

# Systematic Review: Efficacy of Medical Therapy on Outcomes Important to Adult Patients With X-Linked Hypophosphatemia

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## Abstract

**Context:** Understanding the effects of burosumab compared to conventional therapy or no treatment on patient-important outcomes in adults with X-linked hypophosphatemia (XLH) is essential to guide evidence-based treatment recommendations.

**Objective:** To examine the highest certainty evidence addressing the management of XLH in adults to inform treatment recommendations.

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**Methods:** We searched Embase, MEDLINE, Web of Science, and Cochrane Central up to May 2023. Eligible studies included randomized controlled trials (RCTs) and observational studies of individuals aged 18+ with clinically or genetically confirmed XLH. Manuscripts comparing burosumab to no treatment or conventional therapy (phosphate and active vitamin D) and conventional therapy to no treatment were included. Two reviewers independently determined eligibility, extracted data, and assessed risk of bias (RoB). GRADE methodology was used to assess evidence certainty.

**Results:** We screened 4114 records, after removing duplicates, and assessed 254 full texts. One RCT and 2 observational studies were eligible. The RCT of burosumab vs no treatment had low RoB. Burosumab probably improves pain from fracture/pseudofracture healing (moderate certainty) but has little or no impact on direct pain measures (moderate certainty). Burosumab may reduce the need for parathyroidectomy (low certainty) but has little or no impact on fatigue (high certainty), stiffness (moderate certainty), and mobility (low certainty) over 24 weeks. Burosumab may increase dental abscess risk (low certainty). Indirect evidence comparing burosumab to conventional therapy provided low certainty regarding burosumab vs conventional therapy. Two observational studies on conventional therapy vs no treatment had high RoB and very low certainty regarding the impact of conventional therapy on patient-important outcomes.

**Conclusion:** No formal comparisons between burosumab and conventional therapy in adults exist. Evidence for conventional therapy vs no treatment is very uncertain. Our review highlights the need for more data on the long-term effects of burosumab and conventional therapy on patient-important outcomes in adult patients with XLH.

**Key Words:** adult XLH, efficacy, burosumab, conventional therapy, patient-important outcomes

**Abbreviations:** 6MWT, 6-minute walking test; ALP, alkaline phosphatase; BFI, Brief Fatigue Inventory; BPI-SF, Brief Pain Inventory-Short Form; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; iPTH, intact parathyroid hormone; MD, mean difference; MID, minimal important difference; RCT, randomized controlled trial; RoB, risk of bias; SoF, summary of findings; SR, systematic review; SR<sub>Bmab vs Pi/D or no Rx</sub>, SR addressing burosumab vs conventional therapy or no treatment; SR<sub>Pi/D vs no Rx</sub>, SR addressing conventional therapy vs no treatment; TmP/GFR, tubular maximum reabsorption of phosphate to glomerular filtration rate; WOMAC, Western Ontario and McMaster Universities Arthritis Index; XLH, X-linked hypophosphatemia.

## Background

X-linked hypophosphatemia (XLH) is a rare genetic disorder characterized by chronic hypophosphatemia secondary to renal phosphate wasting, which results from elevations in the serum concentrations and activity of fibroblast growth factor (FGF23) (1). The elevation in FGF23 levels is caused by inactivating pathogenic variants in the phosphate regulating endopeptidase homolog, X-linked (*PHEX*) gene (2, 3). XLH is a multisystem disease characterized by impaired bone mineralization resulting in osteomalacia in adults. Patients with XLH may experience chronic musculoskeletal pain, lower limb deformity, pseudofractures, dental infections, fatigue, hearing loss, and difficulties with mobility as well as challenges in physical and mental health (4, 5).

Data from Denmark, Norway, and Japan show that XLH affects approximately 40 to 50 individuals per million people (6-9), whereas a recent population-based cohort study from the UK estimated the prevalence of XLH in children at 15.1 (95% CI 11.3-20.1) per million and in adults 15.7 (95% CI 11.8-20.9) per million (5).

Medical management options include therapy with oral phosphate salts and active vitamin D (conventional therapy) and, more recently, burosumab, a recombinant human IgG1 monoclonal antibody targeting FGF23 (10). Adherence to and continuation of conventional therapy may be particularly challenging due to dosing frequency and intolerance to phosphate preparations (11).

There has been no consensus on thresholds for treatment among adult patients. This review aims to inform the International Working Group's guidelines on XLH management in adults by assessing the efficacy of burosumab compared with conventional therapy and with no treatment. Focusing on patient-important outcomes, the review also evaluates the efficacy of conventional therapy compared with no treatment. Despite the established benefits of early treatment in children, the effectiveness of treatment in adults remains uncertain, which is why this systematic review (SR) is being conducted. It is important to consider potential risks associated with treatment, thus necessitating a careful evaluation of the balance between risks and benefits in adults.

## Methodology

This is a report of 2 SRs that aim to assess treatment efficacy in adult patients with XLH. We refer to the SR addressing burosumab vs conventional therapy or no treatment as (SR<sub>Bmab vs Pi/D or no Rx</sub>); and the SR addressing conventional therapy vs no treatment as (SR<sub>Pi/D vs no Rx</sub>). We adhered to PRISMA reporting guidelines (12), and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for evaluating the certainty of evidence.

## Search Strategy

An experienced health sciences librarian (R.K.C.) led the development of the search strategy for the PICO (Population, Intervention, Comparison, Outcome) questions of the 2 SRs. The search was conducted from inception to May 2023 in 4 databases: MEDLINE, Web of Science, EMBASE, and Cochrane Central. The search utilized keywords X-linked hypophosphatemia, X-linked hypophosphatemic rickets, familial hypophosphatemia, XLH, *PHEX* Phosphate Regulating Neutral Endopeptidase/or *PHEX*, burosumab, active vitamin D, calcitriol, alfacalcidol, phosphate and anti-FGF23 Antibody. The full search strategy is available as supplemental material (13).

## Eligibility Criteria

### SR on burosumab vs no treatment or conventional therapy

Eligible studies were randomized controlled trials (RCTs) involving adult patients (age  $\geq 18$  years) diagnosed with XLH. Diagnosis was based on the presence of a pathogenic variant in the *PHEX* gene or clinical features such as a family history and an X-linked dominant inheritance pattern. Additional criteria included biochemical evidence of chronic hypophosphatemia secondary to renal phosphate wasting, low ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR), elevated alkaline phosphatase (ALP) as a marker for osteomalacia, or radiographic evidence of rickets during childhood. Eligible studies compared burosumab either to no treatment or to conventional therapy.

### SR on conventional therapy vs no treatment

Eligible studies included the same patient population, comparing conventional therapy to no treatment, including RCTs as well as observational studies.

For both SRs, studies were excluded if they (1) were intervention studies of  $\leq 4$  weeks' duration; (2) reported on children or mixed populations of adults and children where distinguishing between those age  $\geq 18$  years old and age  $< 18$  years old was not possible; (3) were published in languages other than English.

### Screening Citations and Extracting Data

We collated the results of the database searches in a reference manager (EndNote) and excluded duplicates. Two reviewers (D.S.A. and F.A.) independently screened articles for eligibility based on title and abstract using Covidence (14). Citations identified as possibly eligible by either reviewer underwent full-text screening. Eligible articles were then reviewed in full text. A third reviewer with methods experience (R.D.M.) resolved conflicts.

Reviewers, including pairs (D.S.A. and F.A., D.S.A. and S.H.), independently extracted data using standardized templates. The templates included details such as author and year of publication, study design and characteristics, sample size, patient demographics (age, sex, body mass index), treatment specifics, follow-up, and patient-important and surrogate outcomes.

### Risk of Bias and Certainty of Evidence

Two reviewers conducted the risk of bias (RoB) assessment in duplicate; any persistent disagreements were resolved by a third reviewer. To inform the RoB assessments, we utilized the Cochrane risk-of-bias tool 1, which was modified by the CLARITY group at McMaster University (15). This includes random sequence generation, allocation concealment, blinding of participants, healthcare providers, outcome adjudicators, as well as missing outcome data. There are 4 levels of RoB (definitely high, probably high, probably low, and definitely low). If a study is definitely high or probably high RoB in any domain, then the entire study is deemed at high RoB.

We used GRADE methodology to assess the certainty of evidence as high, moderate, low, or very low. Certainty of evidence is defined as the adequacy to support a particular recommendation. RCTs begin as high-certainty evidence but may be rated down by 1 or more in each of 5 categories of limitations: RoB, inconsistency, imprecision, indirectness, and publication bias (16). To study the impact of missing outcome data with respect to RoB, we considered imputing missing data using plausible worst cases assuming worse event rates among patients who were lost to follow-up (eg, sensitivity analyses) and reported the impact of missing data on the results and conclusions of the SR (17). We created summary of findings (SoF) tables using optimal formats in the MAGICapp that included relative and absolute effects (18).

### Outcomes of Interest and Measure of Effect

We prespecified outcomes at outset. The guideline International Working Group members, along with a patient partner (E.M.) and input from the methodology team, chose these outcomes. We focused on patient-important outcomes, variables that reflect how a patient feels, functions, or survives. We considered the following outcomes as critical: fractures/pseudofracture

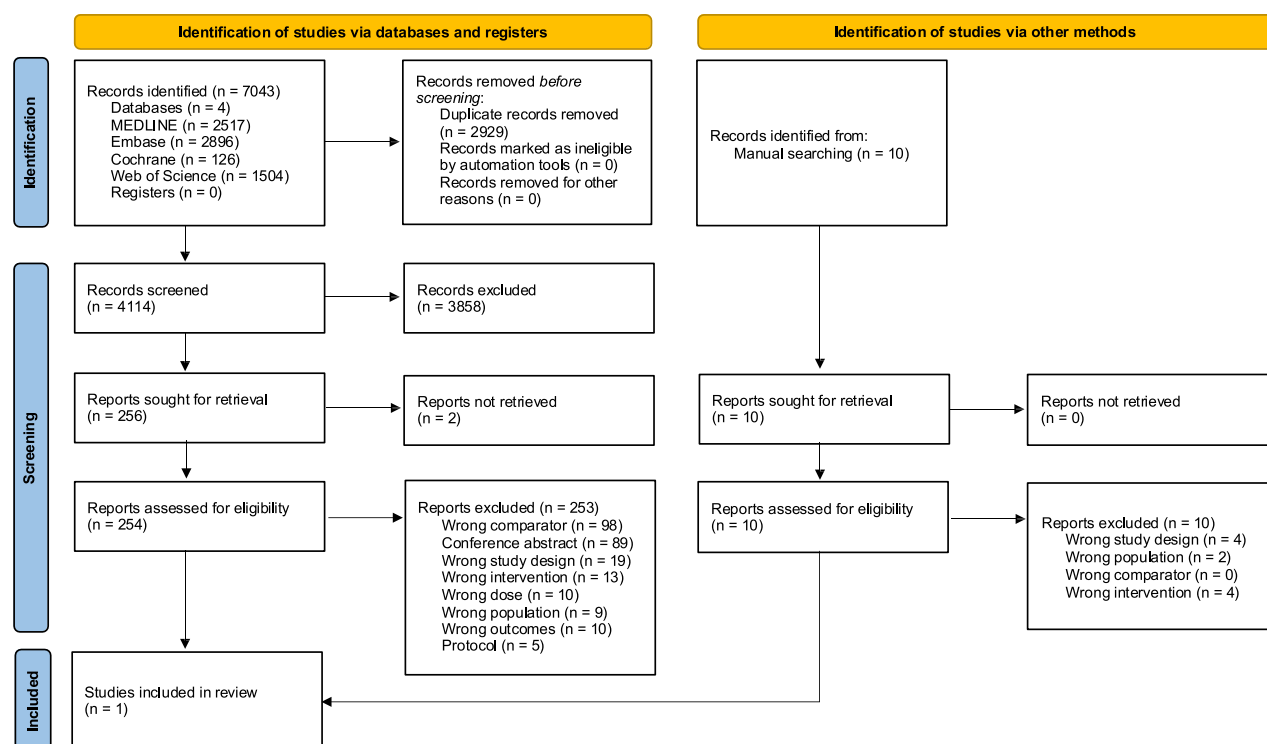
(symptomatic), fracture healing, musculoskeletal pain, treatment-related serious adverse events, and skeletal deformity (eg, spinal stenosis). We considered the following as important: treatment-related adverse events, mobility, stiffness, quality of life (mental, physical, and social), fatigue, dental manifestations (eg, abscesses, periodontal diseases), parathyroidectomy, corrective orthopedic surgeries (lower limb, spinal), and auditory (hearing loss or tinnitus).

We also included surrogate outcomes, including laboratory measurements, radiographic images, physical signs, or other measures that themselves were not a measure of clinical benefit per se but may predict patient-important benefit (19). We evaluated the presence of hypertension, hyperparathyroidism (secondary and tertiary), hypophosphatemia (change in serum phosphorus), raised ALP, and/or bone-specific alkaline phosphatase (bsALP), radiographic evidence of (asymptomatic) pseudofractures, radiographic evidence of nephrocalcinosis/nephrolithiasis, radiographic evidence of joint and ligament damage (including enthesopathy, joint space narrowing (cartilage damage), osteophytes, facet joint hypertrophy), estimated glomerular filtration rate (eGFR), and the TmP/GFR.

Due to the rarity of the disease, direct evidence on the impact of therapy on patient-important outcomes is limited. Therefore, for certain outcomes, we inferred the impact of burosumab and conventional therapy on these outcomes from surrogate measures (indirect evidence). Specifically, in addition to the direct measure of pain from the RCT, the Brief Pain Inventory-Short Form (BPI-SF) scale, we inferred improvement in pain from radiographic fractures and pseudofracture healing. We also inferred the certainty of several patient-important outcomes using surrogates reported in the RCT. These included the reduction in the risk of parathyroidectomy, inferred from reductions in intact parathyroid hormone (iPTH) levels; the risk of progression to chronic kidney disease, inferred from radiographic improvement in nephrocalcinosis scores; and improvement in overall well-being inferred from improvement in serum phosphorus level, TmP/GFR, and reductions in ALP. We reduced our certainty in the evidence when inferring patient-important outcomes from surrogates given the serious indirectness and the very serious indirectness in the latter-most inference.

We assessed dichotomous outcomes using relative risk, and continuous outcomes with mean difference (MD), and for specific outcomes with available minimal important differences (MIDs) for patients with XLH, we applied MID (20-22). Specifically, pain, which was measured in the trial using the BPI-SF, a 0 to 10 numerical rating scale (10 indicates worst pain severity/interference) with 15 items in total, 11 items contributed to the scores reported in the trial. The trial included XLH-specific meaningful change (MID of  $\geq -1.72$  worst pain) (23, 24), which we used in assessing the certainty of evidence. We also used MID for fatigue as measured by the Brief Fatigue Inventory (BFI) scale, a 0 to 10 numerical rating scale where 10 indicates the worst fatigue severity/interference. The XLH-specific MID was set at a change of  $\geq -1.5$ , indicating a worsening of fatigue (25). We assessed mobility through the 6-minute walking test (6MWT). We used the MID for the Western Ontario and McMaster Universities Arthritis Index (WOMAC) stiffness (XLH-specific MID  $\geq -10.0$  stiffness) (20).

In our second review (SR<sub>Pi/D</sub> vs no Rx), where continuous outcomes were measured and reported on a single scale, we conducted a meta-analysis of the mean differences using RevMan (26).



**Figure 1.** PRISMA diagram illustrating the search for the SR on the impact of burosumab compared with phosphate and active vitamin D or no treatment on patient-important outcomes.

## Results

### Study Selection

This systematic search for both reviews revealed a total of 7043 citations, of which 4114 were screened, after the removal of duplicates. After assessing 4114 records and excluding 3858 based on title and abstract, we evaluated 254 reports in full text for eligibility. We conducted a secondary search that identified 10 additional records, all of which we evaluated in full text, but none met the inclusion criteria (see Figs. 1 and 2, PRISMA). In SR<sub>Bimab vs Pi/D or no Rx</sub>, 1 RCT met our eligibility criteria, and in SR<sub>Pi/D vs no Rx</sub>, 2 observational studies met our eligibility criteria (27, 28).

### Study and Patient Characteristics

#### SR on burosumab vs no treatment or conventional therapy

The primary analysis ultimately included 1 RCT that involved 134 adult patients with XLH, of whom 68 were randomized to receive burosumab and 66 received placebo (no treatment) and were followed for 24 weeks (10). Table 1 presents the study characteristics of the included RCT. Among patients in the placebo group, 72.7% had undergone conventional therapy before reaching the age of 18 years, vs 66.2% in the burosumab group (10). We used this RCT to inform the recommendations for burosumab vs no treatment in adults (10).

#### SR on conventional therapy vs no treatment

Table 1 also displays 2 observational studies that met the inclusion criteria for the second SR. The study by Imel et al (28) was a prospective study that involved 8 adult patients, 3 in the intervention group and 5 in the control group. The follow-up period was  $14.4 \pm 12$  months in the intervention

group and  $25 \pm 32$  months in the control group. The study by Shanbhogue et al (27) was also a prospective study that involved 27 adult patients with XLH, 70% were female, 11 patients were in the intervention group, and 16 were in the control group. Patients were followed for 6 years.

### Risk of Bias of Included Studies and Quality of Evidence

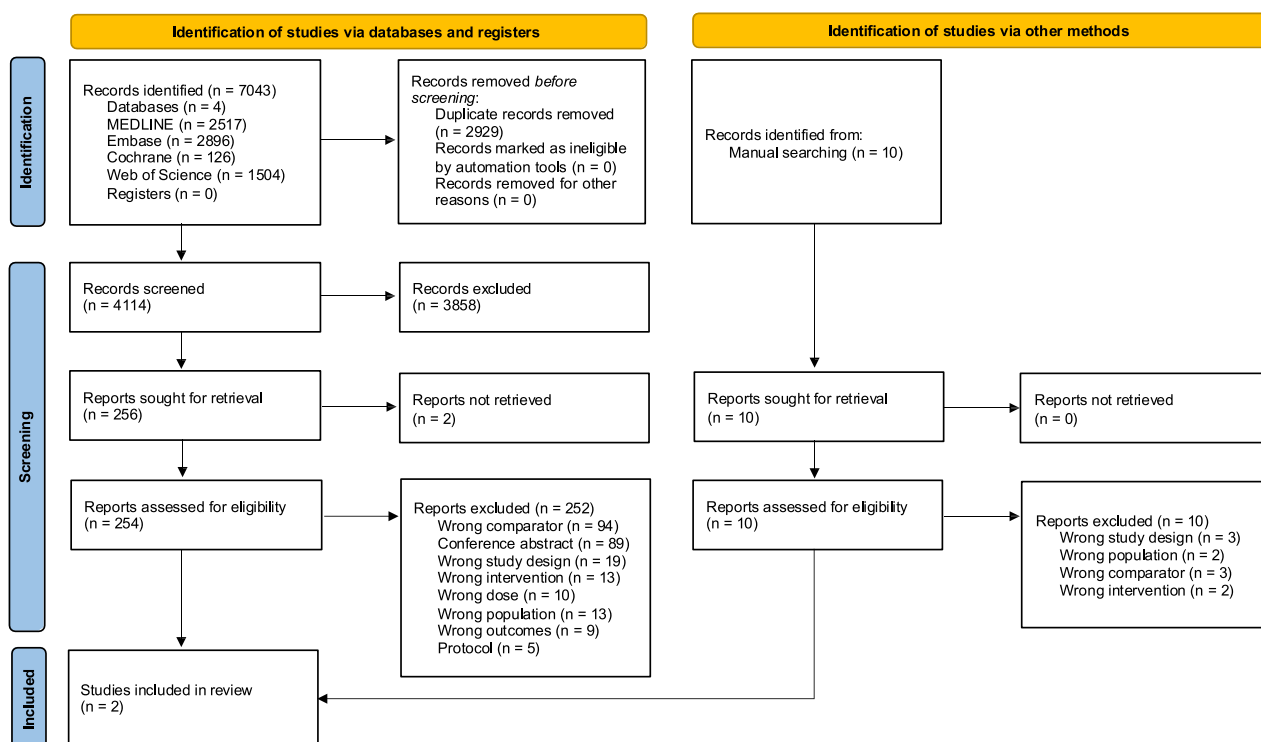
#### SR on burosumab vs no treatment or conventional therapy

All domains of the modified Cochrane RoB tool 1 demonstrated low RoB (Fig. 3). We illustrate our application of GRADE in detail in Table 2.

Within this SR, we generated 2 SoF tables, the first SoF table pertained to the direct comparison between burosumab and no treatment, derived from the RCT data. The second SoF table focused on the comparison between burosumab and conventional therapy. As there are no direct comparisons between burosumab and conventional therapy in adults, we derived inferences based on indirect evidence from studies comparing burosumab vs no treatment and conventional therapy vs no treatment. The estimates in (Table S1 (32)) are identical to those from the RCT of burosumab vs no treatment but (1) are rated down because of the indirect nature of the comparison and (2) are likely overestimates of the effect of burosumab vs conventional therapy because of the likely benefit of conventional therapy over no treatment. We did not reduce estimates; however, because of the very low certainty evidence regarding conventional therapy vs no treatment.

#### SR on conventional therapy vs no treatment

The RoB was high, as seen in Fig. 4. In this SR, we constructed a single SoF table that encompassed outcomes derived from



**Figure 2.** PRISMA diagram illustrating the search for the SR on the impact of phosphate and active vitamin D compared to no treatment on patient-important outcomes.

observational data with very low certainty. [Figure 5](#) illustrates a meta-analysis of the effect of conventional therapy vs no treatment on serum phosphorus level.

## Main Outcomes

### SR on burosumab vs no treatment or conventional therapy

[Table 3](#) presents the quality of evidence in the comparison of burosumab to no treatment among patients with XLH. Improvement in worst pain was evaluated using the worst pain BPI scale (10). The scale ranges from 0 to 10, where lower values are better. Worst pain, defined as the greatest pain in the last 8 days (20), provided moderate certainty evidence of little or no effect (MD between the burosumab and placebo group at 24 weeks  $-0.46$ , 95% CI  $-0.53$  to  $-0.38$ , MID  $\geq -1.72$ ) (20). We also inferred improvement in pain from radiographic fracture or pseudofracture healing: 35% more fractures healed with burosumab compared to no treatment (95% CI 22 to 49, moderate certainty). None of the available studies reported or assessed incident fracture during treatment.

We inferred a reduction in the risk of parathyroidectomy from the reduction in iPTH levels: MD of 21.1 pg/mL less, 95% CI 24 fewer to 18 fewer (low certainty).

We also assessed improvement in worst fatigue using the BFI score, measuring self-reported fatigue with a scale from 0 to 10 (lower being better) with a 24-hour recall. This yielded an MD of  $-0.27$ , (95% CI  $-0.36$  to  $-0.17$ , XLH-specific MID  $\geq -1.5$ ) (20), high certainty that there was no improvement in fatigue).

Stiffness, assessed through the WOMAC physical function score (33), ranging from 0 to 100 (lower being better XLH-specific MID  $\geq -10.0$ ) (20), showed an MD of  $-8.2$ ,

95% CI  $-14.4$  to  $-2.3$  (moderate certainty). Based on this data, our current estimate suggests that the impact of burosumab on stiffness is not clinically significant (the MD of  $-8.2$  is less than the MID of 10). However, it is important to note that the CI includes a potentially significant impact (the upper limit of the CI, 14.4, exceeds the MID of 10). Therefore, due to this imprecision, our certainty is reduced: we are only moderately certain that burosumab is ineffective in improving stiffness.

Mobility, assessed using the 6MWT, showed little or no effect of burosumab over no treatment at 24 weeks (MD 11.63 more meters walked, 95% CI 9 fewer to 32 more, low certainty); we rated down our certainty due to indirectness as the 6MWT is a surrogate for mobility in daily activities (34).

The study also reported on serious adverse events related to treatment (0 per 100, 95% CI  $-3$  to 3, low certainty), adverse events (4 more per 100, 95% CI  $-6$  to 14, low certainty), and dental abscesses (5 more per 100, 95% CI  $-5$  to 16, low certainty) with the use of burosumab compared with no treatment. [Table 3](#) details the remaining outcomes.

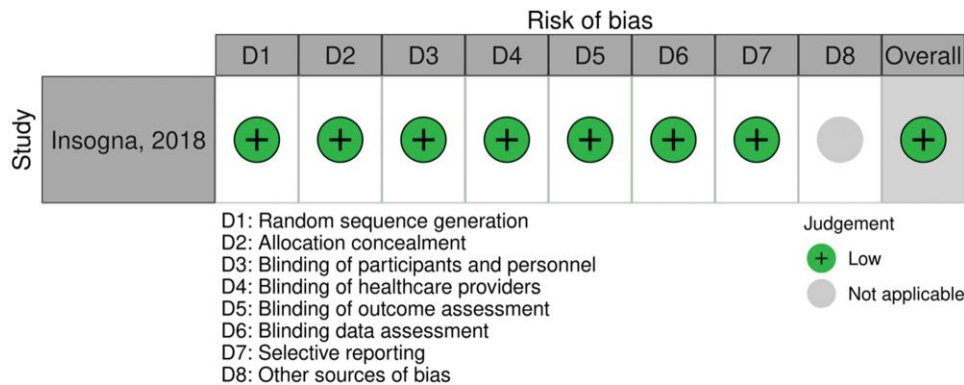
### SR on conventional therapy vs no treatment

When comparing conventional therapy to no treatment, we could only ascertain the following surrogate outcomes: changes in serum phosphorus levels, iPTH, and ALP. Our results indicate significant uncertainty regarding the impact of conventional therapy on improving the burden of symptoms associated with chronic hypophosphatemia. Specifically, we observed lower mean serum phosphorus levels in the treatment group than in no treatment (MD  $-0.16$  mg/dL, 95% CI  $-0.42$  to 0.11, very low certainty, [Table 4](#)), as well as higher mean ALP levels in the treatment group than in no treatment (MD 102 U/L, 95% CI 62 higher to 142 higher, very

Table 1. Characteristics of included studies

| ID                                   | Author, year          | Population                     | Country, site                                                                 | Study design                                 | Sample size  |         | Inclusion criteria | Exclusion criteria                                                                                                                                                                                                                                                                                                                                                                                                                                  | Intervention                                                                                                                                                                                                                                                                                           | Follow-up         |                                                                           |
|--------------------------------------|-----------------------|--------------------------------|-------------------------------------------------------------------------------|----------------------------------------------|--------------|---------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------|
|                                      |                       |                                |                                                                               |                                              | Intervention | Control | Total              |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                        |                   |                                                                           |
| SR <sub>Bimab</sub> vs Pi/D or no Rx |                       |                                |                                                                               |                                              |              |         |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                        |                   |                                                                           |
| 1                                    | Insogna, 2018 (10)    | Adults between 18 and 65 years | United States, France, United Kingdom, Ireland, Italy, Japan, and South Korea | Randomized, double-blind, placebo-controlled | 68           | 134     | 66                 | Adults between 18 and 65 years of age, diagnosis of XLH supported by a confirmed PHEX mutation (self or family member consistent with X-linked inheritance) and/or prespecified clinical findings and laboratory features: serum phosphate concentration below the lower limit of normal <2.5 mg/dL (0.81 mmol/L), ratio of renal TmP/GFR of <2.5 mg/dL, and a BPI worst pain score of 4.                                                           | Key exclusion criteria included corrected serum calcium 10.8 mg/dL (2.7 mmol/L), serum iPTH 2.5-fold the upper limit of normal, and/or use of medication to suppress parathyroid hormone within 60 days before screening; and a recent history (6 months) of traumatic fracture or orthopedic surgery. | Burosumab         | 24 weeks                                                                  |
| SR <sub>Pi/D</sub> vs no Rx          |                       |                                |                                                                               |                                              |              |         |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                        |                   |                                                                           |
| 1                                    | Imel, 2010 (28)       | Adults with XLH                | United States                                                                 | Prospective                                  | 3            | 5       | 8                  | XLH Dx on clinical and biochemical and radiographic evidence.                                                                                                                                                                                                                                                                                                                                                                                       | Clinical evidence of other acquired or inherited renal phosphate wasting disorders.                                                                                                                                                                                                                    | Pi + active vit D | 14.4 ± 12 months (treatment cohort) 25 ± 32 months (no treatment cohort). |
| 2                                    | Shanbhogue, 2018 (27) | Adults aged 18-73              | Denmark                                                                       | Prospective                                  | 11           | 16      | 27                 | Hereditary and FGF23-associated HR. The diagnostic criteria were (1) genetically verified (PHEX mutation, FGF23, or DMP1) and/or (2) biochemically verified HR with at least 1 of the following: serum PO <sub>4</sub> below normal range, low TPO <sub>4</sub> /GFR, or elevated serum FGF23. In addition, a history of childhood rickets or spontaneous endodontic abscesses was required to exclude acquired HR, eg, tumor-induced osteomalacia. | non-FGF23-associated HR, and sporadic, nonhereditary HR, eg, McCune–Albright syndrome, SCL34A3 gene (hereditary HR with hypercalciuria) and the CLCN5 gene (X-linked recessive HR), and biochemical evaluation.                                                                                        | Pi + active vit D | 6 years                                                                   |

Abbreviations: BPI, Brief Pain Inventory; Dx, diagnosis; FGF, fibroblast growth factor; GFR, glomerular filtration rate; HR, hereditary rickets; iPTH, intact parathyroid hormone; Pi, oral phosphate salts; SR<sub>Bimab</sub> vs Pi/D or no Rx, systematic review addressing burosumab vs conventional therapy or no treatment; SR<sub>Pi/D</sub> or no Rx, systematic review addressing conventional therapy vs no treatment; TmP, tubular maximum reabsorption rate of phosphate; XLH, X-linked hypophosphatemia.



**Figure 3.** Illustrates the risk of bias in the study included in the SR comparing burosumab with phosphate and active vitamin D or no treatment.

**Table 2. GRADE application in assessing quality of evidence in our patient-important outcomes**

| Domain                | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Judgment in our study                                                                                                                                                                                                                                                                                   | Example                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias<br>(15)  | A systematic error or deviation from the truth, in results or inferences                                                                                                                                                                                                                                                                                                                                                                                                                                      | In this SR <sub>Bmab vs Pi/D or no Rx</sub> , we included 1 RCT with low RoB. While in this SR <sub>Pi/D vs. no Rx</sub> , we included 2 observational studies both with high RoB and very low certainty evidence. Both studies had a small sample size and rating up was not applicable.               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Indirectness<br>(29)  | Quality of evidence decreases if head to head comparisons are unavailable. Such instances require falling back on indirect comparisons in which, eg, we make inferences about the relative effect of 2 interventions on the basis of their comparison not with one another, but with a third or control condition.                                                                                                                                                                                            | We rated down by 1 or 2 for indirectness when surrogate measures were used to assess for patient-important outcome.                                                                                                                                                                                     | We rated down when radiographic evidence of fracture or pseudofracture healing informed improvement in pain. We rated down when improvement in serum phosphorus, TmP/GFR and ALP were used to assess patients' overall wellbeing. We rated down when reductions in iPTH were used to predict risks of parathyroid surgery.                                                                                                                                                                                                                                                                                                                                                    |
| Imprecision<br>(30)   | GRADE's primary criterion for judging precision is to focus on the 95% CI around the difference in effect between intervention and control for each outcome. If a recommendation or clinical course of action would differ if the upper versus the lower boundary of the CI represented the truth, consider the rating down for imprecision. Even if CIs appear satisfactorily narrow, when effects are large and both sample size and number of events are modest, consider the rating down for imprecision. | When we rated our certainty on an important effect in the presence of wide CI, we rated down by 2 as the CI may have included an important benefit and an important harm. While when we rated our certainty in an un-important effect in the presence of wide CI, we rate down by 1 due to imprecision. | For pain measurements using BPI, we rate down by 1 due to concerns about the validity of the instrument as applied in the study. This is because the pain question selected asked the subjects to rate their worst pain over the past 24 hours. The questionnaire was administered at the end of the 4-week dosing cycle (trough time point), during which the effects of the drug often peaked and declined considerably over the month. As a result, the pain question did not capture the majority of the time interval and may have missed the period of optimal drug efficacy.<br>For adverse events shown on Table 3, we rated down by 2 as we considered 4% important. |
| Inconsistency<br>(31) | GRADE suggests rating down the quality of evidence if large inconsistency (heterogeneity) in study results remains after exploration of a priori hypotheses that might explain heterogeneity, which maybe based on similarity of point estimates, extent of overlap of CIs, and statistical criteria including tests of heterogeneity and I <sup>2</sup> .                                                                                                                                                    | We meta-analyzed the serum phosphorus levels reported in the 2 observational studies (Figure 5).                                                                                                                                                                                                        | We rated down for inconsistency as the direction of the effect was not consistent between the included studies, and the CI of the 2 included studies did not overlap (Figure 5).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Certainty of evidence | RCTs begin as high-quality evidence but may be rated down by 1 or more in each of 5 categories of limitations                                                                                                                                                                                                                                                                                                                                                                                                 | In our evidence from RCT, we rated down primarily due to imprecision and indirectness to moderate and low.                                                                                                                                                                                              | We rated down adverse events, serious adverse events, dental abscesses, mobility, stiffness, and in all outcomes where surrogates were used to assess for patient-important outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; RoB, risk of bias; TmP/GFR, The tubular maximum phosphate reabsorption adjusted for glomerular filtration rate

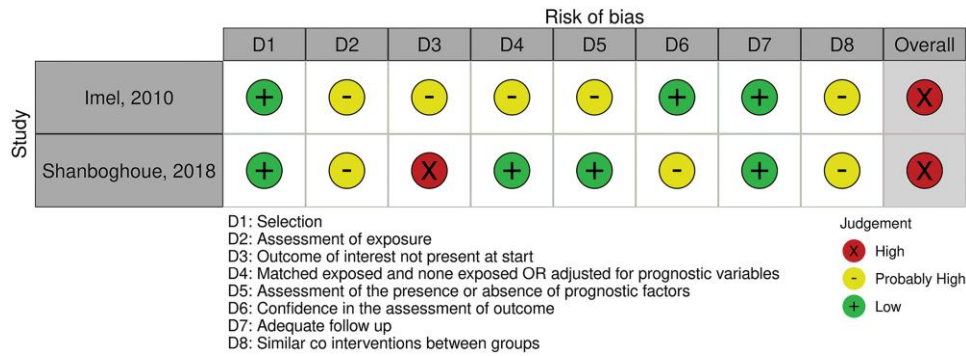


Figure 4. Illustrates the risk of bias in studies included in the SR comparing phosphate and active vitamin D with no treatment.

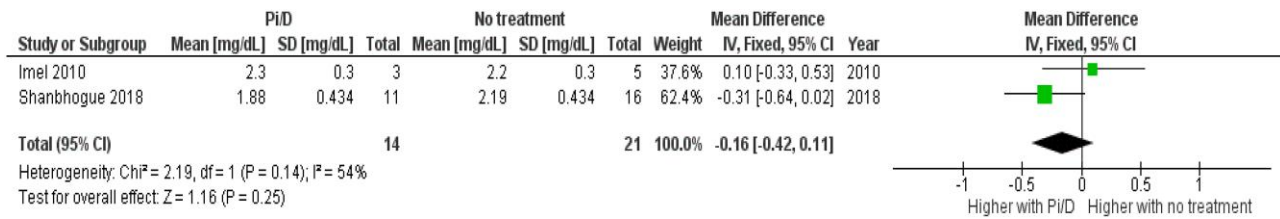


Figure 5. Meta-analysis of the effect of conventional therapy vs no treatment on serum phosphorus level.

low certainty, Table 4). In addition, our results indicate uncertainty about whether conventional therapy reduces the risk of parathyroidectomy, as iPTH levels were higher in 11% of patients in the treatment group compared to no treatment (95% CI -24 to 47, very low certainty, Table 4).

None of the included studies reported patient-important outcomes of skeletal deformity (eg, spinal stenosis), corrective surgeries, and auditory outcomes.

## Discussion

### Main Findings

#### SR on burosumab vs no treatment or conventional therapy

In comparing burosumab to no treatment over 24 weeks, burosumab probably does not result in a change in worst pain. This could be attributed to several factors, including (1) participants in the questionnaire were not restricted to patients with XLH with pseudofractures confirmed by X-rays, thus some participants may not have experienced pain due to osteomalacia at baseline; (2) the majority of adult patients with XLH suffer from arthralgia due to enthesopathy, a unique complication observed exclusively in adult patients with XLH, ARHR1, and ARHR2. Unfortunately, the instrument used for pain assessment (BPI-SF) did not distinguish between pain from bone lesions and enthesopathy, the latter of which has limited data regarding improvement with burosumab (35); (3) the timing of the pain assessment in the trial may have influenced the results, as participants were asked to rate their worst pain experienced over the past 24 hours (as part of the BPI-SF). The questionnaire was administered at the end of the 4-week dosing cycle (trough time point), during which the drug's effects often peaked and declined considerably over the month. For these reasons, we down-rated our certainty to moderate.

In our effort to contextualize clinically the patients' experience of 35% improved radiographic healing of fractures and

pseudofractures with burosumab, we considered the possibility that this difference translated to pain reduction. However, the direct assessment of pain would be more credible, particularly since chronic pain associated with XLH may not necessarily improve entirely with fracture or pseudofracture healing.

We also inferred with low certainty evidence that burosumab compared with no treatment may result in avoidance of potential parathyroidectomy, supported by decreases in iPTH levels. Whether burosumab, when compared with conventional therapy, exhibits similar effects remains very uncertain.

We made inferences regarding patient-important outcomes with biochemical markers (surrogates). Based on the normalization of serum phosphorus and increases in TmP/GFR at 24 weeks, we concluded that burosumab, compared with no treatment, may improve the burden of symptoms caused by chronic hypophosphatemia.

However, direct measurement of fatigue using BFI score demonstrated no impact of burosumab (high certainty evidence). Similarly, there is likely little or no impact on stiffness, as measured by the WOMAC stiffness scale. Furthermore, our assessment suggests that burosumab may have little or no impact on mobility, as assessed by the 6MWT.

The study reported no serious adverse events with burosumab over 24 weeks; however, burosumab may increase adverse events such as restless leg syndrome, limb discomfort, muscle cramps, and headaches with a best estimate of 4% greater incidence.

Possibly because of short follow-up of 24 weeks, the eligible study in this SR did not report patient-important outcomes related to skeletal deformity (eg, spinal stenosis), orthopedic corrective surgeries, auditory outcomes or number of parathyroidectomies performed. We also examined the results of the 48 and 96-week open-label extension trial in which all patients received burosumab (intervention) (20, 36). Although the extension trial only provides very low certainty evidence due to the absence of a control group, the findings proved to

**Table 3. GRADE summary of findings table SR<sub>Bmab</sub> vs no Rx**

| Outcome<br>Timeframe                                                                                                                                           | Study results and<br>measurements                                                                                            | Absolute effect estimates                                                             |                   | Certainty of the<br>Evidence (quality<br>of evidence)                   | Plain language summary                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                |                                                                                                                              | No treatment                                                                          | Burosumab         |                                                                         |                                                                                                                               |
| Adverse events (restless leg syndrome, limb discomfort, muscle cramp, headache)<br>24 weeks                                                                    | Based on data from 134 participants in 1 study <sup>a</sup><br>Follow up 24 weeks                                            | 8<br>per 100<br>Difference: 4 more per 100<br>(CI 95% 6 fewer to 14 more)             | 12<br>per 100     | Low<br>Due to very serious imprecision <sup>b</sup>                     | Burosumab may have little or no difference on adverse events (restless leg syndrome, limb discomfort, muscle cramp, headache) |
| Treatment-related serious adverse events<br>24 weeks                                                                                                           |                                                                                                                              | 0<br>per 100<br>Difference: 0 fewer per 100<br>(CI 95% 3 fewer to 3 more)             | 0<br>per 100      | Low<br>Due to very serious imprecision <sup>c</sup>                     | Burosumab may not increase the frequency of treatment-related serious adverse events                                          |
| Dental abscesses<br>24 weeks                                                                                                                                   |                                                                                                                              | 8<br>per 100<br>Difference: 5 more per 100<br>(CI 95% 5 fewer to 16 more)             | 13<br>per 100     | Low<br>Due to very serious imprecision <sup>d</sup>                     | Burosumab may increase dental abscesses                                                                                       |
| Improvement in BFI worst fatigue (greatest in the last 8 days) score<br>24 weeks                                                                               | Measured by:<br>self-reported, fatigue-specific questionnaire (MID $\geq -1.5$ )<br>Scale: 0-10<br>Lower better <sup>e</sup> | 0.48<br>Mean<br>Difference: MD 0.27 lower<br>(CI 95% 0.36 lower to 0.17 lower)        | 0.75<br>Mean      | High <sup>f</sup>                                                       | Burosumab has little or no impact on fatigue                                                                                  |
| Improvement in BFI fatigue interference score<br>24 weeks                                                                                                      | Measured by:<br>self-reported, fatigue-specific questionnaire (MID $\geq -1.2$ )<br>Scale: 0-10<br>Lower better              | 0.08<br>Mean<br>Difference: MD 0.16 higher<br>(CI 95% 0.05 higher to 0.27 higher)     | 0.08<br>Mean      | High <sup>g</sup>                                                       | Burosumab has little or no impact on fatigue interference with daily activities                                               |
| Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from normalization of serum phosphorus<br>24 weeks                        | Measured by: serum sample: High better % of participants achieving mean serum phosphorus >LLN                                | 8<br>per 100<br>Difference: 86 more per 100<br>(CI 95% 69 more to 100 more)           | 94<br>per 100     | Low<br>Due to very serious indirectness <sup>b</sup>                    | Burosumab may improve the burden of symptoms caused by chronic hypophosphatemia                                               |
| Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from lowering of bone specific alkaline phosphatase.<br>24 weeks          | Measured by: serum sample<br>Scale: 6.5-20.1 ug/L<br>Lower better                                                            | Difference: MD 4.4 higher<br>(CI 95% 0.45 lower to 9.25 higher)                       |                   | Low<br>Due to serious indirectness and serious imprecision <sup>i</sup> | Burosumab may have little or no difference on the burden of symptoms caused by chronic hypophosphatemia                       |
| Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from increase in TmP/GFR and subsequent normalization of serum phosphorus | Measured by: Urine sample<br>Scale: 2.5-4.2<br>High better                                                                   | 0.1<br>mg/dL Mean<br>Difference: MD 0.4 higher<br>(CI 95% 0.37 higher to 0.42 higher) | 0.5<br>mg/dL Mean | Low<br>Due to very serious indirectness <sup>j</sup>                    | Burosumab may improve the burden of symptoms caused by chronic hypophosphatemia                                               |
| Improvement in stiffness<br>24 weeks                                                                                                                           | Measured by:<br>WOMAC stiffness (MID $\geq -10$ ).<br>Scale: 0-100<br>Lower better                                           | 0.20<br>LS Mean<br>Difference: MD 8.2 lower<br>(CI 95% 14.4 lower to 2.3 lower)       | 8.01<br>LS Mean   | Moderate<br>Due to serious imprecision <sup>k</sup>                     | Burosumab probably has little or no impact on stiffness                                                                       |
| Improvement in pain as inferred from fractures or pseudofractures healing.<br>24 weeks                                                                         | Measured by:<br>radiographic assessment                                                                                      | 8<br>per 100<br>Difference: 35 more per 100<br>(CI 95% 22 more to 49 more)            | 43<br>per 100     | Moderate<br>Due to serious indirectness <sup>l</sup>                    | Burosumab probably improves pain                                                                                              |

(continued)

Table 3. Continued

| Outcome<br>Timeframe                                                                                                              | Study results and<br>measurements                                                                      | Absolute effect estimates                                                         |                    | Certainty of the<br>Evidence (quality<br>of evidence)                                                                   | Plain language summary                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
|                                                                                                                                   |                                                                                                        | No treatment                                                                      | Burosumab          |                                                                                                                         |                                                                                                       |
| Improvement in BPI-SF<br>worst pain (greatest in the<br>last 8 days) score from<br>baseline<br>24 weeks                           | Measured by: BPI-SF<br>Worst Pain<br>(MID $\geq -1.72$ )<br>Scale: 0-10<br>Lower better                | 0.38<br>LS Mean<br>Difference: MD 0.46 lower<br>(CI 95% 0.53 lower to 0.38 lower) | 0.84<br>LS Mean    | Moderate<br>Due to concerns<br>about the validity<br>in of the<br>instrument as<br>applied in the<br>study <sup>m</sup> | Burosumab probably has<br>little or no impact on<br>pain (greatest)                                   |
| Improvement in BPI-SF<br>pain interference score<br>24 weeks                                                                      | Measured by: BPI-SF<br>pain interference<br>(MID $\geq -1.0$ )<br>Scale: 0-10<br>Lower better          | 0.28<br>LS Mean<br>Difference: MD 0.13 lower<br>(CI 95% 0.2 lower to 0.05 lower)  | 0.41<br>LS Mean    | Moderate<br>Due to concerns<br>about the validity<br>in of the<br>instrument as<br>applied in the<br>study <sup>n</sup> | Burosumab probably has<br>little or no impact on<br>pain interference with<br>daily activities        |
| Mobility in daily activities<br>24 weeks                                                                                          | Measured by: 6<br>minutes walking test<br>High better                                                  | 5.71<br>LS Mean<br>Difference: MD 11.63 more<br>(CI 95% 9 fewer to 32 more)       | 5.92<br>LS Mean    | Low<br>Due to serious<br>imprecision and<br>serious<br>indirectness <sup>o</sup>                                        | Burosumab may have little<br>or no impact on<br>mobility                                              |
| Reduction in the risk of<br>parathyroidectomy as<br>inferred by lowering of<br>iPTH levels                                        | Measured by: serum<br>sample<br>Scale: 14-72<br>Lower better                                           | 3.8<br>pg/mL Mean<br>Difference: MD 21.2 lower<br>(CI 95% 24.4 lower to 18 lower) | 17.4<br>pg/mL Mean | Low<br>Due to very serious<br>indirectness <sup>o</sup>                                                                 | Burosumab may reduce<br>the risk of<br>parathyroidectomy                                              |
| Reduction in the risk of<br>progression of chronic<br>kidney disease as inferred<br>from improvement in<br>nephrocalcinosis score | Measured by: Renal<br>ultrasound<br>Radiographic<br>nephrocalcinosis<br>score: decreased by 1<br>point | 6<br>per 100<br>Difference: 0 more per 100<br>(CI 95% 8 fewer to 8 more)          | 6<br>per 100       | Very low<br>Due to very serious<br>indirectness and<br>serious<br>imprecision <sup>7</sup>                              | We are uncertain whether<br>burosumab reduces the<br>risk of progression to<br>chronic kidney disease |

Abbreviations: BFI, Brief Fatigue Inventory; BPI-SF, Brief Pain Inventory-Short Form; LLN: lower limit of normal; MD: mean difference; MID: minimally important difference; WOMAC, Western Ontario and the McMaster Universities Osteoarthritis Index.

CI: confidence interval; CIs that were not provided in the trial were calculated using RevMan (26).

<sup>a</sup>Primary study. Baseline/comparator primary study. Supporting references (10).

<sup>b</sup>Imprecision: very serious. Wide CIs,  $P = .410$ , Only data from 1 study.

<sup>c</sup>Imprecision: very serious. Wide CIs, only data from 1 study, low number of patients.

<sup>d</sup>Imprecision: very serious. Wide CI,  $P = .280$ .

<sup>e</sup>Baseline/comparator primary study. Supporting references (2).

<sup>f</sup>Risk of bias: no serious. recall period 24 hours; imprecision: no serious.  $P = .000$ .

<sup>g</sup>Risk of bias: no serious; imprecision: no serious.  $P = .006$ .

<sup>h</sup>Indirectness: very serious. due to surrogate for patient-important outcomes.

<sup>i</sup>Indirectness: serious. due to surrogate for patient-important outcomes; imprecision: serious. Wide CI,  $P = .0760$ .

<sup>j</sup>Indirectness: very serious due to surrogate for patient-important outcomes.

<sup>k</sup>Imprecision: serious.  $P = .012$ , MID  $\geq -10$  points.

<sup>l</sup>Indirectness: serious due to surrogate for patient-important outcome.

<sup>m</sup>Imprecision: no serious.  $P = .000$ ; concerns about the validity of the pain instrument as applied in the study arose because the selected pain question asked subjects to rate their worst pain experienced over the past 24 hours. The questionnaire was administered at the end of the 4-week dosing cycle (trough time point), during which the effects of the drug often peaked and declined considerably over the month. As a result, the pain question did not capture the majority of the time interval and may have missed the period of optimal drug efficacy.

<sup>n</sup>Imprecision: no serious.  $P = .012$ .

<sup>o</sup>Indirectness: serious. We consider 32 meters more representing an unimportant increase in mobility in daily activities.; Imprecision: serious. Wide CIs, Only data from 1 study.

<sup>p</sup>Indirectness: very serious. due to surrogate for patient-important outcomes; imprecision: no serious.  $P = .000$ .

<sup>q</sup>Indirectness: very serious. due to surrogate for patient-important outcome; imprecision: serious. Wide CIs.

be consistent with the results in the blinded portion of the RCT (see Table S2) (20, 32). Some believe burosumab requires more time to show efficacy, and the long-term extension data suggests gains but given the lack of a comparator and open-label study design, this is very low certainty evidence, lower even than the very low certainty evidence from the RCT.

### SR on conventional therapy vs no treatment

In this SR, we mainly obtained surrogate outcomes from eligible studies, we have limited confidence (very low certainty)

regarding whether conventional therapy improves overall well-being or prevents the need for parathyroidectomy in adults with XLH when compared with no treatment. It is recognized that long-term treatment with inorganic phosphate in patients with XLH is generally associated with the development of secondary and tertiary hyperparathyroidism (37, 38). This highlights the importance of avoiding excessive or isolated phosphate supplementation. Based on the available data on conventional therapy in adults, our conclusion is uncertain regarding its benefits compared to no treatment in adults with XLH.

Table 4. GRADE summary of findings table SR<sub>Pi/D</sub> vs no Rx

| Outcome timeframe                                                                                                                             | Study results and measurements                                                                                                      | Absolute effect estimates                                                    |              | Certainty of the evidence (quality of evidence)                                                                                 | Summary                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
|                                                                                                                                               |                                                                                                                                     | No treatment                                                                 | Pi/D         |                                                                                                                                 |                                                                                                  |
| Reduction in the risk of parathyroidectomy inferred by lowering of iPTH levels 72 months                                                      | Based on data from 27 participants in 1 study <sup>a</sup>                                                                          | 25 per 100<br>Difference: 11 more per 100<br>(CI 95% 24 fewer to 47 more)    | 36 per 100   | Very low<br>Due to serious risk of bias, serious indirectness, and serious imprecision <sup>b</sup>                             | We are uncertain whether Pi/D results in reducing the risk of parathyroidectomy                  |
| Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from increases in serum phosphorus.                      | Measured by:<br>Serum sample<br>Scale: 2.5–4.5 mg/dL<br>High better<br>Based on data from 35 participants in 2 studies <sup>c</sup> | Difference: MD 0.16 lower<br>(CI 95% 0.42 lower to 0.11 higher)              |              | Very low<br>Due to serious risk of bias, serious indirectness, serious imprecision, and very serious inconsistency <sup>d</sup> | We are uncertain whether Pi/D improves the burden of symptoms caused by chronic hypophosphatemia |
| Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from decrease in alkaline phosphatase activity 21 months | Measured by:<br>Serum sample<br>Scale: 44–147 Lower better<br>Based on data from 8 participants in 1 study                          | 91 U/L Mean<br>Difference: MD 102 higher<br>(CI 95% 62 higher to 142 higher) | 193 U/L Mean | Very low<br>Due to serious risk of bias and serious indirectness <sup>e</sup>                                                   | We are uncertain whether Pi/D improves the burden of symptoms caused by chronic hypophosphatemia |

CI's that were not provided in the trial were calculated using RevMan (26).  
<sup>a</sup>Baseline/comparator control arm of reference used for intervention. Supporting references (27).  
<sup>b</sup>Risk of bias: serious. Indirectness: serious. due to surrogate for patient important outcome; Imprecision: serious. Wide CIs, *P* = .657.  
<sup>c</sup>Primary study (1, 2) Baseline/comparator: primary study. Supporting references (28).  
<sup>d</sup>Risk of bias: serious. due to outcome of interest was present at start of the study; *P* = .08; Inconsistency: very serious. The direction of the effect is not consistent between the included studies. The CI of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies; indirectness: serious. due to surrogate for patient important outcomes; imprecision: serious. Wide CIs.  
<sup>e</sup>Risk of bias: serious. Indirectness: serious. Due to surrogate for patient-important outcomes; imprecision: no serious. *P* = .007.

Strengths and Limitations

These SRs are the first to address the impact of medical therapy in adult XLH on patient-important outcomes. Their strengths include a rigorously conducted, comprehensive search, a pre-registered protocol with PROSPERO, and the use of GRADE to assess the quality of evidence, with particular attention to limitations of surrogate outcomes including laboratory and imaging assessments.

Limitations stem from the scarcity and quality of literature due to the rarity of the condition, including lack of well-designed trials to understand the impact of conventional therapy in adult XLH; the only RCT available was a short trial of burosumab vs no treatment over 24 weeks. Consequently, our understanding of the long-term effects of burosumab on patient-important outcomes such as pain, fatigue, stiffness, and mobility remains limited. Another limitation arises from the trial's inclusion criteria, which required a BPI worst pain score of 4, thus restricting the applicability of findings to the broader XLH population.

Furthermore, the small sample size in available studies, particularly when evaluating conventional therapy vs no treatment, precluded precise estimates and subgroup analyses. In addition to the short duration of existing studies, the lack of patient-important outcomes led to our reliance on inferences from surrogate outcomes. There is always uncertainty in inferences regarding intervention effects on patient-important outcomes. As a result, we rated down for indirectness when inferring effects on patient-important outcomes from surrogates. For instance, when inferring improvement in the burden of symptoms from lowering of bsALP at 24 weeks, we rated down once for serious indirectness. When inferring improvement in the burden of symptoms from increase in TmP/GFR and subsequent normalization of serum phosphorus we rated

down twice for serious indirectness. These judgments inevitably involve some degree of subjectivity.

In the 24-week RCT compared with placebo (no treatment), burosumab did not improve pain, mobility, stiffness, or fatigue. However, burosumab had moderate to large effects on radiographic healing of fractures and pseudofractures, and improvement in biochemical measures including PTH, ALP, serum phosphorus levels, and TmP/ GFR.

This discrepancy was highlighted further when attempting to infer the clinical implications of these surrogate outcomes, a key recommendation by GRADE for guidelines. We would expect an improvement in radiographic healing of fractures and pseudofractures to improve pain or mobility, but neither was improved according to our analyses. Similarly, one may expect patients to feel better with biochemical normalization, but this was not demonstrated either.

Of note, some clinicians may find inferences regarding general well-being based on biochemical markers to be specious and entirely speculative. We agree, which is why we down-rated our certainty to low and very low. In other words, we suggest cautious clinical conclusions about these biochemical and radiographic findings. Indeed, the clinical data suggested little to no difference in patient-important outcomes between burosumab and placebo (no treatment), consistent with the uncertain inferences from improvements in surrogate outcomes.

The same discrepancies occurred with other outcomes. Direct measurement of fatigue showed high certainty evidence that there was little or no impact of burosumab on fatigue over 24 weeks; 96 weeks of open-label extension data was consistent with the RCT data with moderate certainty evidence. In addition, direct measurement of stiffness over 24 weeks showed likely no impact based on moderate certainty

evidence; similarly, in the extension trial direct measurement of stiffness using the WOMAC scale showed with low certainty evidence that burosumab had little or no impact on stiffness. In addition, there was low certainty of little or no improvement in mobility at 24 and 96 weeks (20, 36).

### Relation to Previous Reviews

Studies that did not focus exclusively on RCTs provided very low-quality evidence. A recent SR (39) included 3 articles derived from RCTs (10, 40, 41) and 3 single-arm studies (42–44). The main difference in outcomes between this SR and our present study may be because the prior SR combined both adult and pediatric studies, where the children's studies had different results than adults. The studies included in the other review aimed to assess the efficacy and safety of burosumab in adults and children with XLH (39); 2 of the RCTs included in this review (40, 41) were excluded from our study for several reasons. First, the RCT conducted by Imel et al (40) focused on children between 1 and 12 years old, whereas our analysis is specifically focused on adults with XLH. Second, the trial carried out by Carpenter et al (41) not only involved children but also used the same drug (burosumab) in both the intervention and control arms, differing only in administration frequency. Our study, on the other hand, was designed to assess the impact of the intervention (burosumab) in comparison to control, which may consist of either conventional therapy with phosphate salts and active vitamin D, or no treatment.

Data from the other review revealed that the incidences of treatment-emergent adverse events, serious treatment-emergent adverse event rate, and the incidence of headache were higher in the burosumab group compared with the control group (39). In our study evaluating serious treatment-related adverse events (as per trial investigators), we conclude with low certainty that burosumab may not increase the frequency of treatment-related serious adverse events in adults.

It is also worth noting that this review labelled the retrospective study by Martín Ramos et al (45) as an open-label trial. For certain outcomes, the authors of the previously published SR meta-analyzed the intervention arms (burosumab) from all the trials including RCTs and single-arm studies (39).

### Implications for Practice and Research

The existing studies were small and offered limited evidence concerning major patient-important outcomes beyond those addressed in our review. Discrepant results from direct measurements of patient experience and surrogate outcomes increased the uncertainty regarding the effects of burosumab on outcomes of importance to patients. This review proposes a greater emphasis on measurable patient-important outcomes, encompassing all domains of quality of life assessment. Additionally, we emphasize the importance of following established guidelines, such as CONSORT (Consolidated Standards of Reporting Trials) for clinical trials, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) for observational studies and PRISMA for SRs, to ensure that future studies provide more robust and reliable data. Adherence to these guidelines will be critical in improving the quality of research in this area, ultimately in the interest of patient care and treatment outcomes.

### Conclusions

While burosumab shows little or no benefit in improving worst pain based on direct measurements using the BPI-SF scale (moderate certainty), it does exhibit an improvement in fracture and pseudofracture healing in adults with XLH compared with no treatment. This led us to speculate that burosumab may have a potential impact on pain relief, as inferred from the observed rates of fracture and pseudofracture healing over a 24-week period (moderate certainty evidence). This may have not been captured by the pain instrument used in the trial. This important observation emphasizes the need for better and more accurate tools to assess pain in patients with chronic diseases, whose baseline is chronic pain.

Additionally, there is an indication, albeit with low certainty, of a reduced likelihood of parathyroidectomy among individuals receiving burosumab, suggesting a potential protective effect against this surgical intervention. It is noteworthy that this review also reveals, with low certainty, an elevated risk of dental abscesses among those treated with burosumab in a short-term RCT (24 weeks). Whether this observation persists over the longer-term remains unclear; nevertheless, this finding underscores the importance of monitoring and managing potential side effects associated with burosumab therapy, particularly in the context of oral health. These review findings pertain specifically to adult patients (aged >18 years) who were administered burosumab during adulthood. They may not necessarily extend to children or adolescents who received burosumab during childhood and subsequently transitioned to adult care.

In contrast, the analysis of conventional therapy vs no treatment in adults with XLH yielded results with very low certainty. This emphasizes the existing uncertainty in the literature regarding the comparative effectiveness of conventional therapy in adults, necessitating personalized strategies that are tailored to individual patients.

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Calcium disorders clinic at McMaster University.

### Author Contributions

Design/conceptualization of project: D.S.A., R.D.M., A.A.K., G.G. Data acquisition, review, analysis, methodology: D.S.A., R.D.M., F.A., S.H., H.A.A., A.A.K., G.G. Project administration, including acquisition of funding: A.A.K. Original drafting and preparation of manuscript: D.S.A., R.D.M., G.G. Review/editing of manuscript: D.S.A., R.D.M., F.A., S.H., H.A.A., N.M.A.-D., S.S.B.-N., M.B.-D., M.L.B., T.O.C., C.C., M.C.-S., R.K.C., K.D., P.F., S.F., Cl.G., P.G., Co.G., E.A.I., S.M.J.d.B., A.L., E.M.L., E.M., L.M.W., A.A.K., G.G.

### Disclosures

D.S.A., R.D.M., F.A., S.H., H.A.A.: nothing to declare; N.M.A.-D.: Kyowa Kirin, UCB and Amgen (Consulting & advisory boards), XLH-Network Netherlands (Patient Advisory

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## Data Availability

The data supporting the results of this study were obtained from publicly available sources. We are pleased to share the data upon request.

## Registration

This study was preregistered at the time of literature screening as 2 systematic reviews CRD42023416716, and CRD4202 3416753.

## References

- Liu S, Tang W, Zhou J, *et al.* Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *J Am Soc Nephrol.* 2006;17(5):1305-1315.
- Beck-Nielsen SS, Mughal Z, Haffner D, *et al.* FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J Rare Dis.* 2019;14(1):58.
- Holm IA, Huang X, Kunkel LM. Mutational analysis of the PEX gene in patients with X-linked hypophosphatemic rickets. *Am J Hum Genet.* 1997;60(4):790-797.
- Seefried L, Dahir K, Petryk A, *et al.* Burden of illness in adults with hypophosphatasia: data from the global hypophosphatasia patient registry. *J Bone Miner Res.* 2020;35(11):2171-2178.
- Hawley S, Shaw NJ, Delmestri A, *et al.* Prevalence and mortality of individuals with X-linked hypophosphatemia: a United Kingdom real-world data analysis. *J Clin Endocrinol Metab.* 2020;105(3):e871-e878.
- Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in Southern Denmark. *Eur J Endocrinol.* 2009;160(3):491-497.
- Endo I, Fukumoto S, Ozono K, *et al.* Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment. *Endocr J.* 2015;62(9):811-816.
- Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. *Eur J Endocrinol.* 2016;174(2):125-136.
- Padidela R, Nilsson O, Makitie O, *et al.* The international X-linked hypophosphataemia (XLH) registry (NCT03193476): rationale for and description of an international, observational study. *Orphanet J Rare Dis.* 2020;15(1):172.
- Insogna KL, Briot K, Imel EA, *et al.* A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res.* 2018;33(8):1383-1393.
- Linglart A, Blosse-Duplan M, Briot K, *et al.* Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect.* 2014;3(1):R13-R30.
- Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
- Ali DS, Mirza RD, Alsarraf F, *et al.* 2024. Systematic Review: Search Strategy. *ResearchGate.* doi:10.13140/RG.2.2.24562.21446. Date of deposit December 2024.
- Covidence systematic review software. 2024. <https://www.covidence.org>
- Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
- Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.ad
- Guyatt GH, Ebrahim S, Alonso-Coello P, *et al.* GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. *J Clin Epidemiol.* 2017;87:14-22. doi:10.1016/j.jclinepi.2017.05.005
- Carrasco-Labra A, Brignardello-Petersen R, Santesso N, *et al.* Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format. *J Clin Epidemiol.* 2016;74:7-18.
- Surrogate Endpoint Resources for Drug and Biologic Development. <https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development>
- Briot K, Portale AA, Brandi ML, *et al.* Burosumab treatment in adults with X-linked hypophosphataemia: 96-week patient-reported outcomes and ambulatory function from a randomised phase 3 trial and open-label extension. *RMD Open.* 2021;7(3):e001714.

21. Schünemann HJ, Guyatt GH. Commentary—goodbye M(C)ID! Hello MID, where do you come from? *Health Serv Res.* 2005; 40(2):593-597.
22. Guyatt G, Montori V, Devereaux PJ, Schünemann H, Bhandari M. Patients at the center: in our practice, and in our use of language. *ACP J Club.* 2004;140(1):A11-2.
23. Skrinar A, Theodore-Oklotia C, Bonner N, Arbuckle R, Williams A, Nixon A. PRO154 confirmatory psychometric validation of the brief pain inventory (BPI-SF) in adult X-linked hypophosphatemia (XLH). *Value Health.* 2019;22:S870.
24. Cleeland CS. *The Brief Pain Inventory User Guide.* The University of Texas MD Anderson Cancer Center; 2009.
25. Mendoza TR, Wang XS, Cleeland CS, *et al.* The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. *Cancer.* 1999;85(5):1186-1196.
26. The Cochrane Collaboration. Review Manager Web (RevMan Web). Edition 1.22.0. 2020.
27. Shanbhogue VV, Hansen S, Jørgensen NR, Beck-Nielsen SS. Impact of conventional medical therapy on bone mineral density and bone turnover in adult patients with X-linked hypophosphatemia: a 6-year prospective cohort study. *Calcif Tissue Int.* 2018;102(3): 321-328.
28. Imel EA, DiMeglio LA, Hui SL, Carpenter TO, Econs MJ. Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. *J Clin Endocrinol Metab.* 2010;95(4):1846-1850.
29. Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol.* 2011;64(12):1303-1310. doi:10.1016/j.jclinepi.2011.04.014
30. Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol.* 2011;64(12):1283-1293. doi:10.1016/j.jclinepi.2011.04.014
31. Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol.* 2011;64(12):1294-1302. doi:10.1016/j.jclinepi.2011.03.017
32. Ali DS, Mirza RD, Alsarraf F, *et al.* 2024. Supplementary Material for Systematic Review: Efficacy of Medical Therapy on Outcomes Important to Adult Patients with X-Linked Hypophosphatemia. *ResearchGate.* doi:10.13140/RG.2.2.21384.23049. Date of deposit 4 October 2024.
33. Bellamy N. The WOMAC knee and hip osteoarthritis indices: development, validation, globalization and influence on the development of the AUCAN hand OA indices. *Clin Exp Rheumatol.* 2005;23(5):S148.
34. Achintya Dinesh S, Mian A, Devasenapathy N, Guyatt G, Karthikeyan G. Percutaneous mitral commissurotomy versus surgical commissurotomy for rheumatic mitral stenosis: a systematic review and meta-analysis of randomised controlled trials. *Heart.* 2020;106(14):1094-1101.
35. Imel EA. Enthesopathy, osteoarthritis, and mobility in X-linked hypophosphatemia1. *J Clin Endocrinol Metab.* 2020;105(7): dgaa242.
36. Portale AA, Carpenter TO, Brandi ML, *et al.* Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif Tissue Int.* 2019;105(3):271-284.
37. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res.* 2011;26(7):1381-1388.
38. DeLacey S, Liu Z, Broyles A, *et al.* Hyperparathyroidism and parathyroidectomy in X-linked hypophosphatemia patients. *Bone.* 2019;127:386-392.
39. Wang S, Wang X, He M, Li Y, Xiao M, Ma H. Efficacy and safety of burosumab in X-linked hypophosphatemia: systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2023;109(1):293-302.
40. Imel EA, Glorieux FH, Whyte MP, *et al.* Burosumab versus conventional therapy in children with X-linked hypophosphatemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet.* 2019;393(10189):2416-2427.
41. Carpenter TO, Whyte MP, Imel EA, *et al.* Burosumab therapy in children with X-linked hypophosphatemia. *N Engl J Med.* 2018;378(21):1987-1998.
42. Linglart A, Imel EA, Whyte MP, *et al.* Sustained efficacy and safety of burosumab, a monoclonal antibody to FGF23, in children with X-linked hypophosphatemia. *J Clin Endocrinol Metab.* 2022;107(3):813-824.
43. Whyte MP, Carpenter TO, Gottesman GS, *et al.* Efficacy and safety of burosumab in children aged 1–4 years with X-linked hypophosphatemia: a multicentre, open-label, phase 2 trial. *Lancet Diabetes Endocrinol.* 2019;7(3):189-199.
44. Insogna KL, Rauch F, Kamenický P, *et al.* Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial. *J Bone Miner Res.* 2019;34(12):2183-2191.
45. Martín Ramos S, Gil-Calvo M, Roldán V, Castellano Martínez A, Santos F. Positive response to one-year treatment with burosumab in pediatric patients with X-linked hypophosphatemia. *Front Pediatr.* 2020;8:48.