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Real-world data of Brazilian adults with X-linked hypophosphatemia (XLH) treated with burosumab and comparison with other worldwide cohorts

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Abstract

Background: Disease-related variants in *PHEX* cause XLH by an increase of fibroblast growth factor 23 (FGF23) circulating levels, resulting in hypophosphatemia and $1,25(OH)_2$ vitamin D deficiency. XLH manifests in early life with rickets and persists in adulthood with osseous and extraosseous manifestations. Conventional therapy (oral phosphate and calcitriol) improves some symptoms, but evidence show that it is not completely effective, and it can lead to nephrocalcinosis (NC) and hyperparathyroidism (HPT). Burosumab (anti-FGF23 antibody) has shown to be effective and safety in the clinical trials.

Methods: The current real-world collaborative study evaluated genetic, clinical and laboratory data of XLH Brazilian adult patients treated with burosumab.

Results: Nineteen unrelated patients were studied. Patients reported pain, limb deformities and claudication, before burosumab initiation. 78% of them were previously treated with conventional therapy. The severity of the disease was

moderate to severe (15 patients with score >5). At the baseline, 3 patients presented NC (16.7%) and 12 HPT (63%). After 16 ± 8.4 months under burosumab, we observed a significant: increase in stature ($p = 0.02$), in serum phosphate from 1.90 ± 0.43 to 2.67 ± 0.52 mg/dL ($p = 0.02$); in TmP/GFR from 1.30 ± 0.46 to 2.27 ± 0.64 mg/dL ($p = 0.0001$), in 1,25 $(OH)_2$ D from 50.5 ± 23.3 to 71.1 ± 19.1 pg/mL ($p = 0.03$), and a decrease in iPTH from 86.8 ± 37.4 pg/mL to 66.5 ± 31.1 ($p = 0.002$). Nineteen variants were found (10 *novel*). HPT tended to develop in patients with truncated *PHEX* variants ($p = 0.06$).

Conclusions: This study confirms the efficacy and safety of burosumab on XLH adult patients observed in clinical trials. Additionally, we observed a decrease in iPTH levels in patients with moderate to severe HPT at the baseline.

KEYWORDS

adulthood, burosumab, FGF23, hyperparathyroidism, PHEX variants, X-linked hypophosphatemia

1 | INTRODUCTION

XLH (OMIM #300550) is the most common form (approximately 80% of cases) of a rare group of inherited metabolic diseases characterized by low serum phosphate and renal phosphate wasting due to increased fibroblast growth factor 23 (FGF23) circulating levels (Lecoq et al., 2020). It is a consequence of a disease-related variant leading to a loss-of-function of the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) (The HYP Consortium, 1995). *PHEX* is mainly expressed in osteoblasts and encodes an enzyme named PHEX, which is primarily responsible for the degradation of osteopontin (OPN) and suppression of FGF23 serum levels (Beck-Nielsen et al., 2019). The downregulation of PHEX leads to increased skeletal deposition of OPN, inhibiting mineralization. The mechanism behind abnormal *PHEX* expression leading to increased FGF23 levels is still unclear. However, the dysfunctional PHEX may cause malfunction of the phosphate sensor in osteocytes resulting in inadequate FGF23 secretion (Beck-Nielsen et al., 2019).

FGF23 regulates phosphate metabolism in different ways: (A) inhibition of renal proximal tubular reabsorption of phosphate by lowering the expression of sodium-dependent phosphate cotransporters (NaPt2a e NaPt2c) in the luminal membrane; (B) suppression of 1-α-hydroxylase (CYP27B1), which converts 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D (1,25$(OH)_2$D); and (C) increases 24-hydroxylase (CYP24A1) activity, inactivating 1,25$(OH)_2$D into other products (Shimada et al., 2004). Therefore, XLH patients present both renal phosphate wasting and low or inappropriate normal circulating levels of 1,25$(OH)_2$D despite hypophosphatemia (Lecoq et al., 2020). Low levels of 1,25$(OH)_2$D culminates in a reduced phosphate absorption by the intestine (Shimada et al., 2004).

Hypophosphatemia impairs caspase-mediated apoptosis of hypertrophic chondrocytes leading to rickets (Sabbagh et al., 2005). Low 1,25$(OH)_2$D compromises osteoblast differentiation and production of matrix vesicles in vitro, thereby inhibiting mineralization (Woeckel et al., 2010). Furthermore, several 1,25$(OH)_2$D-regulated proteins involved in bone mineralization do not function properly (Goltzman, 2018).

Clinically, pediatric patients present signs of rickets, bone and muscle pain, deformities mainly in the lower limbs, gait abnormalities, and delayed growth (Carpenter et al., 2011; Linglart et al., 2014; Vaisbich & Koch, 2006). In addition, dental abnormalities have also been observed in childhood (Souza et al., 2010). XLH is a progressive disease that persists in adulthood with a wide presence of clinical manifestation such as disproportionately short stature, osteomalacia, bone and muscle pain, osteoarthritis, pseudofractures, pathological fractures, enthesopathy, and dental disease (Carpenter et al., 2011; Ito et al., 2022). XLH adult patients may also suffer from hearing impairment and fatigue, contributing to poor quality of life (QoL) (Lecoq et al., 2020). Lower limb pain and deformity culminate in mobility difficulties and the use of crutches, walkers or wheelchair can be required (Linglart et al., 2014). Therefore, the burden of XLH in both pediatric and adult population is substantial and it has a direct impact on impaired QoL and healthcare costs (Ito et al., 2022).

For decades, XLH patients have been treated with oral phosphate and calcitriol supplementation (Linglart

et al., 2014; Vaisbich & Koch, 2006). This conventional therapy can improve symptoms, especially in children but it induces adverse effects such as secondary-tertiary hyperparathyroidism (HPT), hypercalciuria and nephrocalcinosis (NC) (Linglart et al., 2014; Vaisbich & Koch, 2006). In addition, it fails to prevent enthesopathy and osteoarthropathy in adulthood (Lecoq et al., 2020), and increases the circulating levels of FGF23 and PTH, potentially exacerbating hypophosphatemia (Imel et al., 2010).

Conventional therapy has been recommended in childhood, but its maintenance after completing the growth process is controversial. It has been recommended for symptomatic patients, those with biochemical evidence of osteomalacia, high alkaline phosphatase levels, recurrent pseudofractures or stress fractures, and upcoming orthopedic or dental surgery (Carpenter et al., 2011; Lecoq et al., 2020).

Burosumab is a fully human IgG1 monoclonal antibody that binds to circulating active full-length FGF23 and blocks its biological effects on target organs (Aono et al., 2009; Carpenter et al., 2014). Burosumab is approved for the treatment of XLH patients by several Health Regulatory Agencies, including ANVISA (Brazilian Agency), and recently it was incorporated into the Brazilian Unified Health System (*Sistema Único de Saúde—SUS*) to treat pediatric XLH patients. However, burosumab has not yet been incorporated into SUS for the purpose of treating adult patients unless they have started treatment before completing 18 years of age and have shown some notable benefit.

In addition to normalizing serum phosphate concentrations, clinical trials have demonstrated the ability of burosumab to significantly alleviate osteoarticular stiffness, contribute to fracture healing, increase levels of bone turnover markers, and improve histomorphometric measurements related to osteomalacia in adults (Insogna et al., 2019; Portale et al., 2019).

In the rare diseases landscape, real-life data are of great importance to determine the efficacy and safety in different populations and locations not included in clinical trials (Wu et al., 2020). Furthermore, the genetic profile of XLH, in which may have some influence on the response to burosumab has been poorly characterized in developing countries, in non-Caucasian populations, and mainly in highly mixed populations such as Brazil.

Our goal here is to report clinical, laboratory, and genetic data of a Brazilian cohort of XLH adult patients treated with burosumab by analyzing the benefits of the therapy and its safety profile. A genotype–phenotype correlation was also explored. Additionally, our results were compared to those obtained elsewhere in studies selected by a systematic review.

2 | PATIENTS AND METHODS

This is a descriptive collaborative study of XLH adult patients (≥18 years of age) treated with burosumab. Data were obtained from medical records by the treating physicians. Clinical and laboratory characteristics were analyzed at the baseline and final assessment. Genetic profile was also included to investigate the *PHEX* gene variants. A genotype–phenotype correlation was investigated in the population.

3 | STUDY PROTOCOL

3.1 | Clinical parameters

Clinical data surveyed included: age at onset, age at rickets/osteomalacia diagnosis, age at burosumab initiation, family and patient history. We also verified the presence of NC, HPT, hypertension, and other comorbidities. Anthropometric data, stature, and the body mass index (BMI) were evaluated. To gauge the severity and burden of the disease based on available data such as mobility impairment, number of previous surgeries and fractures, pain relief medication use, and dental abnormalities, a clinical severity score was generated and applied in this study (Table 1). Patients were classified as it follows: mild to moderate clinical condition (score ≤ 5), moderate (score > 5 and ≤9) and severe (score > 10). Maximum score = 14.

3.2 | Laboratory parameters

The biochemical parameters analyzed were serum creatinine, phosphorus, total calcium, alkaline phosphatase, iPTH, 25-hydroxyvitamin D, 1,25-$(OH)_2$ D. The following rates were calculated: renal tubular reabsorption of phosphate (TRP), ratio of the renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and urinary calcium/creatinine ratio. Glomerular filtration rate was estimated using the CKD-EPI formula (Levey et al., 2009).

3.3 | Burosumab administration

Burosumab dosage prescribed was 1.0 mg/kg (rounded to the nearest 10 mg) and administered subcutaneously every 4 weeks. The dose was titrated throughout follow-up based on serum phosphate. Adverse events were reported.

TABLE 1 Clinical score of disease severity designed in this study.

	Graduation		Graduation
Mobility		*Number of previous surgeries in the lower limbs*	
Normal walking	0	None	0
Unusual gait	1	1–3	1
Walking device use (crutches)	2	4–6	2
Wheelchair use	3	>6	3
Pain relief medication use		*Number of previous fractures*	
None	0	None	0
Sporadically	1	1–3	1
1 or 2 times/week	2	>3	2
Frequently (>2 times/week)	3	*Dental abnormalities*	
		Not reported	0
		Sporadic tooth infections	1
		Sporadic root canal treatment and spontaneous abscess	2
		>2 spontaneous abscess, root canal treatments and dental loss	3

3.4 | Genetic testing

All patients were submitted to next generation sequencing (NGS; Illumina platform) panel evaluating the following genes: *ALPL*, *BCS1L*, *CLCN5*, *CYP27B1*, *CYP2R1*, *DMP1*, *ENPP1*, *FAH*, *FGF23*, *KL*, *PHEX*, *SLC34A1*, *SLC34A3*, and *VDR*. Alignment and identification of variants using bioinformatic protocols, with reference to the GRCh37 version of the human genome. If no disease-related variant was detected by NGS, MLPA for *PHEX* was indicated (Multiplex Ligation-dependent Probe Amplification; according to the protocol supplied by the manufacturer of the SALSA- MLPA Kit P266—MRC-Holland, Amsterdam, The Netherlands). Segregation analysis was performed according to parental availability. All variants were classified according to the ACMG classification (Richards et al., 2015) into: pathogenic, likely pathogenic, variant of unknown significance, likely benign and benign. The allelic frequency of the variants was verified in gnomAD.

3.5 | Systematic review of the literature

In this study, we performed a systematic review of the literature seeking studies reporting the outcome of XLH adult patients treated with burosumab in worldwide cohorts. The search strategy was as follows: ("X-linked Hypophosphatemia" OR "Hypophosphatemic Osteomalacia" OR "Hypophosphatemic rickets") AND (burosumab OR KRN23) AND adults. No filters were applied. The search was carried out at the PubMed, Cochrane Central Register of Controlled Trials (Cochrane Library), EMBASE and LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), a research site of Latin-American Scientific Literature, up to July 3, 2023.

We utilized the new 2020 format for the PRISMA flow-diagram for reporting systematic reviews available on https://prisma-statement.org/PRISMAStatement/FlowDiagram (Page et al., 2021).

This protocol was approved by the University of Sao Paulo Ethical Review Board, Sao Paulo, Brazil (reference number 52533021.6.0000.0068).

3.6 | Statistical analyses

Data with homogeneous distribution are represented by mean and standard deviation; non-normal distributed data are shown as median and range. The paired samples *t*-test was performed to compare variables with a normal distribution, and the Wilcoxon signed-rank test was used to compare paired samples with non-normally distributed variables. Categorical variables are presented as frequencies or percentages. Statistical significance was defined at $p < 0.05$.

4 | RESULTS

4.1 | Study population

In this study, 19 adults with XLH were included (13 females), and one patient was excluded from the burosumab treatment evaluation as he started the treatment and stopped shortly after due to a lack of medication supply. His data are included in clinical manifestations and genetic findings. The age at diagnosis of rickets/osteomalacia

varied from 1.5 to 59 years of age (median = 6.5). Six patients were diagnosed above 18 years old, despite being symptomatic since childhood. Previous use of conventional treatment was reported by 14/19 patients (77.8%) and the therapy was initiated when two patients were above 20 years old (Table 2).

All patients reported lower limb pain and deformities, and mobility impairment. Pain relief medication use was reported by all but one patient, and 12 patients reported using analgesics or anti-inflammatories at least once to twice/week. At the baseline, four patients were classified within score ≤5, 12 patients within score >5 to ≤9, and 3 cases within score >9 according to the clinical severity score; data can be seen in Table 2. Therefore, at the baseline, most cases had significant impairment caused by XLH.

NC was observed in three patients at the baseline (cases 2, 8, and 16). Patients 2 and 8 received conventional treatment for a long time, and patient 16 received it for less than 1 year. Recurrent nephrolithiasis was reported in case 9, but no information about etiology was available.

Hyperparathyroidism was observed in 12/19 (63.1%) patients at the baseline (cases 2, 5, 6, 7, 9, 10, 14, 15, 16, 17, 18, and 19); 7 of these patients had received conventional treatment for a long time (2, 5, 7, 9, 10, 14, and 18), one patient received it less than a year (case 16), three patients (cases 14, 17 and 18) had never received it, and one patient (case 6) received only calcitriol.

Hypertension was detected in 2/19 patients (cases 11 and 16). Case 11, a 22-year-old male patient was diagnosed with left ventricular hypertrophy by doppler echocardiography performed before burosumab initiation. Hypothyroidism was reported in case 3, and depression signs were present in Case 9 (Table 2).

4.2 | Bone images

Radiology assessments were not available for most patients. As an example of bone involvement in this cohort, Figure 1 shows the bone abnormalities in case 4, a 38-year-old man.

4.3 | Burosumab treatment

Burosumab was initiated at a median age of 30 years (18–62), the initial dosage was: median (range) = 60 mg (30–80), and the final: median (range) = 60 (40–90). Patients received burosumab for 16 ± 8.4 months. Two patients presented erythema at the site of burosumab administration, one patient complained of nausea after his first administration, one presented transient constipation, and two presented dental complications: a patient lost her dental implant and the other one had a new fistulized dental abscess requiring endodontic treatment (Table 3). No serious side effects were observed, and the treatment was not discontinued in any of these cases.

4.4 | Comparison of the parameters at the baseline and final assessment

Anthropometric data of all patients are shown in Table S1. At the baseline, stature was 144.2 ± 12.5 cm, BMI was 28.3 ± 6.3 and at final evaluation was 146.4 ± 10.2 cm and 27.4 ± 5.8, respectively. Paired samples *t*-test showed no difference in BMI, but a significant difference in stature ($p = 0.02$) (Table 4).

From the baseline to the last follow-up, we observed a significant increase in serum phosphate from 1.90 ± 0.43 to 2.67 ± 0.52 mg/dL ($p = 0.02$), TmP/GFR from 1.30 ± 0.46 to 2.27 ± 0.64 mg/dL ($p = 0.0001$), TRP (%), median (range), from 67.9 (35.1–92) to med = 84.2 (63–94) ($p = 0.0001$) and 1,25 $(OH)_2$ D from 50.5 ± 23.3 to 71.1 ± 19.1 pg/mL ($p = 0.03$); a significant decrease in iPTH was found, from 86.8 ± 37.4 pg/mL to 66.5 ± 31.1 ($p = 0.002$) (Table 4). Normal calcemia and calciuria were observed during the study.

Figure 2 shows the main parameters (serum phosphate, TmP/GFR, and 1,25 $(OH)_2$ vitamin D) evaluated at the baseline and final assessment. All biochemical data for each patient is presented in Table S2, including missing values.

4.5 | PHEX variants

Likely pathogenic or pathogenic variant was identified in all patients by NGS; 19 variants were identified, 10 (52.6%) are *novel* and 9 had been previously described. The same variant was found in just two patients (cases 18 and 19). Patient 11 harbors 2 disease-causing variants. Table 2 shows the genetic results. The number (%) and type of variants identified were 7 splicing (37%), 4 missense (21%), 3 nonsense (15.8%), 2 deletions (10.5%), 2 small deletions, and 1 small insertion. Most of them resulting in truncated proteins, 14/19 (84.2%), as summarized in Table 5. Figure 3 shows the distribution of the genetic variants identified in this XLH Brazilian cohort.

In 12/19 patients, there was no past family history suggestive of XLH assuming De novo mutation and in 9 of these cases it was confirmed by segregation analysis.

TABLE 2 Clinical data of adult patients with X-linked hypophosphatemia included in the study.

Number of case	Gender (F/M)	Age at rickets diagnosis (y)	Past family history: Rickets/ Osteomalacia (yes/No) (relative)	Conventional treatment (yes/No)	Age at conventional treatment initiation (years)	Relevant symptoms according to the patient	Use of pain relief medications
1	F	4	No	Yes	7	Disabling bone pain; osteoarthritis (left knee), unusual gait	Frequent use of anti-inflammatories and analgesics
2	F	4	No	Yes	4	Lower limb pain and deformities	Sporadically analgesics
3	F	2	No	Yes	3.5	Pain and lower limb pain and deformities	Sporadically analgesics
4	M	4	Yes	Yes	4	Lower limb pain and deformities; mobility restrictions; unusual gait	Sporadically analgesics
5	F	20	No	Yes	35	Lower limb pain and deformities. Unusual gait	Analgesics and anti-inflammatories 1 or 2 times/week
6	F	34	No	Yes (only calcitriol)	4	Pain in the heels, knees, and hips, osteoarthritis, need for crutches	Analgesics and anti-inflammatories 1 or 2 times/week
7	M	3	No	Yes	3	Pain in the hips and heels. mobility restrictions. Joint stiffness, fatigue Unusual gait	Sporadically analgesics
8	F	1.5	No	Yes	2	Lower limb pain and deformities short stature Unusual gait	Analgesics and anti-inflammatories 1 or 2 times/week
9	F	3	No	Yes	7	Lower limb pain and deformities short stature; pseudofractures and unusual gait	Analgesics and anti-inflammatories 1 or 2 times/week
10	F	6.5	No	Yes	6.5	Lower limb pain and deformities Unusual gait	Analgesics and anti-inflammatories 1 or 2 times/week
11	M	6	No	Yes	6	Lower limb pain and deformities; mobility restrictions, Unusual gait	Analgesics and anti-inflammatories 1 or 2 times/week
12	F	7	Yes	Yes	7	Lower limb deformities 13(especially in th14e knees); fatig15ue Unusual gait	Sporadically analgesics
13	F	6	No	Yes	6	Lower limb pain and deformities; muscle pain; Unusual gait	Sporadically analgesics
14	F	45	Yes	No	–	Pain in the hits, knees, wrist and feet. Unusual gait	Frequently analgesics and anti-inflammatories
15	M	9	Yes	Yes	9	Short stature; lower limb pain and deformities, unusual gait	Analgesics 1 or 2 times/week
16	M	47	No	Yes	47	Lower limb pain and deformities; short stature and unusual gait	Analgesics 1 or 2 times/week
17	F	17	No	No	–	Pain in the knees, unusual gait	No
18	M	24	Yes	No	–	Lower limb pain and deformities he uses wheelchair	Frequently analgesics and anti-inflammatories
19	F	2	Yes	Yes	2	Lower limb pain and deformities; mobility restrictions (unusual gait), depression symptoms	Alprazolam; frequently anti-inflammatories and analgesics

Abbreviation: LVH, left ventricular hypertrophy.

Number of previous surgeries in the lower limbs	Number of previous fractures	Severity score	Nephrocalcinosis (yes/no)	Hyperparathyroidism (yes/no)	Hypertension (yes/no)	Heart disease (yes/no)	Dental problems	Chiari	Comorbidities
10	7	11/14	No	No	No	No	Yes	yes	No
4	0	7/14	Yes	Yes	No	No	Yes	No	No
4	4	8/14	No	No	No	No	Yes	No	Yes (hypothyroidism)
5	4	8/14	No	No	No	No	Yes	No	Yes (obesity)
12	>10	10/14	No	Yes	No	No	Yes	No	Yes (obesity; bariatric surgery in 2018)
3	3	10/14	No	Yes	No	No	Yes	No	No
0	2	5/14	No	Yes	No	No	Yes	Yes	No
12	1	8/14	Yes	No	No	No	Yes	No	Obesity
13	10	9/14	No	Yes	No	No	Yes	No	No
3	2	7/11	No	Yes	No	No	Yes	No	No
7	0	7/14	No	No	Yes	No	Yes	No	HAS
6	0	5/14	No	No	No	No	Yes	No	No
5	0	5/14	No	No	No	No	Yes	No	Epilepsy
6	0	7/14	No	Yes	No	No	Yes	No	No
7	2	7/14	No	Yes	No	No	No	No	No
1	2	6/14	Yes	Yes	Yes	Yes (LVH)	Yes	No	Yes (Hypertension)
0	0	1/14	No	Yes	No	No	No	No	No
2	2	8/14	No	Yes	No	No	No	No	Yes (lactose intolerance; bilateral paresthesia)
0	0	6/14	No	Yes	No	No	Yes	No	Yes (nephrolithiasis; depression; osteoporosis)

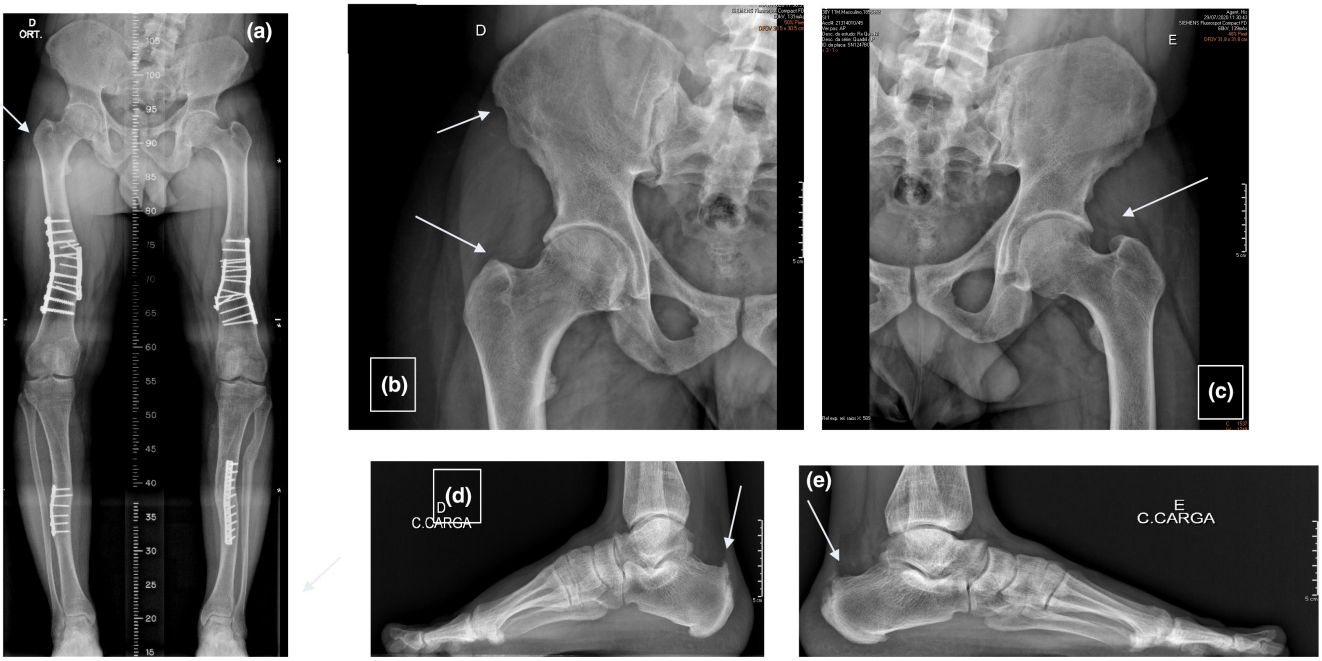

FIGURE 1 X-rays of a 38-year-old adult XLH Brazilian patient. (a) Main findings: Discret enlargement of the distal metaphysis (distal femur). Osteosynthesis in the middle and distal third of the right (R) and left (L) femur, and in the middle third of the diaphysis of the legs with metal plates and screws. Medial arching of the diaphysis. Consolidated fracture in the proximal diaphysis of the L fibula. Bilateral femorotibial varus with rotational component. (b) Hypertrophic reactions at the lateral acetabular border; increased degree of acetabular coverage over the femoral head. Prominence of the transition between the femoral head and neck (femoral bump). Reduction of superolateral femoroacetabular joints. Enthesophytes at tendon-ligament attachment sites in the iliacus, ischiopubic regions and minor trochanter of the femur. (c) Reduction of the cervico-diaphyseal angle of the fêmur with *coxa vara*. Linear trace of bone sclerosis on the medial border of the femoral neck, transverse to the bone trabeculae (incomplete fracture). Femoral bump. Reduction of superolateral femoroacetabular joint spaces. Enthesophytes in tendon-ligamentous attachment sites in the iliacus, ischiopubic regions and in the minor trochanter of the femur. (d,e) Bilateral anterior tibiotalar and marginal talonavicular osteophytosis. Mild metatarsophalangeal marginal osteophytosis of the hallux and second finger (L). Calcaneal enthesophytes close to the Achilles tendon attachment area. Plantar enthesophyte adjacent to the plantar fascia to the calcaneus. Sequelary irregularity of the base of the proximal phalanx (L fifth finger).

4.6 | Genotype–phenotype correlation

To investigate a genotype–phenotype correlation, we adopted the division of the variants previously used by Morey et al. (2011). Therefore, two groups were stablished:

- Group 1: composed of copy number variations, which included nonsense variants, insertion or deletion and splice site variants, resulting in truncated proteins.
- Group 2: comprised variants resulting in not truncated proteins and included missense mutations and a splicing variant within intron 14, the c.1586 + 5G>A, due to this variant does not directly change the encoded aminoacids sequence of the PHEX protein. It affects a nucleotide within the consensus splice site of the intron.

In case 11, the effect on protein caused by the c.2138dupC; p.Gln714Ser fs*26 was supposed to prevail over the c.2132G>T; p.Ser711Ile effect. Therefore, a truncated protein was considered in this patient for the ascertaining genotype–phenotype correlation.

In this Brazilian cohort, the comparison between Group 1 and 2 (Mann–Whitney test) at the baseline revealed no significant differentiation in the following parameters: score of severity ($p > 0.05$), serum phosphate ($p = 0.54$), TRP ($p = 0.68$), $1,25(OH)_2D$ serum levels ($p = 0.63$) and TmP/RFG ($p = 0.46$), but a tendency of significance was observed for the iPTH levels ($p = 0.06$).

Figure 4 represents the systematic review of literature carried out. The search yielded 69 results. After removing duplicates and guidelines/reviews or studies performed only in childhood, 25 studies were included: 17 clinical trials, one review of clinical trials, one case series, one registry data and 5 case reports. The characteristics of each included study are listed in Table 6. One similar real-world study was found, an Italian cohort (8 adults) which demonstrated burosumab led to a significant increase in serum phosphate in the first 6 months of treatment and a decline thereafter; however, patients

TABLE 3 Burosumab administration protocol.

Case number	Age at burosumab initiation (years)	Initial dose of burosumab (mg/dose)	Final dose of burosumab (mg/dose)	Time of burosumab treatment (months)	Adverse events
1	35	60	70	20	Site administration erythema
2	18	50	90	29	New dental abscess/transient constipation
3	24	60	60	26	No
4	40	60	80	11	No
5	46	40	60	15	No
6	62	60	60	6	No
7	34	60	70	8	Nausea after the 1st dose
8	23	70	70	10	No
9	37	40	40	19	Loss of dental implant
10	24	50	60	27	No
11	22	60	–	1	No
12	30	40	40	25	No
13	17	30	40	26	No
14	49	80	80	17	Site administration erythema
15	24	80	80	22	No
16	56	60	60	7	No
17	20	60	60	5	No
18	25	60	70	19	No
19	49	60	60	6	Transient constipation

TABLE 4 Body Mass Index (BMI; kg/stature^2), stature (cm) and biochemical parameters evaluated at the baseline and final assessment in 18 Brazilian adult patients with XLH treated with burosumab. Case 11 was not included in these parameters' evaluation.

Parameter	Initial	Final	Number of paired samples	Statistical test used to compare initial vs final values	*p*
Stature (cm)	144.19 ± 12.49	146.44 ± 10.26	18	Paired samples *t*-test	0.02
BMI (kg/m^2)	28.32 ± 6.27	27.45 ± 5.86	18	Paired samples *t*-test	0.38
Serum phosphate (mg/dL)	1.90 ± 0.43	2.67 ± 0.52	18	Paired samples *t*-test	$p < 0.0001$
Serum calcium (mg/dL)	med = 9.1 (7.8–10.7)	med = 9.1 (8.1–10.3)	18	Paired samples Wilcoxon test	$p = 0.9$
Serum 1,25 $(OH)_2$ D (pg/mL)	50.5 ± 23.3	71.1 + 19.1	12	Paired samples *t*-test	$p = 0.03$
Intact PTH (pg/mL)	86.8 ± 37.4	66.5 + 31.1	17	Paired samples t-test	$p = 0.002$
Alkaline phosphatase	120.3 + 40.0	123.8 + 34.2	16	Paired samples *t*-test	$p = 0.6$
eGFR (CKD-EPI) mL/min/1.73 m^2	119.5 + 15.4	119.6 + 17.7	18	Paired samples *t*-test	$p = 0.9$
Urinary calcium/creatinine ratio (mg/mg)	med = 0.09 (0.07–0.13)	med = 0.16 (0.05–0.21)	9	Paired samples Wilcoxon test	$p = 0.02$
Phosphate Tubular Reabsorption (TPR) (%)	med = 67.9 (35.1–92)	med = 84.2 (63–94)	14	Paired samples Wilcoxon test	$p = 0.0001$
TmP/RFG (mg/dL)	1.30 + 0.46	2.27 + 0.64	14	Paired samples *t*-test	$p = 0.0001$

Note: Data with normal distribution are reported as mean (SD). Median (range) is used for non-normal distributed data.

continued to show improvement in their general condition and physical performance (Marcellino et al., 2023). Poor response to burosumab treatment has been reported in cases of hyperparathyroidism and according to the genetic variant in case reports (Takashi et al., 2022; Zagari et al., 2022).

5 | DISCUSSION

The burden of XLH in adult patients is substantial, and there is no consensus about treating these patients with conventional therapy (Lecoq et al., 2020). Burosumab emerges as an option of a specific treatment by targeting the increased levels of FGF23 in XLH patients. Clinical trials demonstrated benefits in adults without major side effects. The main benefits observed are an improvement in phosphate metabolism by increasing serum phosphorus, serum 1,25$(OH)_2$D, and TmP/GFR associated with improvement in functional tests, radiologic signs, and in patient reported-QoL (Arcidiacono et al., 2022; Brandi, Jan de Beur, et al., 2022; Cheong et al., 2018; Insogna et al., 2018; Portale et al., 2019; Ruppe et al., 2016; Schindeler et al., 2020; Weber et al., 2022). Moreover, Kamenicky et al. demonstrated patients in use of burosumab present improvement in biochemical parameters, patient-reported outcomes, and ambulatory function. When the medication was discontinued, symptoms recurred, but improved after restarting the therapy (Kamenicky et al., 2023). Burosumab is subcutaneously administered every 4 weeks, improving the adherence to therapy by adult patients, and self-administration showed to be safe both in children and adults (Kubota et al., 2023).

Clinical trials are the most important tool available to verify the effects of a treatment. However, there is a consensus about the need of real-world evidence, especially in rare diseases, confirming efficacy and safety in a less controlled environment (Wu et al., 2020). In addition, we must be aware of genetic and environment differences in world populations that can influence the response to treatments. Brazilian population is unique owing to its diverse ancestry and high rate of miscegenation (Pena et al., 2020). Therefore, Brazilian data can contribute with new information.

This is a retrospective collaborative study including 19 unrelated Brazilian XLH adult patients followed in different medical centers with different protocols of follow-up. Most of the physicians who treated these patients did not follow an established protocol for case monitoring. Therefore, it was not possible to accurately assess functional, radiological, or quality of life improvements. For that reason, we created a score based on clinical available

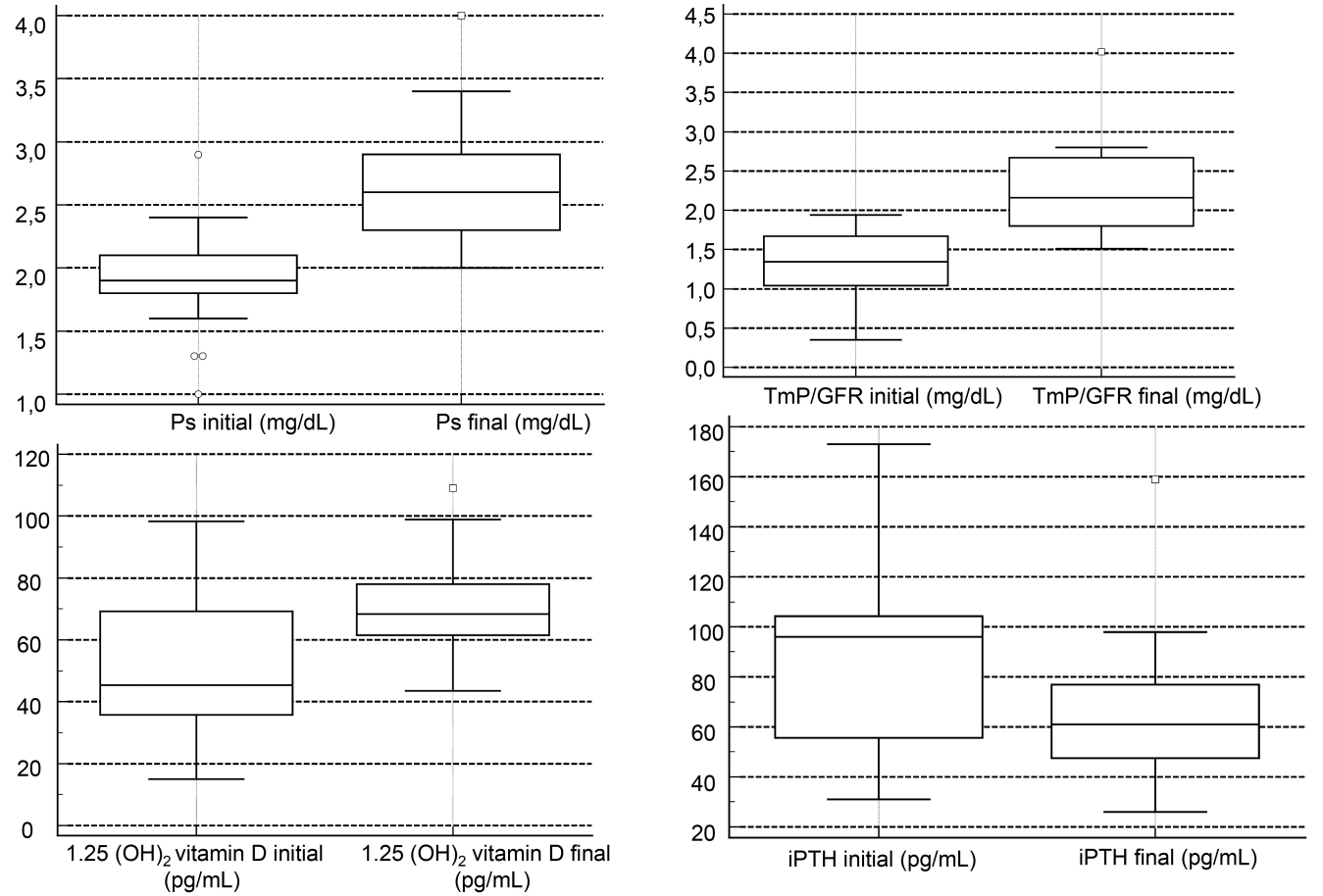

FIGURE 2 Graphic representation (Boxplot) of the main parameters involved with burosumab benefits such as the significant increase in serum phosphate, TmP/GFR and 1,25 $(OH)_2$ vitamin D. The significant reduction of iPTH is also represented. PS, Serum Phosphate; 1,25 (OH)2D, 1,25 $(OH)_2$ vitamin D.

data, as an indicator of the benefits measured at burosumab initiation and last assessment. The score created in this study, while not standardized or validated across different populations, proved to be useful for standardizing patient clinical data and classifying them based on disease severity. Despite variable follow-up period, a normally distributed pattern allowed the calculation of mean and standard deviation, indicating a relatively consistent treatment duration across cases and ensuring the reliability of the results.

Patients had a moderate to severe initial clinical picture with a severity score ± 5 in 14/19 patients (73.7%). A severe phenotype has been observed by other authors. Skrinar et al. reported abnormal gait and short stature in 86% of 232 patients, 44% had fractures, and 67% of adults took analgesics at least once a week (Skrinar et al., 2019).

Our results confirmed the clinical and biochemical improvements with burosumab described in clinical trials (Brandi, Jan de Beur, et al., 2022; Kamenicky et al., 2023; Weber et al., 2022). Patients presented a significant improvement in serum phosphate, TmP/GFR, TRP, and 1,25-$(OH)_2$ D. No patient had hyperphosphatemia, and almost all of them referred less pain and fatigue during the treatment. Patients reported a decrease in the use of analgesics and anti-inflammatory drugs and a better physical performance. Surprisingly, as mentioned in the results, patients experienced a significant increase in stature during treatment with burosumab, despite being adults and having already completed the growth period. This finding could be attributed to the improvement of deformities in the lower limbs with a better bone mineralization in different compartments (Fratzl-Zelman et al., 2022).

In this study, a significant decrease in iPTH was detected in the adult XLH population. Hyperparathyroidism (HPT) is a common clinical manifestation, and it has been reported in 62–87% of the cases (DeLacey et al., 2019). This event is traditionally explained by the use of chronic phosphorus therapy (Lecoq et al., 2020; Morey et al., 2011), and more recently it was observed in patients never treated by conventional therapy (Lecoq et al., 2020; Zhang et al., 2019). Among the factors contributing to HPT, we can list (A) an abnormal increase in the nocturnal pulse

TABLE 5 Genetic testing results of the XLH Brazilian adult patients included in this study.

Case number	*PHEX* variant	Aminoacid change	Type of variant	ACMG classification	Effect on PHEX protein	Location	Reference of previous description Clinvar entry/population described https://rarediseasesgenes.com variant entry Citation: Reference
1	c.2071-1G>C	Splice acceptor	Splicing	Pathogenic	Splice acceptor – This variant disrupts RNA splicing leading to loss of protein function. Truncated protein	Intron 20	Previously described ClinVar entry – Variation ID: 1339456 Population described: 1 patient from India (7/2/22), 1 patient (this patient) from Brazil – Mendelics (4/5/22); Invitae (27/9/22) no characterized population Reported in https://rarediseasesgenes.com variant ID: 1084 Citation: Marik et al. (2022)
2	c.664–3 C>G	Splice acceptor	Splicing	Likely pathogenic	Splice acceptor – Probably leads to abnormal mRNA. Truncated protein	Intron 5	Novel Clinvar, HGMD, or https://rarediseasesgenes.com – No entry
3	c.1586+5G>A	intronic	Splicing	pathogenic	Intronic –ACCEPTOR SPLICE SITE. This sequence does not directly change the encoded amino acid sequence of the PHEX protein. It affects a nucleotide within the consensus splice site of the intron. Probably leads to not truncated protein	Intron 14	Novel ClinVar entry – Variation ID: 803760 1st in Clinvar: 11 jan 2020 provided by Mendelics (28/05/2019). When this variant was identified in this patient, there was no previous report; however, it was also reported later in Clinvar by Invitae (2021) Reported in https://rarediseasesgenes.com variant ID: 869 Citation: Sarafrazi et al. (2022)
4	c.2104C>T	p.Arg702*	nonsense	Pathogenic	Nonsense – it is expected to disrupt the last 48 amino acid(s) of the PHEX protein. Truncated protein	Exon 21	Previously described ClinVar entry – Variation ID:279872. Reported in https://rarediseasesgenes.com variant ID: 743 Citation: Sarafrazi et al. (2022)
5	c.?	del exons 18–20	deletion	Pathogenic	deletion – Truncated protein	Exon 18–20	Novel No Clinvar entry Reported in https://rarediseasesgenes.com variant ID: 1138
6	c.1965+1G>A		Splicing	Pathogenic	Splice donor – Truncated	Intron 19	Previously described Clinvar entry Variation ID 438485 Reported in https://rarediseasesgenes.com variant ID: 668 Citation: Sarafrazi et al. (2022)

TABLE 5 (Continued)

Case number	*PHEX* variant	Aminoacid change	Type of variant	ACMG classification	Effect on PHEX protein	Location	Reference of previous description Clinvar entry/population described https://rarediseasesgenes.com variant entry Citation: Reference
7	c.349 + 1G>T	Splice donor	Splicing	Pathogenic	Splice donor – Truncated	Intron 3	Previously described Clinvar entry Variation ID: 1454954 1st in CLINVAR em 28/3/22 (Invitae) Reported in https://rarediseasesgenes.com variant ID: 821 Citation: Sarafrazi et al. (2022)
8	c.1958C>A	p.Ala653Asp	missense	Pathogenic ou likely pathogenic	Missense – Not truncated	Exon 19	Previously described Clinvar entry Variation ID: 929663 Reported in https://rarediseasesgenes.com variant ID: 664 Citation: Quinlan et al. (2012)
9	c.1044delA	p.Asp349Ile fs*6	Small deletion	Pathogenic	Frame shift * – Truncated	Exon 9	Previously described Clinvar entry Variation ID 422146 Reported in https://rarediseasesgenes.com variant ID: 315 Citation: Sarafrazi et al. (2022)
10	c.1793delA	p.ASn598Thrfs*21	Small deletion	Pathogenic	Frameshift* – Truncated	Exon 18	Novel No Clinvar entry Not reported in https://rarediseasesgenes.com
11	c.2132G>T; c.2138dupC	p.Ser711Ile; p.Gln714Ser fs*26	missense; small insertion	Pathogenic/Likely pathogenic	Missense – Not truncated/Frameshift* – Truncated (this mutation prevails)	Exon 21 Exon 21	- Allele 1 c.2132G>T; p.Ser711Ile Novel Clinvar entry Variation ID: 1678066 1st in Clinvar, reported by Mendelics in 28/5/22, probably this patient https://rarediseasesgenes.com No entry - Allele 2 c.2138dupC; p.Gln714Ser fs*26 Previously described Clinvar entry Variation ID: 265089 https://rarediseasesgenes.com No entry Citation: Sarafrazi et al. (2022)
12	c.1646-?_2070 +?del	del exons 16–20	CNV deletion	Pathogenic	Deletion – Truncated	Intron 15	Novel Clinvar entry No https://rarediseasesgenes.com variant ID:507 Citation: Sarafrazi et al. (2022)
13	c.1714G>T	p.Gly572Cys	missense	Likely pathogenic	Missense – Not truncated	Exon 17	Novel Clinvar entry variation ID: 792232 1st in Clinvar in 11/01/2020 (reported by Mendelics) https://rarediseasesgenes.com No entry Citation: Sarafrazi et al. (2022)

(Continues)

TABLE 5 (Continued)

Case number	*PHEX* variant	Aminoacid change	Type of variant	ACMG classification	Effect on PHEX protein	Location	Reference of previous description Clinvar entry/population described https://rarediseasesgenes.com variant entry Citation: Reference
14	c.1645+1G>A	p?	splicing	Pathogenic	Splice donor – Truncated	Intron 15	Previously described Clinvar entry Variation: 264998 https://rarediseasesgenes.com variant ID: 503 This variant has been reported several times in literature in familial as well as in sporadic cases. Citation: Sarafrazi et al. (2022)
15	c.2133T>G	p.Ser211Arg	missense	Pathogenic	Missense – Not truncated	Exon 21	Novel Clinvar entry Variation: 803775 1st in Clinvar in 11/01/2020 – single submitter. Reported by Mendelics (probably this patient) https://rarediseasesgenes.com No entry
16	c.934-1G>T	p?	Splicing	Pathogenic	Splice acceptor – Truncated	Intron 8	Novel Clinvar entry Variation ID: 803749 1st in Clinvar in 11/01/2020. Reported by Mendelics (probably this patient) Later reported by Invitae (2021) https://rarediseasesgenes.com variant ID: 282 Citation: Sarafrazi et al. (2022)
17	c.200T>A	p.Leu67* or p.Leu67Ter	nonsense	Pathogenic	Nonsense – Truncated	Exon 3	Novel Clinvar entry Variation ID: 1686023 – single submitter 1st in Clinvar in 28/05/2022 reported by Mendelics (probably this patient) https://rarediseasesgenes.com No entry
18	c.58C>T	p.Arg20*	nonsense	Pathogenic	Nonsense – Truncated	Exon1	Previously described Clinvar entry Variation ID:379502- multiple submitters (5) https://rarediseasesgenes.com variant ID: 27 Citation: Sarafrazi et al. (2022)
19	c.58C>T	p.Arg20*	nonsense	Pathogenic	Nonsense – Truncated	Exon1	Same variant detected in case number 18

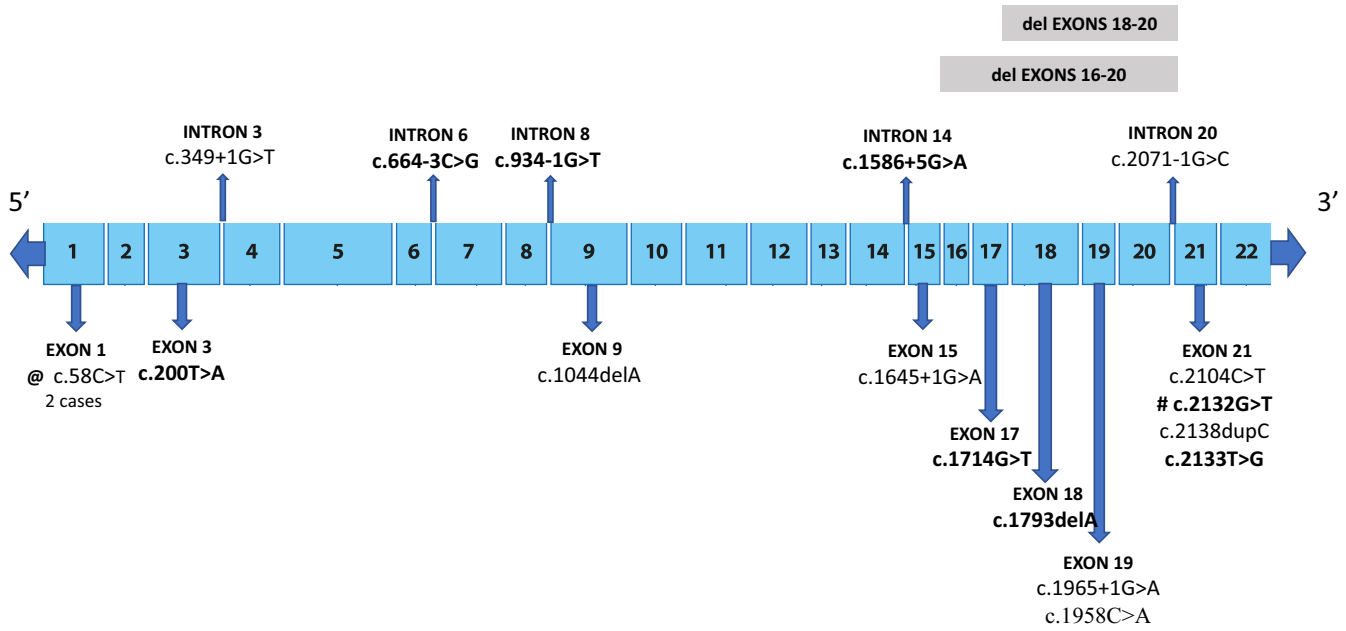

FIGURE 3 *PHEX* schematic representation showing the 19 disease-related variants identified in this study. The numbers in the blue box indicate the 22 exons in *PHEX*. The *novel* variants are in bold. Abnormal splicing variants are represented above the gene. @ represents the previously described variants. #c.2132G>T and c.2138dupC were found in the same patient.

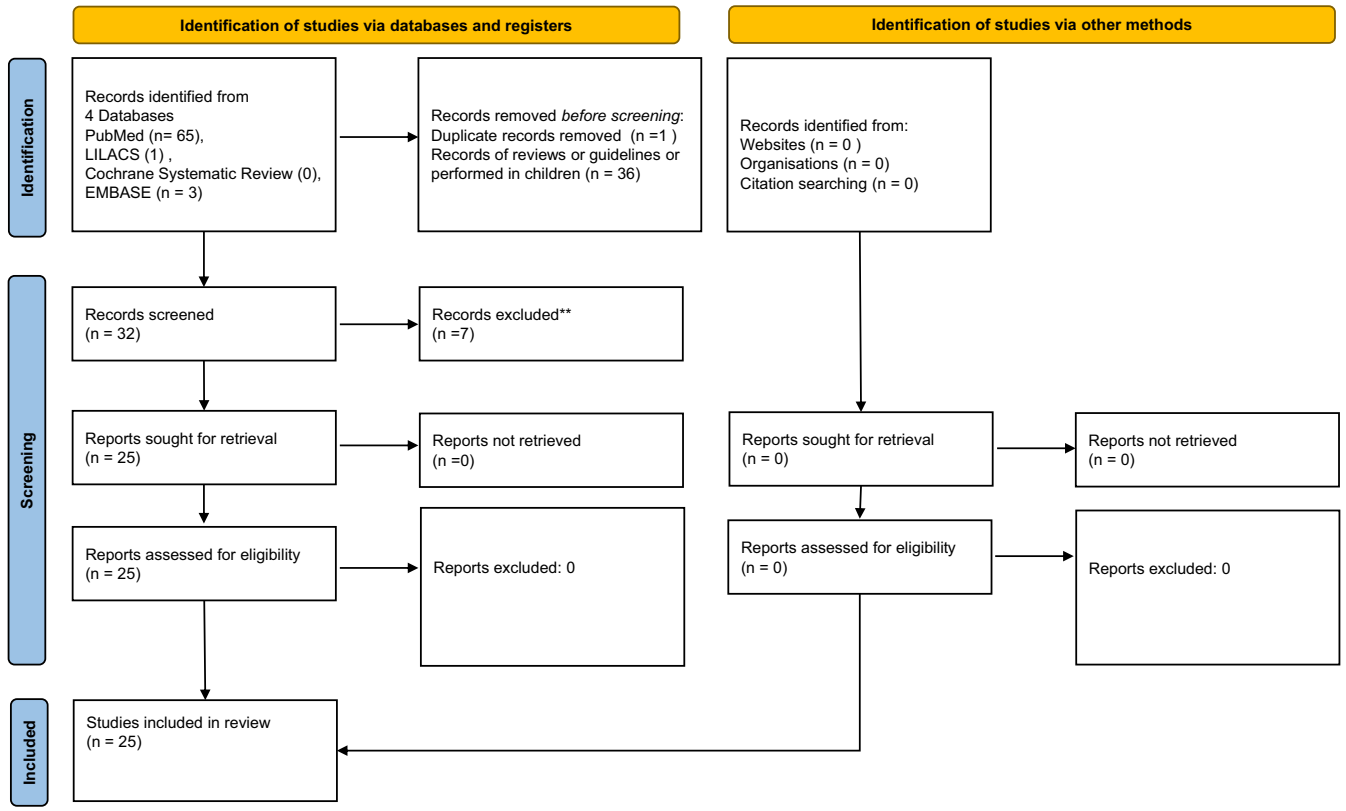

FIGURE 4 Schematic representation of the methodology used for the Systematic Review.

of PTH; (B) low serum levels of $1,25(OH)_2D$, occasional low serum 25-hydroxyvitamin D; and (C) osteomalacia, in what can limit the ability of PTH to induce resorption of mineralized bone to maintain the normal serum calcium, generating secondary HPT (Zhang et al., 2019). Some authors suggest that more severe *PHEX* variants are correlated with HPT (Sarafrazi et al., 2022). In our cohort, HPT was detected at the baseline in 12/19 patients

TABLE 6 Use of burosumab for the treatment of Adult XLH Patients – Results of Literature Review.

Authors, year	Title	Design	Patients and Methods
Marcellino et al. (2023)	Efficacy of Burosumab Every 2 weeks in an Adult with X-Linked Hypophosphatemia: Should We Learn from Children?	Case Report	$n=1$; a patient not responsive to 90 mg of burosumab each 4 weeks. A schedule 90 mg each 2 weeks was introduced
Arcidiacono et al. (2023)	Different Efficacy of Burosumab on Physical Performance and Serum Phosphate in Adult Patients with X-Linked Hyphophosphatemic Rickets during the First Six-Month of Treatment	Case Series Follow-up = 24 weeks	$N=8$ adult patients treated according to the recommended schedule of burosumab. The results obtained in the first 6 months of therapy were observed
Kamenicky et al. (2023)	Benefit of burosumab in adults with XLH is maintained with long-term treatment.	Phase 3, extension study of the reference 74. Follow-up: 48 weeks.	$n=31$ patients, 7 discontinued burosumab between the studies and 23 received at least one dose
Kubota et al. (2023)	Self-Administration of Burosumab in Children and Adults with XLH in Two Open-Label, Single-Arm Clinical Studies	KRN23-004- Follow-up of 2 previous studies in adults (Marik et al., 2022; Sarafrazi et al., 2022) – patients from Japan and South Korea.	$n=4$ Japanese XLH adults from UX023-CL303 or UX023-CL304 studies. Self-administration was permitted from Week 4
Zagari et al. (2022)	The Variant p.Ala84Pro Is Causative of X-Linked Hypophosphatemic Rickets: Possible Relationship with Burosumab Swinging Response in Adults	Case report Follow-up: 24 weeks	$n=2$ XLH adult patients. Correlation of the genetic finding with burosumab treatment response
Takashi et al. (2022)	Combined treatment by burosumab and a calcimimetic can ameliorate hypophosphatemia due to excessive actions of FGF23 and PTH in adult XLH with tertiary hyperparathyroidism: A case report	Case report	$N=1$
Aiello et al. (2022)	Rare PHEX intron variant causes complete and severe phenotype in a family with hypophosphatemic rickets: a case report	Case report	1 family
Brandi, Ariceta, et al. (2022)	Post-authorisation safety study of burosumab use in pediatric, adolescent and adult patients with X-linked hypophosphataemia: rationale and description	10-year retrospective and prospective cohort study – data from the International XLH Registry (NCT03193476)	Registry Follow-up: From april/2019 to december/2028. It will be the largest real-world safety study of burosumab

Outcomes	Results	Conclusions	Reference
Increase in Ps and decrease in iPTH	Patient evolved with iPTH reduction and improvement in Ps	Burosumab dosage can be personalized in adults according to the response	Marcellino et al. (2023)
Effects on Ps and physical performance (chair test and walking test), BPI scores	A significant increase in Ps was observed, but from the 16th week, Ps became significantly lower than its value in the 4th week. No patient had Ps < normal range at the 10th week, but 7 patients had at the 20th and 24th week. All patients improved the execution time of the physical tests (maximum at the 12th week). BPI scores significantly decreased during 24 weeks	Burosumab improved the general condition and physical performance of patients, although its effect on Ps may decline after the first weeks of treatment. Physical performance tests should be included in the follow-up protocols	Arcidiacono et al. (2023)
Primary efficacy –fasting Ps; secondary outcomes – serum 1,25 $(OH)_2$ D, renal phosphate reabsorption, PROs and ambulatory function	Improvements in fasting Ps, serum 1,25 $(OH)_2$D and renal phosphate reabsorption. Improvements maintained in stiffness and physical function, pain and fatigue endpoints, and in ambulatory function	This post-hoc exploratory analysis showed that the benefits of burosumab on clinical laboratory tests of efficacy, PROs and ambulatory function may be lost when treatment is interrupted but recover over time when treatment is reinstated	Kamenicky et al. (2023)
Evolution with self-administration.	Ps and active vitamin D levels increased from the baseline. No patient reported serious treatment-emergent adverse events ≥ grade 3	Burosumab had an acceptable safety profile with mainly mild-to-moderate adverse events. Self-administration is a viable option for patients with XLH	Kubota et al. (2023)
Improvements on burosumab/genotype–phenotype correlation	Patient 1: reduced the bone pain, and improved the functional test performance. Biomarkers had not improved substantially after 24 weeks. Genetic finding: c.250G>C (p.Ala84Pro) Patient 2: presented better clinical benefits than patient 1 and significant improvement in biomarkers. Genetic finding: c.118 + 1G>A	Probably the type of mutation can interfere in the burosumab response. However, patient 1 had hyperparathyroidism.	Zagari et al. (2022)
Improvements under burosumab treatment in patient with HPT at the baseline	Response to burosumab in patients with HPT. Association with calcimimetics	HPT can influence the response to burosumab. In this report, authors conclude calcimimetics can contribute in cases with HPT.	Takashi et al. (2022)
The authors report a family with a novel variant c.1586 + 6T>C. Despite previous prediction of a mild phenotype in functional study, the patients of this family presented a severe clinical picture	Burosumab therapy improved biochemical and radiologic findings in children and ameliorated QoL in adults	This case demonstrated c.1586 + 6T>C causes a severe XLH phenotype, responsive to burosumab	Aiello et al. (2022)
Clinical and biochemical parameters. QoL improvements. Side effects	This PASS will provide data on the long-term safety of burosumab treatment for XLH patients and describe safety outcomes for patients receiving burosumab contrasted with those patients receiving other XLH treatments	The expected date of the final study report is 31 December 2028, with two interim reports	Brandi, Ariceta et al. (2022)

(Continues)

TABLE 6 (Continued)

Authors, year	Title	Design	Patients and Methods
Weber et al. (2022)	Long-term Burosumab Administration Is Safe and Effective in Adults With X-linked Hypophosphatemia	UX023-CL203 (NCT02312687) was a Phase 2b, open-label, single-arm, long-term extension study of adults with XLH who participated in KRN23-INT-001 or KRN23-INT-002 studies.	Participants received burosumab based on the last dose in the prior KRN23-INT-001 or KRN23-INT-002 studies At Week 12, burosumab could be titrated upward/downward to achieve fasting Ps levels within the normal range. Follow-up: 12 weeks
Brandi, Jan de Beur, et al. (2022)	Efficacy of Burosumab in Adults with XLH: A Post Hoc Subgroup Analysis of a Randomized Double-Blind Placebo-Controlled Phase 3 Study	A Post Hoc Subgroup Analysis of a Randomized Double-Blind Placebo-Controlled Phase 3 Study	Placebo controlled study. Burosumab in 14 clinically subgroups characterized by baseline demographic and functional criteria. Follow-up: 24 weeks
Fratzl-Zelman et al. (2022)	Bone Matrix Mineralization and Response to Burosumab in Adult Patients With X-Linked Hypophosphatemia: Results From the Phase 3, Single-Arm International Trial	Phase 3, Single-Arm International Trial UX023-CL304	11 adult XLH subjects
Arcidiacono et al. (2022)	Efficacy of burosumab in healing a long-standing femoral fracture in an adult patient with X-linked hypophosphatemic rickets	Case report	• 1 adult treated with burosumab 1 mg/kg every 28 days. He had at the baseline an unconsolidated surgical fracture in right femur
Briot et al. (2021)	Burosumab treatment in adults with X-linked hypophosphataemia: 96-week patient-reported outcomes and ambulatory function from a randomized phase 3 trial and open-label extension	Double-blinded clinical trial and extension period – 96 weeks	$N = 134$ subjects were randomized to burosumab ($n = 68$) or placebo ($n = 66$) for 24 weeks. Thereafter, all subjects received burosumab every 4 weeks until week 96
Lee et al. (2022)	Population Pharmacokinetics and Pharmacodynamics of Burosumab in Adult and Pediatric Patients With XLH	PK of burosumab and the PK-PD relationship between burosumab and Ps in adult and pediatric patients with XLH	277 subjects from 9 clinical studies – 2844 serum concentrations of burosumab and 6047 Ps – PK and PK-PD modeling
Kubota et al. (2020)	Long-term outcomes for Asian patients with XLH: rationale and design of the SUNFLOWER longitudinal, observational cohort study	Study of longitUdinal observatioN For patients with X-Linked hypOphosphataemic rickets/osteomalacia in collaboration With Asian partnERs study	Longitudinal observational cohort study of patients with XLH. The sample size planned for analyses is 160 patients (100 from Japan and 60 patients from Korea). Data from April 2018 to April 2022

Outcomes	Results	Conclusions	Reference
Primary objectives- long-term safety, the proportion of subjects achieving normal fasting Ps, changes in bone turnover markers, PROs for pain, stiffness and mobility	Fasting Ps levels at the midpoint of the dosing interval (2 weeks postdose) were within the normal range in 85% to 100% of subjects. Measures of phosphate metabolism and bone biomarkers improved, approaching their normal ranges by study end. Improvements in PROs and mobility were sustained. No new safety findings emerged	These data support the conclusion that burosumab therapy may be a safe and effective long-term treatment option for adult patients with XLH	Weber et al. (2022)
Primary endpoint: fasting Ps	Higher proportions of subjects achieved mean Ps above the lower limit of normal (the primary endpoint) with burosumab than with placebo in all subgroups. Improvements with burosumab in secondary endpoints compared to placebo	Burosumab was largely superior to placebo across endpoints in the 14 clinically relevant subgroup variables at 24 weeks and is likely to benefit for all symptomatic adults with active XLH	Brandi, Jan de Beur et al. (2022)
The effect of burosumab on bone material properties. Parameters were analyzed from transiliac bone biopsy samples from 11 individuals before and after 48 weeks of burosumab (1.0 mg/kg SC every 4 weeks)	At the baseline, the mineralization was lower than in controls. CaLow (fraction of lowly mineralized matrix) and CaHigh (fraction of highly mineralized matrix) were high. Burosumab led to normal CaHigh, whereas CaLow and CaWidth remained elevated. The mineralized bone volume increased (+35.9%). The size of the periosteocytic lesions was lower than in untreated patients	Highly mineralized regions represent old bone packets, probably protected from osteoclastic resorption by osteoid seams. The authors gave us an explanation why there is an improvement in osteomalacia with burosumab	Fratzl-Zelman et al. (2022)
	Increase in Ps, PmP/GFR and 1,25 $(OH)_2D$. After 10 months under burosumab, a new x-ray of the right femur showed a complete resolution of the femoral fracture	Authors conclude burosumab was able to heal osteomalacia and fracture/pseudofractures confirming CTs findings	Arcidiacono et al. (2022)
PROs: WOMAC, BPI-Short Form (BPI-SF) and BFI, and ambulatory function (6 min walk test, 6MWT). Follow-up: 24 weeks and 96 weeks	At week 24, burosumab significantly improved some BPI-SF scores, BFI worst fatigue and WOMAC stiffness. At week 48, all WOMAC and BPI-SF scores significantly improved, from the baseline. At week 96, all WOMAC, BPI-SF and BFI were significantly improved. 6MWT distance improved at all time points from 24 weeks	Adults with XLH have substantial burden of disease. Burosumab treatment improved phosphate homoeostasis and it was associated with a sustained improvement in PROs and ambulatory function	Briot et al. (2021)
PK and PD parameters. The serum concentration of burosumab following a SC injection described by a PK model comprising a first-order absorption, 1-compartmental distribution, and a linear elimination	The relationship between serum burosumab and Ps was adequately described by a sigmoid maximal efficacy model. Body weight was the only covariate associated with PK and PK-PD parameters	Further simulations helped to guide the dosing regimen of burosumab in adult and pediatric patients with XLH	Lee et al. (2022)
Characteristics and burdens (physical, emotional and financial) of this disease and to evaluate the impact of treatment (including the use of burosumab) on clinical outcomes	Not yet	Up to 5 years of observation are planned per patient. To evaluate variables, including height/growth, rickets severity score, QOL, motor function and biomarkers for phosphate metabolism and bone turnover	Kubota et al. (2020)

(Continues)

TABLE 6 (Continued)

Authors, year	Title	Design	Patients and Methods
Schindeler et al. (2020)	Clinical Evidence for the Benefits of Burosumab Therapy for X-Linked Hypophosphatemia (XLH) and Other Conditions in Adults and Children	Review of the main clinical trials in adults and children	XLH Adults and children under burosumab treatment in clinical trials
Insogna et al. (2019)	Burosumab Improved Histomorphometric Measures of Osteomalacia in Adults with X-Linked Hypophosphatemia: A Phase 3, Single-Arm, International Trial	A Phase 3, Single-Arm, International Trial	14 subjects enrolled, 13 completed 48 weeks, and 11 completed paired biopsies. Follow-up: 48 weeks
Portale et al. (2019)	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	Randomized clinical trial + extension period from reference 74 (all receiving burosumab)	$N = 134$ XLH adults. initial 24-week: randomized, controlled trial, burosumab 1 mg/kg ($n = 68$) or placebo ($n = 66$) every 4 weeks
Cheong et al. (2018)	First-in-Asian Phase I Study of the Anti-Fibroblast Growth Factor 23 Monoclonal Antibody, Burosumab: Safety and Pharmacodynamics in Adults With X-linked Hypophosphatemia	Multicenter, sequential dose scalation, open-label, single-dose study. Clinical Trial Phase 1 safety and PD	Japanese and Korean adults with XLH. Cohort 1 -burosumab 0.3 mg/kg s.c., after which the dose was escalated sequentially in cohort 2 (0.6 mg/kg s.c. dose); cohort 3 -(1.0 mg/kg s.c.)
Insogna et al. (2018)	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.	Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial	Subjects received: burosumab 1 mg/kg SC every 4 weeks ($n = 68$) or placebo ($n = 66$)
Ruppe et al. (2016)	Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia	Evaluation of QoL parameters of patients from the previous dose escalation study (reference 76)	The primary Phase 1/2 study was an open-label, dose-escalation trial of KRN23 in adults (reference 76). This current study evaluated Health related QoL utilizing two well-established PRO instruments: SF-36v2 and WOMAC

Outcomes	Results	Conclusions	Reference
Summary of results from clinical trials	This review summarizes the clinical trial data from clinical trials currently underway	Burosumab appears transformative for the treatment of XLH. Long-term follow-up studies would be required to allay concerns over the potential for nephrocalcinosis and cardiac calcification	Schindeler et al. (2020)
Primary endpoint: improvement in osteoid/bone volumes from the baseline to week 48. Other points: Ps, markers of bone turnover, bone healing	Histological measures improved significantly at week 48. Mean Ps at the mid-point of the dose interval was 3.3 mg/dL (increase of 50% from the baseline). Markers of bone activity increased significantly	By normalizing phosphate homeostasis, burosumab significantly improved osteomalacia in adults with XLH, which likely explains the improved fracture healing and amelioration of skeletal complications	Insogna et al. (2019)
Efficacy and safety of burosumab. 24–48 week: all subjects under burosumab	At week-48: Ps remained normal in 83.8% of burosumab group and normalized in 89.4% of placebo 1st treated patients; 63.1% of baseline fractures/pseudofractures healed fully with burosumab, compared with 35.2% with burosumab after placebo. Burosumab was associated with sustained improvement in PROs. Nephrocalcinosis scores did not change from the baseline by more than one grade	Continued treatment with burosumab is well tolerated and leads to sustained correction of Ps levels, continued healing of fractures and pseudofractures, and sustained improvement in key musculoskeletal impairments. No treatment-related serious adverse events	Portale et al. (2019)
Safety, tolerability, PK, PD (Ps, serum $1,25[OH]_2D3$, and TmP/GFR), and expression of antidrug antibodies	The PK of burosumab were linear within the dose range of 0.3 to 1.0 mg/kg. The area under the receiver-operating characteristic curve from 0 to t (AUC0-t) values calculated using the change from the baseline of Ps, serum $1,25(OH)_2D3$, and TmP/GFR were correlated with the AUC0-t of burosumab. No serious AEs, remarkable increase or decrease in calcium or iPTH levels, or signs of nephrocalcinosis or its worsening	The positive effects and acceptable safety profile seen in this study are encouraging for Japanese and Korean patients with XLH	Cheong et al. (2018)
Biochemical and functional evaluation Follow-up: 24 weeks	Across midpoints of dosing intervals, 94.1% of burosumab-treated group attained mean Ps > lower normal limit compared with 7.6% of those receiving placebo ($p < 0.001$). Burosumab improved WOMAC physical function subscale compared with placebo ($p = 0.01$) and increased markers of bone activity. At week 24, 43.1% (burosumab) and 7.7% (placebo) of baseline active fractures were fully healed ($p < 0.001$)	Burosumab is a novel therapeutic addressing an important medical need in adults with XLH. It is safe and no serious adverse events were observed	Insogna et al. (2018)
-Baseline quality of life in XLH, interpret changes in PRO scales over time, and validate PRO analyses implementation in XLH patients. Lower score SF-36v2 and higher score WOMAC indicate worse functioning PRO assessments were undertaken at the baseline in the 28 patients who were enrolled in the study and in the 26 patients who completed the study	At endpoint, mean scores for all SF-36v2 scales increased and those for WOMAC decreased from the baseline. Compared to the general US population, the XLH trial patients showed lower physical HRQoL. SF-36v2 and WOMAC were validated for use in XLH	The instruments show decreased HRQoL scores in XLH patients, and significant improvement following four doses of KRN23 given every 28 days. These PRO instruments provide a valuable addition criterion in evaluating new treatment options in adults with XLH	Ruppe et al. (2016)

(Continues)

TABLE 6 (Continued)

Authors, year	Title	Design	Patients and Methods
Zhang, Peyret, et al. (2016)	Population pharmacokinetic and pharmacodynamic analyses from a 4-month intradose escalation and its subsequent 12-month dose titration studies for a human monoclonal anti-FGF23 antibody (KRN23) in adults with X-linked hypophosphatemia	Dose escalation of KRN23 and Pk e PD analysis following SC dosing every 28 days over an initial 4-month and a subsequent 12-month titration period (0.1–1.0 mg/kg) Data from 3 previous studies about PK and PD: IV or SC single dose, escalation dose	PK and PD models of KRN23 in XLH adults
Zhang, Imel, et al. (2016)	Pharmacokinetics and pharmacodynamics of a human monoclonal anti-FGF23 antibody (KRN23) in the first multiple ascending-dose trial treating adults with X-linked hypophosphatemia	PK and PD correlation in dose escalation model of burosumab for XLH adult patients	$N = 29$ XLH adults. Up to 4 SC doses of KRN23 every 28 days. The mean time to reach maximum serum KRN23 levels was 7.0 to 8.5 days. The mean KRN23 half-life was 16.4 days
Imel et al. (2015)	Prolonged Correction of Serum Phosphorus in Adults With X-Linked Hypophosphatemia Using Monthly Doses of KRN23	Phase 1/2 open-label, dose-escalation study in adults with XLH to evaluate the safety and efficacy of SC KRN23 administered every 28 days for four doses, followed by a 12-month extension study	Screening: 31 patients. 28 included in safety analysis and 27 in efficacy analysis. Extension study: 22 patients
Carpenter et al. (2014)	Phase I, double-blind, randomized, placebo-controlled, single-dose, dose-escalation study of KRN23 administered i.v. or s.c. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia	Safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of KRN23 following a single i.v. or s.c. dose of KRN23 in adults with XLH	38

Abbreviations: BPI, Brief Pain Inventory; HPT, hyperparathyroidism; PROs, patient reported outcomes; Ps, serum phosphate.

(63.1%), where nine patients were previously treated with conventional therapy. Moreover, all patients with HPT presented a truncated protein, and we found a trend indicating the presence of a truncated protein correlates with higher serum iPTH levels ($p = 0.06$).

In use of burosumab, patients showed a decrease in iPTH levels. Then, parathyroidectomy could be avoided as well as the addition of other medications such as calcimimetics, which can cause hypocalcemia (Lecoq et al., 2020). In the literature, there are a few cases reported with tertiary HPT and burosumab treatment. Takashi reported the association of a calcimimetic (evocalcet) improving PTH serum levels more rapidly; however, they decided to associate this drug after just 4 weeks

Outcomes	Results	Conclusions	Reference
Pk e PD (Pi) correlation Follow-up: 12 months	The PK of KRN23 was described by a 1-compartmental model with first-order absorption and elimination at doses ≥0.1 mg/kg. Covariates did not affect KRN23 PK. Mean peak serum Pi was at 7–10 days after dosing and increased after each of the initial 4 doses. It remained from the sixth through tenth doses with a slight decrease thereafter.	The results from the present population PK and PK-PD model analysis are valuable for guiding further studies of KRN23 in the treatment of XLH.	Zhang, Peyret, et al. (2016)
AUC burosumab vs biochemical markers of XLH Follow-up: 4 months	The mean area under the concentration-time curve (AUCn) for each dosing interval increased proportionally with increases in KRN23 dose. The mean intersubject variability in AUCn ranged from 30% to 37%. The area under the effect concentration-time curve (AUECn) for change from the baseline in TmP/GFR, Ps, $1,25(OH)_2$ D, and bone markers for each dosing interval increased linearly with increases in KRN23 AUCn	Linear correlation between serum KRN23 concentrations and increase in Ps support KRN23 dose adjustments based on predose serum Pi concentration	Zhang, Imel, et al. (2016)
Primary outcome: proportion of subjects achieving maximum fasting serum Pi within the normal range. Secondary outcomes: changes from baseline in calculated TmP/GFR, Ps, and $1,25(OH)_2D$ Follow-up: 4 months Extension study: 12 months	Inclusion criteria: serum calcium <10.8 mg/dL (probably no patient with tertiary hyperparathyroidism was included). TmP/GFR, Ps, and serum $1,25(OH)_2D$ correlated with serum KRN23	Improvement in biochemical markers correlated with the dosage of KRN23	Imel et al. (2015)
A single dose of KRN23 (0.003–0.3 mg/kg i.v. or 0.1–1 mg/kg s.c.) or placebo. PK, PD, immunogenicity, safety, and tolerability were assessed. Follow-up: 50 days	KRN23 increased the TmP/GFR, Ps, and $1,25(OH)_2D$ compared with placebo ($p < 0.01$). The maximum Ps concentration occurred 8–15 days later following s.c. dosing compared with i.v. dosing (0.5–4 days). The effect duration persisted longer in patients who received s.c. administration. TmP/GFR, Ps, and serum $1,25(OH)_2D$ correlated with serum KRN23. No increasing in nephrocalcinosis or develop hypercalciuria, hypercalcemia, anti-KRN23 antibodies, or elevated serum PTH or creatinine	KRN23 increased TmP/GFR, Ps, and serum 1,25(OH)2D. The positive effect of KR23 on serum Pi and its favorable safety profile suggest utility for KRN23 in XLH patients	Carpenter et al. (2014)

with burosumab (Takashi et al., 2022). In our experience, the increase of serum phosphate and TmP/GFR can be slower in tertiary HPT such as showed in our case 2.

Nephrocalcinosis, another conventional treatment-related complication, has been observed in adults with a incidence of 17%–79% (Keskin et al., 2015). Presence of hypercalcemia and hypercalciuria secondary to conventional therapy, and formation of calcium oxalate crystals are the main predictive factors for this event (Keskin et al., 2015). Additionally, Andrukhova et al. showed a potential role for FGF23 in enhancing renal calcium reabsorption in XLH disease through the transient receptor potential cation channel subfamily V member 5 (TRPV5) channel, promoting calcifications

(Andrukhova et al., 2014). In our series, three patients previously treated with conventional therapy had nephrocalcinosis at the baseline.

Genotype–phenotype correlation is an important issue to search factors that may influence the therapy response and disease prognosis (Zagari et al., 2022). Many *PHEX* variants have been continuously described; for example, 30.7% *novel* variants were recently reported in a Chinese cohort (Lin et al., 2020). Our study contributes to broadening the spectrum of *PHEX* mutations and supports the hypothesis of private familial variant profile (Lin et al., 2020; Sarafrazi et al., 2022). We found only one variant present in more than one patient, the c.58C>T;p.Arg20*.

Sarafrazi et al. (2022), reported the creation of a new public interactive website of *PHEX* variants (Sarafrazi et al., 2022) (https://www.rarediseasegenes.com/). The most frequent variants identified in our cohort were 7 splicing (37%), 4 missense (21%), and 3 nonsense (15.8%), which corroborated with the distribution reported by Sarafrazi et al. (2022). Controversy exists regarding the *PHEX* genotype and the severity of XLH phenotype (Sarafrazi et al., 2022). Some studies reported differences in phenotype according to gender and position of the variant (Holm et al., 2001; Morey et al., 2011; Song et al., 2007). Filisetti et al. (1999) reported a high density of mutations in exons 15 and 17; however, Safarazzi et al. made an extensive review on *PHEX* variants and concluded that there is an enormous number of variants, which occur across the entire length of the gene, with no apparent concentration of variants at one or more locations within the gene (Sarafrazi et al., 2022).

A recent study, comparing truncating to non-truncating variants, found no correlation with phenotype severity (Zhang et al., 2019) and an evidence-based experimental study revealed similar functional portrait of different type of mutations (Zheng et al., 2020). Variations in XLH phenotype have been observed in patients with the same genotype, including members of the same family (Holm et al., 2001; Thiele et al., 2020). In the current Brazilian cohort, 14 out of 19 detected variants lead to a truncated protein. We found no correlation between the type of variant, truncating or non-truncating, and the severity of the clinical picture or biochemical parameters. However, a trend for higher iPTH levels was correlated with truncated variants ($p = 0.06$).

Our results and from others indicate the *PHEX* variant identification may have limited predictive value for the prognosis of XLH patients. We recommend genetic testing to confirm the XLH diagnosis since an overlap of signs and symptoms exists with other types of hypophosphatemic rickets, and some forms such as those caused by *ENPP1* mutation may even have unfavorable effects from burosumab (Zheng et al., 2020).

The current real-world Brazilian study has some limitations. It is retrospective study and information was highly dependent on treating clinicians' opinion. The absence of radiologic images, functional tests and quality of life questionnaires for most patients underscores the importance of developing guidelines for the diagnosis and treatment of adults with XLH, incorporating standardized recommendations for patient follow-up. Our study expands the genotype spectrum of XLH and provides evidence of the burosumab safety and efficacy to treat adult XLH patients, including those with significant HPT.

AUTHOR CONTRIBUTIONS

All authors contributed with data of at least one patient. MHV was responsible for the data analysis, review of literature, and writing the paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated in this study are available. Figures S1 and S2 show all clinical and laboratory data evaluated during this study.

ETHICAL APPROVAL

This study protocol was reviewed and approved by the Local Ethical Review Board of Hospital das Clinicas, University of Sao Paulo, Comissão de Ética para Análise de Projetos de Pesquisa—CAPPesq, São Paulo, Brazil (reference number 3.261.257).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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