serum phosphate was significantly higher than baseline at all time points from 6 to 18 months. Serum ALP decreased significantly from baseline at 12 and 18 months. Serum PTH concentration decreased significantly from baseline at 6 and 18 months. Significant increases from baseline in serum calcium concentration were seen at all time points. The concentration of 25-hydroxyvitamin D increased from baseline at

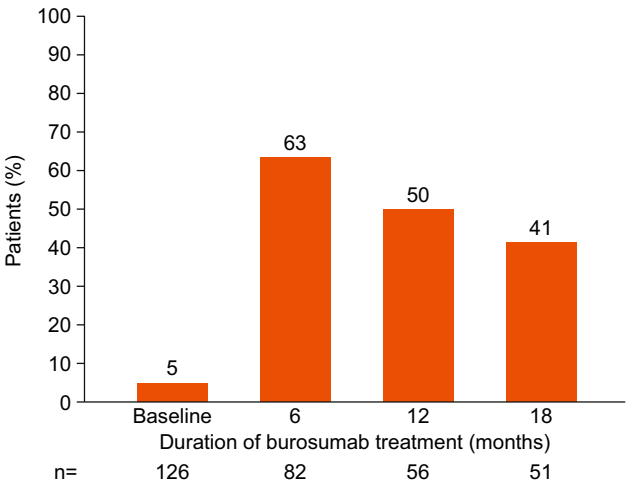
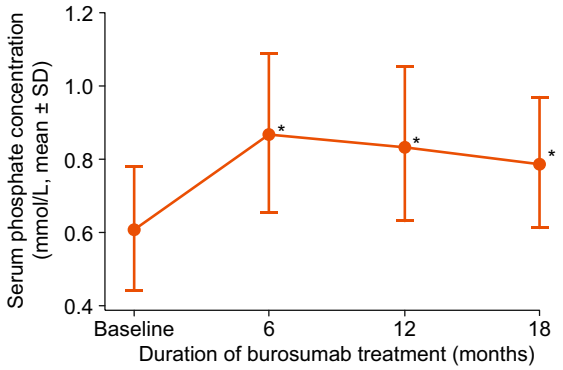


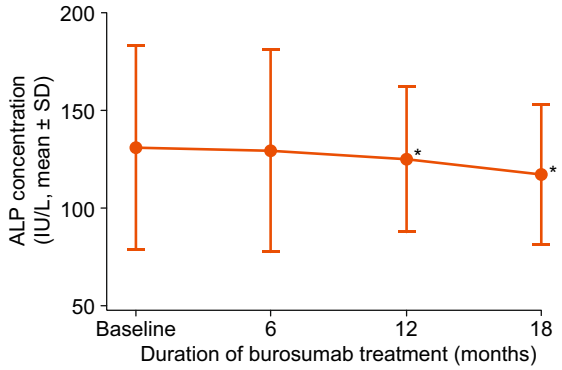
Fig. 1 Proportion of patients with serum phosphate concentrations above the lower limit of normal (LLN). Serum phosphate concentrations are reported as above or below the LLN by each laboratory based on the local reference range

A. Serum phosphate



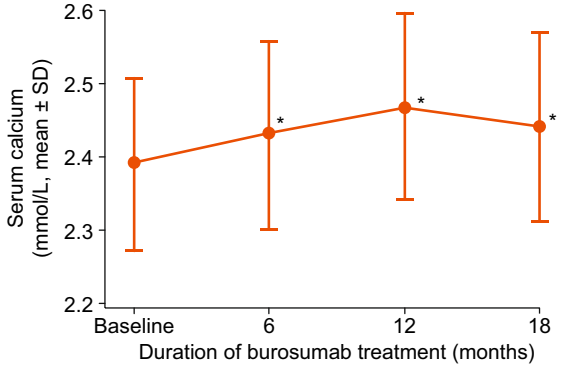
n	126	82	56	51
Mean	0.61	0.87	0.84	0.79
SD	0.17	0.22	0.21	0.18

B. Serum ALP



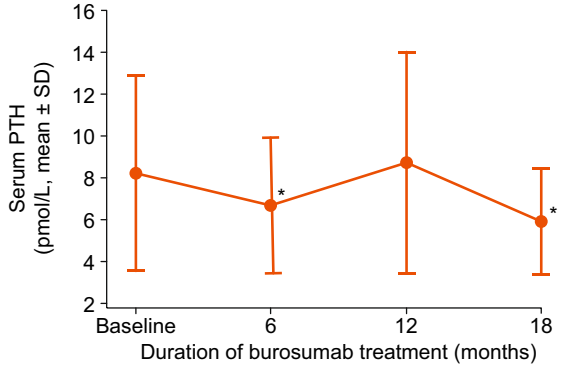
n	116	76	56	51
Mean	131.1	129.5	125.2	117.3
SD	53.0	52.6	38.0	36.7

C. Serum calcium



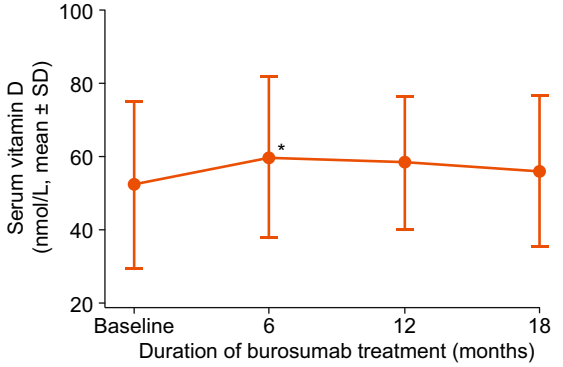
n	117	73	54	51
Mean	2.39	2.43	2.47	2.44
SD	0.12	0.13	0.13	0.13

D. Serum PTH



n	100	63	46	41
Mean	8.20	6.66	8.71	5.89
SD	4.74	3.31	5.36	2.60

E. Serum vitamin D



n	76	51	41	37
Mean	52.5	59.7	58.3	56.0
SD	23.0	22.2	18.3	20.6

Fig. 2 Mean biochemistry concentrations during burosumab treatment. Asterisks indicate significant change from baseline ($p < 0.05$). Reference ranges used in the UK are as follows, provided for reference (laboratories used local reference ranges, which may differ slightly from these): serum phosphate: 0.8–1.50 mmol/L; serum ALP: 30–130 IU/L; serum calcium (adjusted): 2.20–2.60 mmol/L; serum vitamin D: 50–99 nmol/mL; serum PTH: 1.5–7.6 pmol/L [47]. One centre measured PTH levels in plasma. Vitamin D was measured as 25-hydroxyvitamin D. *ALP*: alkaline phosphatase, *PTH*: parathyroid hormone, *SE*: standard error

all time points; the improvement was statistically significant at 6 months.

Biochemistry measures at baseline and after 6 months' burosumab treatment were similar in patients who were and were not taking phosphate supplements and/or active vitamin D before starting burosumab (Supplementary Table S4). The mean change from baseline did not differ significantly between the two groups for any of the biochemistry measures.

Patient-Reported Outcomes

PRO scores at baseline are reported in Table 1 and mean changes in PRO scores from baseline are shown in Fig. 3. The proportions of patients with clinically relevant improvements on the BPI-SF and WOMAC (i.e. exceeding the MCID) are reported in Fig. 3. There are no XLH-specific MCIDs for the EQ-5D-5L.

For the BPI-SF (each item scored 0–10, with 10 being the worst score), the mean Worst Pain score was 6.9 (SD 2.1) at baseline and decreased by a mean of 1.8 (SD 2.3) after 6 months' burosumab treatment (i.e. less pain). Mean decreases in scores were significant at all time points from 6 to 18 months and were clinically relevant in 36% (12/33) to 48% (10/21) of patients. The mean BPI-SF Pain Severity score was 5.5 (SD 2.1) at baseline and decreased by a mean of 1.6 (SD 2.1) points after 6 months' burosumab treatment (i.e. less severe pain). Decreases in BPI-SF Pain Severity scores from baseline were statistically significant at all time points from 6 to 18 months. The mean BPI-SF Pain Interference score was 5.7 (SD 2.5) at baseline and decreased by a mean of 1.9 (SD 2.2) points after 6 months' burosumab treatment (i.e. less pain interference). Decreases in the Pain Interference score from baseline were statistically significant at 6–18 months and clinically relevant in 59% (19/32) to 69% (22/32) of patients (See Table 2).

For the WOMAC Index (each domain score transformed to 0–100 scale, with higher scores indicating worse symptoms), the mean Stiffness score decreased from 65.1 (SD 23.9) at baseline by a mean of 15.9 (SD 29.7) points at 6 months. Decreases in Stiffness score from baseline were significant at 6, 12 and 18 months and improvements were clinically relevant in 55% (16/29) to 64% (21/33) of patients. The mean WOMAC Pain score decreased from 51.2 (SD 21.0) at baseline by a mean of 11.4 (SD 24.3) points at 6 months (i.e. less pain). The mean decrease in Pain score from baseline was significant at 6, 12 and 18 months and decreases in Pain score were clinically relevant in 52% (17/33) to 64% (14/22) of patients. The mean WOMAC Physical Function score improved from 50.5 (SD 23.8) at baseline by a mean of 15.7 (SD 19.7) points at 6 months (i.e. better function). Mean improvements in the Physical Function score from baseline were significant at all time points from 6 to 18 months and were clinically relevant in 55% (16/29) to 68% (9/13) of patients. The mean WOMAC total score also improved, from 52.0 (SD 22.3) at baseline by a mean of 15.4 (SD 18.3) points at 6 months. The mean improvement in WOMAC total score was significant at all time points from 6 to 18 months and was clinically relevant in 45% (13/29) to 68% (15/22) of patients.

For the EQ-5D-5L utility (range 0–1, with higher scores indicating better utility) the mean score improved from 0.51 (SD 0.28) at baseline by a mean of 0.16 (SD 0.22) points after 6 months' burosumab treatment. Change from baseline was statistically significant at 6, 12 and 18 months. Mean EQ-VAS score (range 0–100, with higher scores indicating better HRQL) also improved, from 54.2 (SD 20.5) at baseline by a mean of 17.0 (SD 21.6) points after 6 months' burosumab treatment. Change from baseline was significant at all three time points.

PRO scores at baseline did not differ significantly between patients who were and were not taking phosphate supplements and/or active vitamin D immediately before starting burosumab (Supplementary Table S5). The mean change from baseline was not significantly different between the two groups for any PRO score.

Duration of Burosumab Treatment

The mean duration of burosumab treatment within the EAP was 1.8 (SD 0.85) years (median 1.7 [range 0.2–3.9]). Most patients (71%; 97/136) remained on the same dose of burosumab throughout treatment (Table 3). Ninety percentage of patients ($n = 123$) were still receiving burosumab at the end of the data collection period (31 December 2022). The Kaplan–Meier survival curve for persistence with treatment is provided in Supplementary Figure S1. Four patients stopped treatment because of treatment- or administration-related adverse reactions, five because of lack of benefit perceived by the patient ($n = 3$) or physician ($n = 2$), and one each because of pregnancy, increase in pain, starting a family, and starting chemotherapy.

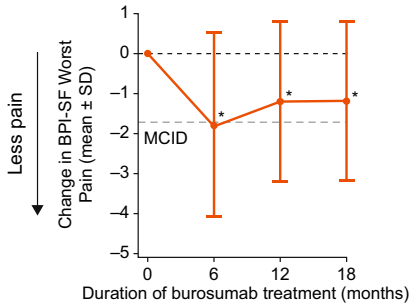
Just over half of patients were taking pain medication (opioid and/or non-opioid) before starting burosumab (58%; 77/134), with similar proportions of patients taking pain medication throughout the study (Supplementary Table S6). At most time points, around one-fifth of patients were not taking pain medication. Approximately one-fifth of patients (22%; 30/134) were taking opioids at baseline; 15–24% of patients were taking opioids at 6, 12 and 18 months.

Safety

The frequency of safety events by system organ class (SOC) is presented in Supplementary Table S7. Overall, 924 safety events were reported, of which 411 (44%) were reported

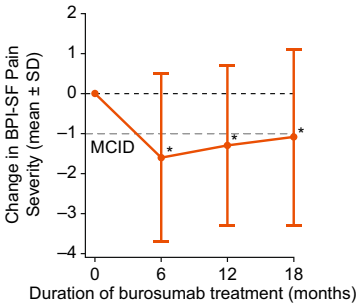
BPI-SF

a Worst Pain



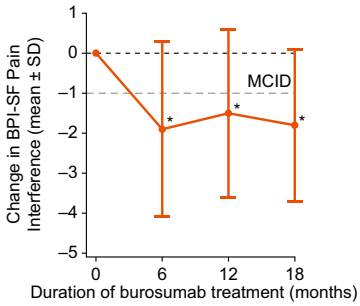
n	32	33	21
Mean	−1.8	−1.2	−1.2
SD	2.3	2.0	2.0

b Pain Severity



n	32	32	21
Mean	−1.6	−1.3	−1.1
SD	2.1	2.0	2.2

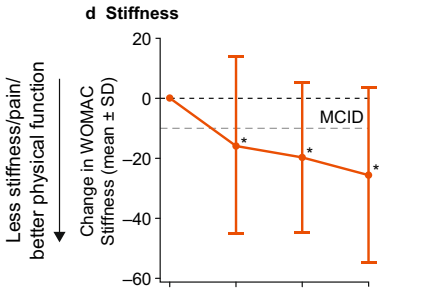
c Pain Interference



n	32	32	20
Mean	−1.9	−1.5	−1.8
SD	2.2	2.1	1.9

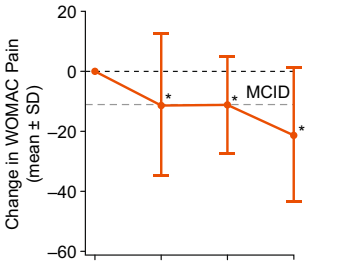
WOMAC

d Stiffness



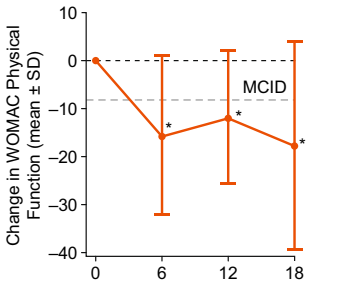
n	29	33	22
Mean	−15.9	−19.7	−25.6
SD	29.7	24.8	29.0

e Pain



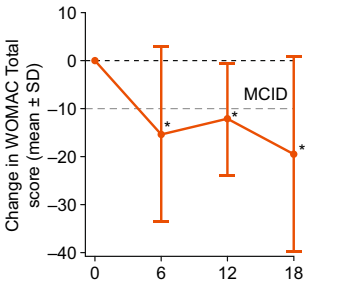
n	29	33	22
Mean	−11.4	−11.1	−21.4
SD	24.3	16.1	22.5

f Physical Function



n	29	33	22
Mean	−15.7	−11.9	−17.8
SD	16.7	13.9	21.6

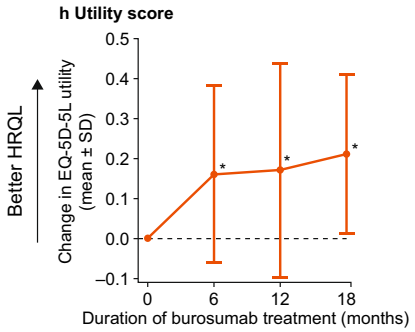
g Total score



n	29	33	22
Mean	−15.4	−12.1	−19.6
SD	18.3	11.7	20.3

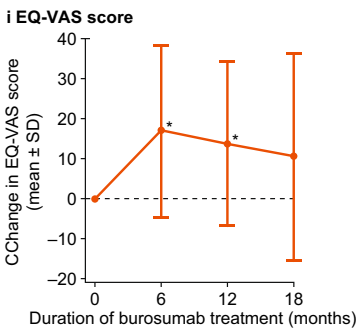
EQ-5D-5L

h Utility score



n	34	32	21
Mean	0.16	0.17	0.21
SD	0.22	0.27	0.20

i EQ-VAS score



n	31	31	20
Mean	17.0	13.7	10.4
SD	21.6	20.5	25.9

◂**Fig. 3** Mean changes from baseline in PRO scores during burosumab treatment. Asterisks indicate significant change from baseline ($p < 0.05$). *BPI-SF* Brief Pain Inventory short-form, *EQ-5D-5L* EuroQol 5-Dimension 5-Level, *EQ-VAS* EuroQol visual analogue scale, *HRQL* health-related quality of life, *MCID* minimum clinically important difference, *SE* standard error, *WOMAC* Western Ontario McMaster Universities Osteoarthritis Index

as being related to burosumab treatment. The most frequently reported safety events were in the musculoskeletal and connective tissue disorders SOC (192/924 events). The most common events within this SOC were: arthralgia ($n = 32$) back pain ($n = 30$) and pain in the extremities ($n = 28$). A total of 114 events in this SOC were reported as being related to burosumab treatment. Serious safety events reported are summarised in Supplementary Table S8. Overall, 105 safety events were recorded as serious. The most frequent serious events were in the surgical and medical procedures SOC (19 events), infections and infestations SOC (12) and musculoskeletal and connective tissues disorders SOC (11) (Supplementary Table S8).

Discussion

In this longitudinal, real-world study in burosumab-naïve adults with XLH treated with burosumab, almost two-thirds of patients had serum phosphate above the LLN at 6 months (primary objective), with significant increases from baseline in serum phosphate at 6, 12, and 18 months. Burosumab treatment was also associated with increases in serum 25-hydroxyvitamin D and calcium, and decreases in serum ALP and PTH. Statistically significant and clinically meaningful improvements (i.e. exceeding the MCID) were observed in patient-reported pain, stiffness, and physical function (measured using the BPI-SF and WOMAC) at 6, 12, and 18 months and in HRQL measured using the EQ-5D-5L. Improvements were similar in patients who had and had not been taking oral phosphate/active vitamin D supplements immediately before starting burosumab in the EAP.

Real-world studies reporting patient-centred insights into the experience of disease and treatments are particularly relevant in rare diseases where knowledge can be limited by the small patient population. Such evidence is increasingly valuable to regulators and to support health technology assessment and reassessment [32, 33]. The real-world evidence reported in the current study provides an important addition to the evidence base for burosumab in the treatment of XLH. The significant improvement in serum phosphate concentration observed in the current real-world study generally supports findings from the phase 3 randomised controlled trial (RCT) of burosumab in adults with XLH, in which the majority of patients achieved a serum phosphate concentration above the LLN after 24 weeks' burosumab treatment [15], with improvements sustained through to 144 weeks. However, in the current study, fewer patients had serum phosphate > LLN after 6 months' treatment (63%) than in the RCT over 24 weeks, averaged across the midpoints between monthly doses (94%). This difference may reflect variation in serum phosphate measurement and local reference ranges in the real-world setting compared with clinical trials; tests may be fasting or non-fasting in clinical practice, and the timing of measurements relative to burosumab administration may vary in clinical practice (in the RCT measurements were made at the midpoint between doses whereas in the real-world setting measurements could be taken at any time). This is supported by the lower mean proportion of patients with serum phosphate above the LLN across end-of-dose intervals over 24 weeks (68%) in the RCT. A recently published real-world study in Italy ($n = 27$ adults) also reported that the increase in serum phosphate was less pronounced than in clinical trials [34]. This study demonstrated that higher serum phosphate levels at baseline predicted higher phosphate levels following burosumab treatment, whereas higher baseline PTH and FGF23 levels predicted lower phosphate levels following treatment [34]. Thus, the relatively low proportion of patients with normal serum phosphate levels following burosumab treatment in the current study versus the RCT may partly reflect differences in the study populations, including the possibility of previous or current hyperparathyroidism. However, the studies had comparable biochemical profiles and PRO scores at baseline, so specific reasons for the difference are difficult to ascertain, particularly given the complexity of bone homeostasis.

Improvements in other markers of bone biochemistry (calcium, ALP, PTH) in the current analysis are also consistent with results from the phase 3 RCT [15, 16, 18]. We noted that serum levels of 25-hydroxyvitamin D increased from baseline, which was unexpected, given that, based on its mechanism of action, burosumab would not be expected to cause an increase in 25-hydroxyvitamin D levels. A post-hoc analysis of data from patients naïve to burosumab at baseline found no significant difference in mean serum 25-hydroxyvitamin D levels between patients who did and did not have normal serum phosphate levels after 6 months' burosumab treatment (mean [SD] 58.5 [24.4] [$n = 35$] vs 61.8 [17.3] [$n = 15$] nmol/L, respectively). Thus, the improvement in 25-hydroxyvitamin D levels may be due to other factors, including the use of native vitamin D supplements (which was not recorded in this study).

In the RCT, improvements in bone biochemistry markers were associated with improvements in osteomalacia and fracture healing and amelioration of skeletal symptoms. Thus, while data on skeletal symptoms (including fractures and pseudofractures) were not included in the current analysis, similar improvements might be expected in real-world

Table 2 Proportions of patients achieving MCID for the BPI-SF and WOMAC

PRO	Months from baseline[a]		
	6	12	18
BPI-SF			
Worst pain	$n=32$	$n=33$	$n=21$
	15 (47%)	12 (36%)	10 (48%)
Pain interference	$n=32$	$n=32$	$n=20$
	19 (59%)	22 (69%)	13 (65.0%)
WOMAC			
n	29	33	22
Pain	18 (62%)	17 (52%)	14 (64%)
Stiffness	16 (55%)	21 (64%)	14 (64%)
Physical function	16 (55%)	20 (61%)	15 (68%)
Total sore	13 (45%)	18 (55%)	15 (68%)

Values are *n* (%) of patients with change from baseline data that achieved the MCID

MCIDs: BPI-SF, ≥ 1.72 for Worst Pain; ≥ 1.0 for Pain Interference [31]. There is no MCID for Pain Severity; WOMAC, ≥ 11.0 for Pain, ≥ 10.0 for Stiffness, ≥ 8.0 for Physical Function, ≥ 10.0 for total score [30]

[a]Analysed at each time point ± 3 months

BPI-SF Brief Pain Inventory short-form, *EQ-5D* EuroQol 5-Dimension, *MCID* minimum clinically important difference, *WOMAC* Western Ontario McMaster Universities Osteoarthritis Index

Table 3 Changes to burosumab dose during the early access programme

Variable	Burosumab-naïve patients ($N=136$)
Number (%) of patients with given number of dose changes reported	
0	97 (71%)
1	23 (17%)
2	12 (9%)
3	4 (3%)
Direction of change from previous dose level[a]	
Number of dose changes[a]	59
Decrease	21 (36%)
Increase	36 (61%)
Uncertain[b]	2 (3%)
Reason for dose change[c]	
Number of patients with dose changes	39
Hypophosphataemia	16 (41%)
Weight change	5 (13%)
Investigator decision	8 (21%)
Safety event other than hypophosphataemia	4 (10%)
Other	11 (28%)

[a]Patients could have more than one dose change

[b]Case report form indicated a change in dose but direction of change is uncertain in the available data

[c]The number of unique patients is reported for each category, patients could have more than one reason for a dose change

clinical practice given the comparable improvements in bone biochemistry markers.

PROs complement clinical outcomes, providing insight into the humanistic burden of disease and the impact of treatment on aspects of the condition that are relevant to patients. This study provides an important opportunity to compare changes in PROs following burosumab treatment in clinical trials with those observed in real-world practice. Improvements in BPI-SF and WOMAC scores in the current study are generally comparable to, or greater than, improvements seen in the phase 3 RCT. Interestingly, use of pain medication appeared to remain stable through the study, even though pain scores decreased. This finding may reflect a reluctance in patients with chronic symptoms to discontinue pain medication in the short term, despite an improvement in pain levels, particularly for patients taking pain medication associated with withdrawal symptoms, such as opioids. Additionally, the dichotomous data collected in this study may have been insufficiently detailed to detect changes in pain medication use; data on pain medication dose and frequency may have shown reduced use following treatment. It would be interesting to explore use of pain medication during burosumab treatment in future long-term studies.

HRQL is an important measure of patient wellbeing and is valued by regulators and payers in the assessment of treatment benefit. While HRQL has been reported to be impaired in patients with XLH, the effect of burosumab treatment on generic HRQL has not been reported to date. The EQ-5D-5L was not included in the RCT but is a widely used generic measure of HRQL and is frequently used in health economic assessments to estimate quality-adjusted life-years [35]. To the authors' best knowledge, the current analysis is the first to assess change in EQ-5D-5L utility for adults with XLH following treatment with burosumab. The improvement in utility observed during burosumab treatment in the EAP (mean increase of 0.17 [SE 0.05] after 12 months' treatment) was similar to the improvement predicted by mapping improvement in WOMAC scores in the RCT to EQ-5D-5L utility, used in the economic evaluation conducted for the NICE appraisal of burosumab for adult XLH (mean improvements of 0.147 [SE 0.011] and 0.193 [0.011] after 1 and 2 years on treatment, respectively) [23]. The improvement in EQ-5D-5L utility associated with burosumab treatment is broadly comparable to improvements reported for other biologic therapies in musculoskeletal disorders such as psoriatic arthritis [36], severe osteoarthritis [37] and rheumatoid arthritis [38].

The baseline characteristics of patients enrolled in the EAP were generally comparable with those in the phase

3 RCT. Mean serum phosphate concentrations at baseline were similar in the two studies (0.64 [SD 0.10] mmol/L in the RCT; 0.61 [SD 0.17] mmol/L in the current analysis). PRO scores at baseline were also comparable in the two populations: mean BPI-SF Worst Pain scores were 6.9 (SD 2.1) in the EAP analysis and 6.7 (1.4) in the RCT [6]; mean (SD) WOMAC total scores were 52.0 (22.3) in the EAP analysis and 49.1 (18.2) in the RCT, with comparable scores for WOMAC Pain, Stiffness and Physical Function. This is consistent with both populations comprising adults with symptomatic disease: patients in the EAP were required to have persistent symptoms of XLH despite treatment with phosphate/active vitamin D supplements, including slow-healing fractures or pseudofractures considered to compromise HRQL, while eligibility for the RCT required a serum phosphate concentration below the LLN and a BPI-SF Worst Pain score of at least 4 [6]. The severity of symptoms in the EAP population is further demonstrated by the mean EQ-5D-5L utility score of 0.51 at baseline, which is lower than mean EQ-5D estimates from previous studies in adult XLH, which range from 0.56 to 0.65 [39–41].

Burosumab was generally well tolerated in the EAP, with few treatment discontinuations; 90% of patients were still receiving burosumab at the end of the data collection period. Reported safety events were largely consistent with adverse events (AEs) reported in the RCT. The RCT reported similar AE profiles in patients receiving burosumab or placebo, and the AE profile did not change with longer duration of treatment (from 24 to 48 weeks) [16]. Most AEs were mild to moderate in severity, and no participant stopped burosumab or withdrew from the study because of an AE. There were no treatment-related serious AEs, life-threatening AEs, or deaths [16]. It should be noted that reporting of safety data in the EAP differed from that of the RCT: in the current study, safety data were taken from the pharmacovigilance safety database for burosumab, rather than captured prospectively as part of a trial. Therefore, absolute numbers of events are not directly comparable between the two studies. For instance, a number of safety events in the EAP related to incorrect product use, which would not be considered AEs in a clinical trial.

This study has a number of limitations. First, because the EAP, by its design, included only patients treated with burosumab, outcomes were assessed in terms of change from baseline. Variation between centres in the timing and frequency of assessments relative to administration of burosumab introduces some uncertainty in the results, although both this study and clinical trials have shown consistent improvements in bone biochemistry markers and PROs with burosumab treatment. In addition, concentrations of bone biochemistry markers were measured at local laboratories, which may introduce wider variation than seen in clinical trials, and the timing of measurements relative to burosumab administration was not specified as it was in the RCT. Reference values may also differ between laboratories. Patients could receive treatment prescribed by their clinicians, so it is possible that some patients received vitamin D supplementation during the study, which may have affected bone biochemistry and PROs; however, this information was not collected. As the EAP was a retrospective study, only data collected as part of routine clinical practice were available. A recent study found that muscle strength and ATP synthesis did not change with burosumab treatment, leading the authors to attribute the improvements in physical performance seen with burosumab treatment to concomitant reductions in pain, stiffness and fatigue rather than changes in muscle [42]. Assessing such outcomes using the larger sample of the EAP would have been an interesting research topic, but these data were not available.

Attrition in the sample size with time was due mostly to variation in the duration of follow-up rather than discontinuation of treatment: 90% of burosumab-naïve patients were still receiving burosumab at the end of the data collection period. Perhaps most importantly, the COVID-19 pandemic also affected the ability to follow-up patients, potentially affecting data completeness. To assess the potential impact of attrition bias on study outcomes, the proportion of patients with serum phosphate concentrations > LLN (the primary endpoint) was assessed in a subsample of patients with data at all time points (baseline, 6, 12 and 18 months). Outcomes were broadly comparable to the overall sample, indicating that attrition in sample size did not substantially affect results.

The study may also have been subject to selection bias in that patients involved in clinical trials were not eligible, and the study likely included patients with XLH that had not responded to phosphate and active vitamin D supplementation. Thus, care is needed in extrapolating the findings.

Further research is needed to assess the benefits of burosumab in a broader population of adults with XLH with no restrictions based on disease severity, and in adolescents, for whom data are currently limited. Evidence for the long-term effects of burosumab on disease progression is also required. Further research into the benefits of continued treatment with burosumab is also warranted: an exploratory analysis in seven patients whose treatment was interrupted for up to 15 months showed a decrease in serum phosphate concentration and worsening of PROs during the interruption, followed by an improvement when treatment was resumed [18]. In addition, two case series in adolescents reported decreased serum phosphate and worsening of symptoms after stopping burosumab treatment at the end of skeletal growth [43, 44].

Further real-world evidence will become available from the International XLH Registry, which was established in 2017 to collect natural history data on XLH over 10 years

[45, 46], and the XLH Disease Monitoring Programme [10] which was established in 2018 to collect data relating to disease manifestations and treatment.

The current study, based on a large sample, demonstrates the effectiveness of burosumab treatment in adults with XLH in real-world clinical practice in terms of improvements in bone biochemistry outcomes and PROs, supporting the efficacy findings in clinical trials, and provides new evidence showing improvement in generic HRQL following burosumab treatment. It also reports high rates of persistence with treatment, data for which are currently lacking. Further real-world evidence will be important to understand the long-term benefits of burosumab, particularly on disease progression and PROs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00223-025-01433-2.

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Data Availability Data that underlie the results reported in this article may be requested. Kyowa Kirin International will review requests individually to determine whether requests are legitimate, relevant, and meet sound scientific principles, and are within the scope of the participants' informed consent.

Declarations

Conflict of interest JB received support from Kyowa Kirin for the data collection and analysis and medical writing for the current study and paper, and has received advisory board consultancy fees and honouraria from Kyowa Kirin. EM has been a clinical investigator on other burosumab studies. MS has received honouraria/speaking fees and funding for conference attendance from UCB. GPRC has received medical writing, consultation fees, honouraria, support for conference attendance and funding for a research nurse from Kyowa Kirin, and honouraria from Pharmacosmos. MR has received funding to attend conference from Eli Lilly. RK has received payments from KKI for data collection and analysis, medical writing, consultancy, speaker honouraria and travel support for conference attendance. DS contracted to Bionical Emas Ltd and received payment for services relating data collection and resulting publications in the current study. RD is a full-time employee of Bionical Emas Ltd, which received payment for services relating to data collection and resulting publications in the current study. BJ, GL and VH are employees of Kyowa Kirin. AB, HB and MN were employed by, or contracted to, Chilli Consulting Ltd at the time of the study and received payment from Kyowa Kirin for data analysis and medical writing. RL, GK, JW, LM, SS, YL and RK have no conflicts of interest to declare.

Human and Animal Rights The study protocol and supporting documents were approved by the East Midlands – Leicester South Research Ethics Committee (ref 23/EM/0078) and the NHS Health Research Authority and Health Research Wales (IRAS project ID 321609; 9 May 2023).

Informed Consent Informed consent was not collected from patients as no identifiable data were accessed outside the direct care team.

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