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Clinical Research Article

Safety and Efficacy of Burosumab in Pediatric Patients With X-Linked Hypophosphatemia: A Phase 3/4 Open-Label Trial

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Abstract

Objective: Burosumab, an anti-fibroblast growth factor 23 antibody, was recently approved for the treatment of X-linked hypophosphatemia (XLH).

We evaluated the safety and efficacy of burosumab in pediatric XLH patients.

Methods: This open-label, phase 3/4 trial of ≤ 124 weeks' duration was conducted at 4 Japanese medical centers. Fifteen children aged 1 to 12 years with XLH were included. All had previously been treated with phosphorus or vitamin D. Subcutaneous burosumab was administered every 2 weeks, starting with 0.8 mg/kg, and adjusted based on serum phosphorus levels and any safety concerns (maximum 2 mg/kg). Safety assessments included the frequency of treatment-emergent adverse events (TEAEs). Efficacy of burosumab on biochemical markers, clinical markers of rickets, motor function, and growth was also evaluated.

Results: The average treatment duration was 121.7 weeks. Frequently reported TEAEs were nasopharyngitis (46.7%), dental caries (40.0%), and influenza (33.3%). At baseline, patients had low serum phosphorus concentrations (2.6 ± 0.3 mg/dL) and low-to-normal 1,25-dihydroxyvitamin D concentrations (24.7 ± 12.7 pg/mL), which increased with burosumab treatment and were maintained during the study period. Alkaline phosphatase decreased continuously. At baseline, the mean ± SD total Thacher Rickets Severity Score (RSS) was 1.3 ± 1.2, and 4 patients (26.7%) had an RSS ≥ 2.0. Mean Radiographic Global Impression of Change and RSS tended to improve, particularly in patients with higher baseline RSS. There was a trend toward increased 6-minute walk test distance. No apparent changes in growth rate were observed.

Conclusion: Burosumab has a good safety profile and is effective in pediatric patients with XLH.

Key Words: X-linked hypophosphatemia, hypophosphatemia, rickets, burosumab, pediatric

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D (active vitamin D); 25(OH)D, 25-hydroxyvitamin D; 6MWT, 6-minute walk test; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; GFR, glomerular filtration rate; iFGF23, intact fibroblast growth factor 23; iPTH, intact parathyroid hormone; RGI-C, Radiographic Global Impression of Change; RSS, Thacher Rickets Severity Score; SC, subcutaneous(ly); TmP, tubular maximum reabsorption threshold of phosphate; TRP, tubular reabsorption of phosphate; XLH, X-linked hypophosphatemia.

Fibroblast growth factors (FGFs) are a superfamily of proteins involved in multiple biological processes [1]. FGF23 is predominantly produced by bone cells and has endocrine and paracrine effects; inappropriate increases in FGF23 result in a range of clinical disorders, including hypophosphatemia [1]. FGF23-associated disorders of phosphate wasting are caused by an excess of FGF23, which reduces serum phosphorus levels via decreased renal reabsorption of phosphorus and decreased absorption of phosphorus from the intestinal tract attributable to reduced 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) activity [2, 3]. As phosphate is critical in many biological processes, including musculoskeletal development, FGF23-dependent reductions in serum phosphorus levels lead to abnormal bone mineralization and poor muscle function [4]. The resulting musculoskeletal disorders comprise a group of related diseases, of which X-linked hypophosphatemia (XLH) is the most common [2, 3, 5]; the causative gene varies but clinical musculoskeletal characteristics of these diseases are similar, manifesting as rickets in children with open growth plates and osteomalacia in adolescents and adults [2, 4].

The incidence of XLH is estimated to be around 1 in 20 000 [6-8]; as an X-linked dominant disease, XLH affects more females than males (approximate ratio 2:1) [9]. The underlying cause of XLH is an inactivating mutation of the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) [10], and several hundred different mutations have been identified to date [11]. However, the exact mechanism by which the *PHEX* gene regulates FGF23 remains unclear [11]. Biochemical findings in patients with

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XLH include high serum FGF23 concentration, low serum phosphorus concentration, low or normal $1,25(OH)_2D$, low ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR), normal serum calcium, and high alkaline phosphatase (ALP) levels [12, 13]. These markers are important in distinguishing XLH from other disorders [14, 15], such as hereditary hypophosphatemic rickets with hypercalciuria [16] or Fanconi syndrome [17]. In childhood, the clinical signs of XLH manifest as rickets, with varus and valgus deformity of the knees, and growth disorders including short stature, a delay in the start of walking and walking disorders, and reduced quality of life [4, 18-20]. In adulthood, osteomalacia leads to bone pain, fractures, pseudo-fractures, joint pain, and muscle weakness. Additionally, ossification of the spinal ligaments can lead to complications of spine compression and pain [18, 21, 22].

Until recently, the only therapy for XLH aimed to supplement the phosphate lost in urine via administration of oral phosphate and active vitamin D preparations [2, 23]. Because serum phosphorus and serum calcium concentrations can fluctuate greatly during such treatments, side effects such as secondary or tertiary hyperparathyroidism and renal calcification may occur, requiring additional therapeutic management and the need for careful monitoring [2, 23]. Because of these side effects, it is difficult to normalize serum phosphorus levels using oral phosphate preparations. Moreover, medication compliance is often poor because of the need to administer multiple doses throughout the day and, as a result, the therapeutic effect is often limited [23, 24]. Additionally, the usefulness of these treatments is limited by their effect of further increasing FGF23 levels [25].

Burosumab (KRN23), a fully human monoclonal antibody targeted to inhibit excess FGF23 activity, has recently been approved in several countries for the treatment of XLH [26-29]. Burosumab is administered subcutaneously (SC), every 2 weeks (for children) or every 4 weeks (for adults), and has demonstrated efficacy with an acceptable safety profile in both pediatric and adult XLH cohorts [30, 31]. To date, data from 3 clinical trials in pediatric patients have been reported [32-34]. The results of these studies indicate that burosumab treatment improved the radiographic findings of rickets as well as demonstrating improvements in growth and physical functioning.

This open-label, phase 3/4 clinical trial in Japanese pediatric patients aged 1 to 12 years with XLH aimed to evaluate the safety and efficacy of burosumab over time. Although the age group of the trial population is similar to that of the recently published international phase 3 trial [34], the present trial enrolled patients with a wider range of Thacher Rickets Severity Scores (RSS) at baseline, which allowed the inclusion of patients with milder symptoms. This facilitated the exploration of burosumab's effects on a target population that more closely represents patients seen in clinical practice.

Methods

Study Design

This study commenced as a phase 3, multicenter, open-label, single-arm trial (Fig. 1) and was conducted at 4 medical centers in Japan and registered at ClinicalTrials.gov (NCT03233126). The study was initiated in July 2017 and continued until February 2020. During that time, burosumab was approved in Japan (September 2019) to treat FGF23-related hypophosphatemic rickets and osteomalacia (which includes XLH) and this study was continued as a phase 4, postmarketing study for up to 6 months from the date of obtaining marketing approval.

The study was conducted in accordance with the principles described in the Declaration of Helsinki, and all applicable local and national laws, including Japanese Good Clinical Practice guidelines and the Japanese Ministry of Health, Labour and Welfare ordinance on postmarketing studies. The study protocol and all related documentation were reviewed and approved by the Institutional Review Board at each investigative site.

Patients

The key inclusion criteria were children aged ≥ 1 and ≤ 12 years at the time of consent; male or female; open growth plate at screening; diagnosis of XLH and either an identified *PHEX* mutation (patient or immediate X-linked family member) or serum intact FGF23 (iFGF23) ≥ 30 pg/mL at screening; evidence of rickets; meeting laboratory test criteria for XLH; and ability to safely participate in and cooperatively complete study procedures. Intact FGF23 was measured using an enzyme-linked immunosorbent assay (KAINOS Laboratories, Inc., Tokyo, Japan). Evidence of rickets was defined, by the judgment of the investigator, as cupping, flaring, and fraying of the metaphyseal end or widening of the epiphyseal line by x-ray evaluation, and/or from clinical symptoms such as genu varum or genu valgum. Laboratory tests related to XLH included serum phosphorus level < 3.0 mg/dL, serum creatinine within the age-adjusted normal limits, and serum 25-hydroxyvitamin D (25[OH]D) ≥ 16 ng/mL. If 25(OH)D was below the normal range, supplementation was prescribed, and rescreening was allowed after treatment.

Key exclusion criteria included height > 50^{th} percentile (based on age-adjusted Japanese norms [35]) at screening; receipt of aluminum hydroxide antacids, systemic corticosteroids, acetazolamide, or thiazides within 7 days prior to screening, medication to suppress parathyroid hormone (eg, cinacalcet) within 60 days prior to screening, blood or blood products within 60 days prior to screening, a therapeutic monoclonal antibody other than burosumab within 90 days prior to screening, or growth hormone therapy within 12 months prior to screening; current or previous use of leuprorelin, triptorelin, goserelin, or other drugs known to delay puberty; serum calcium levels outside the age-adjusted normal limits, evidence of hyperparathyroidism (intact parathyroid hormone [iPTH] levels ≥ 163 pg/mL), or presence of Grade 4 nephrocalcinosis on renal ultrasound (ie, stone formation); planned orthopedic surgery during the study period; history of malignancy (within 5 years prior to registration), infection, or immunodeficiency; previous (within 4 months prior to screening) or planned use of any investigational product or investigational medical device; participation in previous burosumab trials; history of allergic or anaphylactic reactions to burosumab, its excipients, or any other monoclonal antibodies; or any other reason at the discretion of the investigator.

Written informed consent from a legally acceptable representative was obtained for each study participant, and assent from the patient (orally or in writing) was also obtained, if appropriate. Additional informed consent was required prior to participation in the extended treatment period up to the

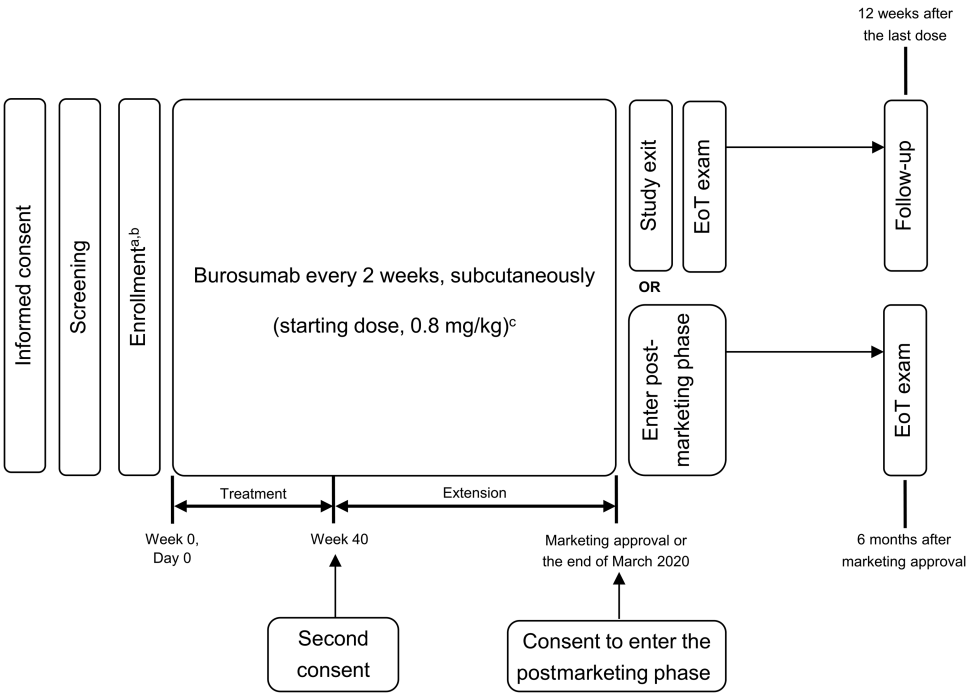


Figure 1. Study design. [a]Enrollment took place within 28 days of providing informed consent. If the inclusion criterion for 25(OH)D was not met, enrollment within 49 days was allowed in view of supplement administration and rescreening. [b]After eligibility was confirmed, oral phosphate and active vitamin D therapy were washed out for at least 7 days before the start of burosumab administration. However, washout could be started at the discretion of the investigator or sub-investigator before confirmation of all eligibility criteria. [c]Treatment was started within 7 days of enrollment. Abbreviation: EoT, end of treatment.

time of marketing approval and prior to participation in the postmarketing phase.

Treatment

Burosumab administration was initiated within 7 days after enrollment (Week 0) and was administered SC every 2 weeks, with an initial dose of 0.8 mg/kg. Subsequent doses could be adjusted up to 1.2 mg/kg at Week 6 if the following dose escalation criteria were met: serum phosphorus level remained below the lower limit of normal and the latest increase from baseline in serum phosphorus level available at the time of adjustment was ≤ 0.5 mg/dL.

The initial treatment period was 40 weeks, and patients could then continue burosumab injections during an extended treatment period until the date of marketing approval (Fig. 1). At Week 64, the dose was rounded to the nearest 10 mg, based on the most recent body weight measurement. If dose escalation criteria were met, the dose could be increased further, up to ~2 mg/kg, but not exceeding 90 mg.

The dose could be decreased by 0.2 mg/kg if there were any safety concerns, and then increased again if the dose escalation criteria were met. The dose could also be interrupted if the serum phosphorus level exceeded the upper limit of normal or if there were safety concerns. Treatment was to be resumed at half the previous dose. Dosage was based on previous clinical study data obtained from adult [36-39] and pediatric [32] patients with XLH and was in line with other recent clinical studies of burosumab in pediatric patients [33, 34].

Following marketing approval, patients could continue in the postmarketing phase of the study if it was necessary and appropriate; however, the next scheduled visit for each patient after market approval was converted to the end of treatment visit. During the postmarketing period, burosumab was administered at the approved dose and dosing regimen (0.8 mg/kg SC once every 2 weeks, adjusted according to the serum phosphorus concentration and symptoms; maximum dose 2 mg/kg) [9]. A follow-up examination was conducted in every patient 12 weeks after their final dose in the study to confirm safety outcomes after the completion of treatment.

Safety Outcomes

The primary study objective was to evaluate the safety of repeated doses of burosumab, administered SC every 2 weeks, in pediatric patients with XLH. Safety was assessed by measurement of the frequency of treatment-emergent adverse events (TEAEs; classified using the Medical Dictionary for Regulatory Activities [MedDRA], Japanese version 21.0) and by evaluating data obtained from laboratory tests (including calcium and iPTH levels), vital signs examinations, 12-lead electrocardiogram, renal ultrasound, and echocardiogram. All adverse events reported after the day of marketing approval were regarded as postmarketing events.

Efficacy Outcomes

Secondary objectives were to evaluate the effect of burosumab on biochemical markers, clinical markers of rickets, motor function, and growth in pediatric patients with XLH at each time point. Biochemical markers were changes from baseline in serum levels of phosphorus, $1,25(OH)_2D$, and ALP, and urinary levels of tubular reabsorption of phosphate (TRP) and TmP/GFR. Blood and urine samples were collected in the morning after a fast of ≥ 4 hours at Weeks 1, 2, 4, 8, 16, 24, and 32, and every 12 weeks thereafter. All tests were

Table 1. Patient baseline demographic and clinical characteristics (full analysis set and safety analysis set)

Parameter	N = 15	Normal range
Sex, *n* (%)		
Female	13 (86.7)	
Male	2 (13.3)	
Age (years)	6.7 ± 3.2	
<5	4 (26.7%)	
≥5	11 (73.3%)	
Weight, kg (Z-score)	20.9 ± 7.0 (−1.3 ± 1.0)	
Height, cm (Z-score)	113.8 ± 20.2 (−1.7 ± 0.9)	
Duration of conventional treatment (years)[a]	6.0 ± 3.4	
PHEX mutation positive, *n* (%)	13 (100.0)[b]	
Serum phosphorus (mg/dL)[c]	2.6 ± 0.3	3.6–6.2[d]
Calcium corrected (mg/dL)[c]	9.7 ± 0.2	8.7–10.6
1,25-dihydroxyvitamin D (pg/mL)	24.7 ± 12.7	20.0–70.0
25-hydroxyvitamin D (ng/mL)	27.1 ± 4.3	≥20.0
iPTH (pg/mL)	36.1 ± 11.1	10.0–65.0
eGFR (mL/min/1.73 m^2)[c]	114.6 ± 16.8	
1–1.5 y		83.3–132.6
1.5–16 y		83.5–156.7
iFGF23 (pg/mL)	182.6 ± 67.3	19.9–52.9
TmP/GFR (mg/dL)[c]	2.4 ± 0.5	
1–10 y		5.31 ± 0.4
10–15 y		4.52 ± 1.1
Alkaline phosphatase (U/L)[c,e]	1589.3 ± 366.9	395.0–1500.0[d]
RSS		
Total	1.3 ± 1.2	
Wrist	0.4 ± 0.5	
Knee	0.9 ± 0.7	
RSS ≥ 2, *n* (%)	4 (26.7)	

Data are mean ± SD unless otherwise specified.
[a]Duration of treatment according to standard of care, prior to trial participation.
[b]Only 13 patients were tested for *PHEX* mutations.
[c]Age-dependent normal range.
[d]Normative values of serum phosphorus [41, 42] and alkaline phosphatase [41-43] by age are available.
[e]Alkaline phosphatase was measured and changes were calculated using the methods of the Japan Society of Clinical Chemistry (JSCC) [43]. Values according to the International Federation of Clinical Chemistry and Laboratory Medicine measurement methods can be estimated as approximately 0.35 × the JSCC values.
Abbreviations: eGFR, estimated glomerular filtration rate; iFGF23, intact fibroblast growth factor 23; iPTH, intact parathyroid hormone; *PHEX*, phosphate-regulating gene with homologies to endopeptidases on the X chromosome; RSS, rickets severity score; TmP/GFR, ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate.

performed at a central laboratory (SRL Medisearch Inc., Tokyo, Japan; Toray Research Center, Inc., Tokyo, Japan). Improvement in rickets was assessed by the Radiographic Global Impression of Change (RGI-C) global score and changes from baseline in the total RSS. Changes from baseline in motor function were assessed using the 6-minute walk test (6MWT). Changes from baseline in growth were evaluated using the height Z-score using the LMS method (root parameter for Box-Cox transformation [L], median [M], and coefficient of variation [S]) [40].

Statistical Methods

The number of patients enrolled in the study was based on estimates of the number of pediatric patients with XLH in Japan [8] and the minimum number of study sites involved (4) and was set at more than 10 patients. The safety analysis set included all patients who received any dose of burosumab. The full analysis set included all patients from the safety analysis set who had any efficacy data recorded following the start of treatment.

Categorical data were summarized using frequency and percentage; continuous data were summarized using mean and SD. Patient sex was not considered a factor in the statistical analysis of the data. No statistical tests were performed for efficacy variables. The level of significance was not prespecified because no hypothesis testing was performed. However, for exploratory analysis, a 2-sided P value of < 0.05 was considered significant. Missing data were not imputed, and no adjustments were made for multiplicity. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

Of the 16 patients who provided consent for participation, 1 was found to be ineligible during screening. Fifteen patients

Table 2. Summary of TEAEs occurring in > 10% of patients (safety analysis set)

Parameter	*N* = 15	
	Any TEAE	Drug related
Patients with any TEAE	15 (100)	2 (13.3)
Patients with any serious TEAE	1 (6.7)	0
TEAE leading to death	0	0
TEAEs according to MedDRA preferred term		
Nasopharyngitis	7 (46.7)	0
Dental caries	6 (40.0)	0
Influenza	5 (33.3)	0
Otitis media	3 (20.0)	0
Pharyngitis	3 (20.0)	0
Upper respiratory tract infection	3 (20.0)	0
Diarrhea	2 (13.3)	1 (6.7)
Erythema infectiosum	2 (13.3)	0

Data are *n* (%).
Abbreviations: MedDRA, medical dictionary for regulatory activities; TEAE, treatment-emergent adverse event.

were enrolled, received treatment, and were included in the safety and full analysis sets. Administration of burosumab continued for an average of 121.7 weeks. One patient discontinued during the postmarketing phase (due to inconvenience) and 14 patients completed the study.

Patient demographic and other baseline characteristics are shown in Table 1. The majority of patients were female (13/15; 86.7%). The mean ± SD age was 6.7 ± 3.2 years, with 4/15 patients (26.7%) aged 1 to 4 years and 11/15 (73.3%) aged 5 to 12 years. At baseline, patients had low serum phosphorus concentrations (2.6 ± 0.3 mg/dL), low-to-normal $1,25(OH)_2D$ concentrations (24.7 ± 12.7 pg/mL), high iFGF23 concentrations (182.6 ± 67.3 pg/mL), and low TmP/GFR (2.4 ± 0.5 mg/dL). The mean ± SD total RSS was 1.3 ± 1.2, and 4 patients (26.7%) had an RSS ≥ 2.0. The mean ± SD height was 113.8 ± 20.2 cm and the height Z-score was −1.7 ± 0.9. All patients had a history of treatment with phosphorus or vitamin D preparations, with 13/15 using both concomitantly and 2/15 having received vitamin D only. Doses ranged from 0.3 to 3.0 g/day for phosphorus and 0.15 to 4.0 µg/day for vitamin D. At baseline, the mean ± SD duration of conventional therapy was 6.0 ± 3.4 years.

During the treatment period, 4 patients met the criteria for dose escalation. Of these, 3 had an RSS of ≥ 2.0 at baseline.

Safety

All 15 patients reported at least 1 TEAE during the study (Table 2). The most frequently reported TEAEs (in > 2 patients) were nasopharyngitis (7/15; 46.7%), dental caries (6/15; 40.0%), influenza (5/15; 33.3%), otitis media (3/15; 20.0%), pharyngitis (3/15; 20.0%), and upper respiratory tract infection (3/15; 20.0%). Around half of patients (8/15) had the first onset of a TEAE within the first 11 weeks of the study, and there were no unexpected or noteworthy late-onset TEAEs.

Six TEAEs (all of which occurred in 2 patients) were thought to be drug related, in the opinion of the investigator. These were diarrhea, dizziness, headache, injection site pruritus, and nausea in 1 patient, and reduced blood

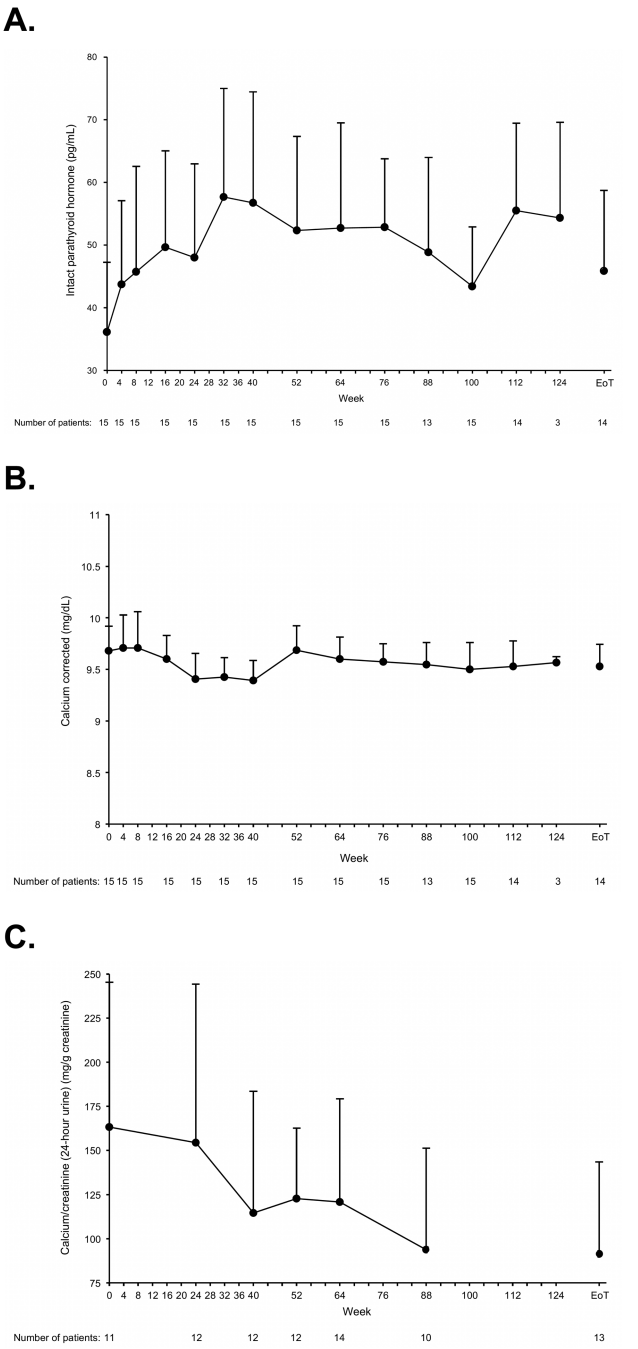


Figure 2. Mean + SD changes in laboratory parameters (safety analysis set). **A**, Intact parathyroid hormone. **B**, Calcium corrected. **C**, Calcium/creatinine (24-hour urine). Abbreviation: EoT, end of treatment.

25-hydroxycholecalciferol in the second patient. There was 1 serious TEAE (Grade 3 tonsillitis), but this was not thought by the investigator to be drug related. There were no TEAEs leading to death during the study.

There were no notable changes in laboratory test results, vital signs examinations, 12-lead electrocardiogram, renal ultrasound, or echocardiogram. No clinically meaningful changes were observed in iPTH, serum calcium, or calcium/creatinine (24-hour urine) (Fig. 2A-2C) and no hyperphosphatemia-related events occurred. Of note, there were no abnormal findings in the 4 patients who underwent burosumab dose escalation.

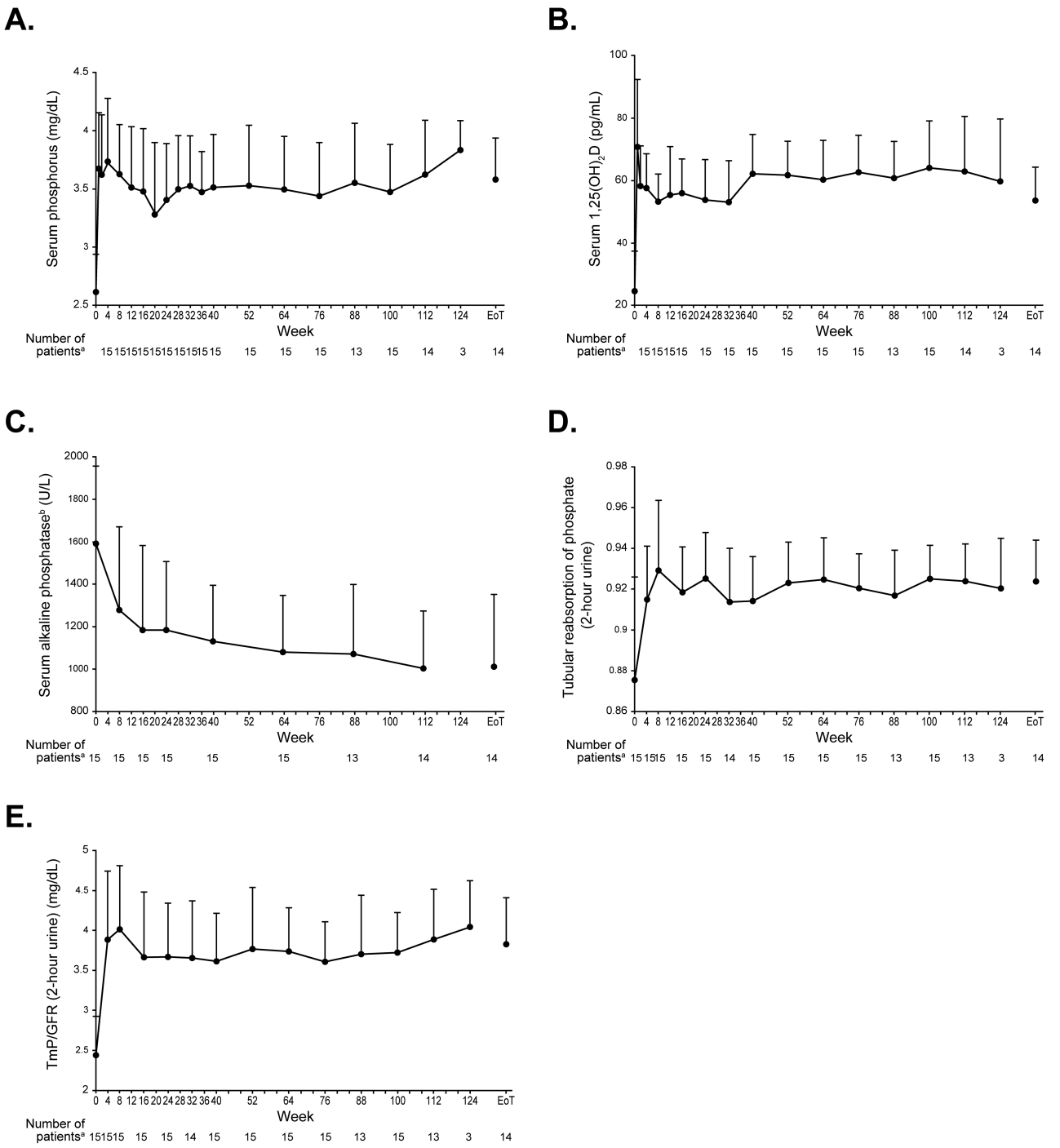
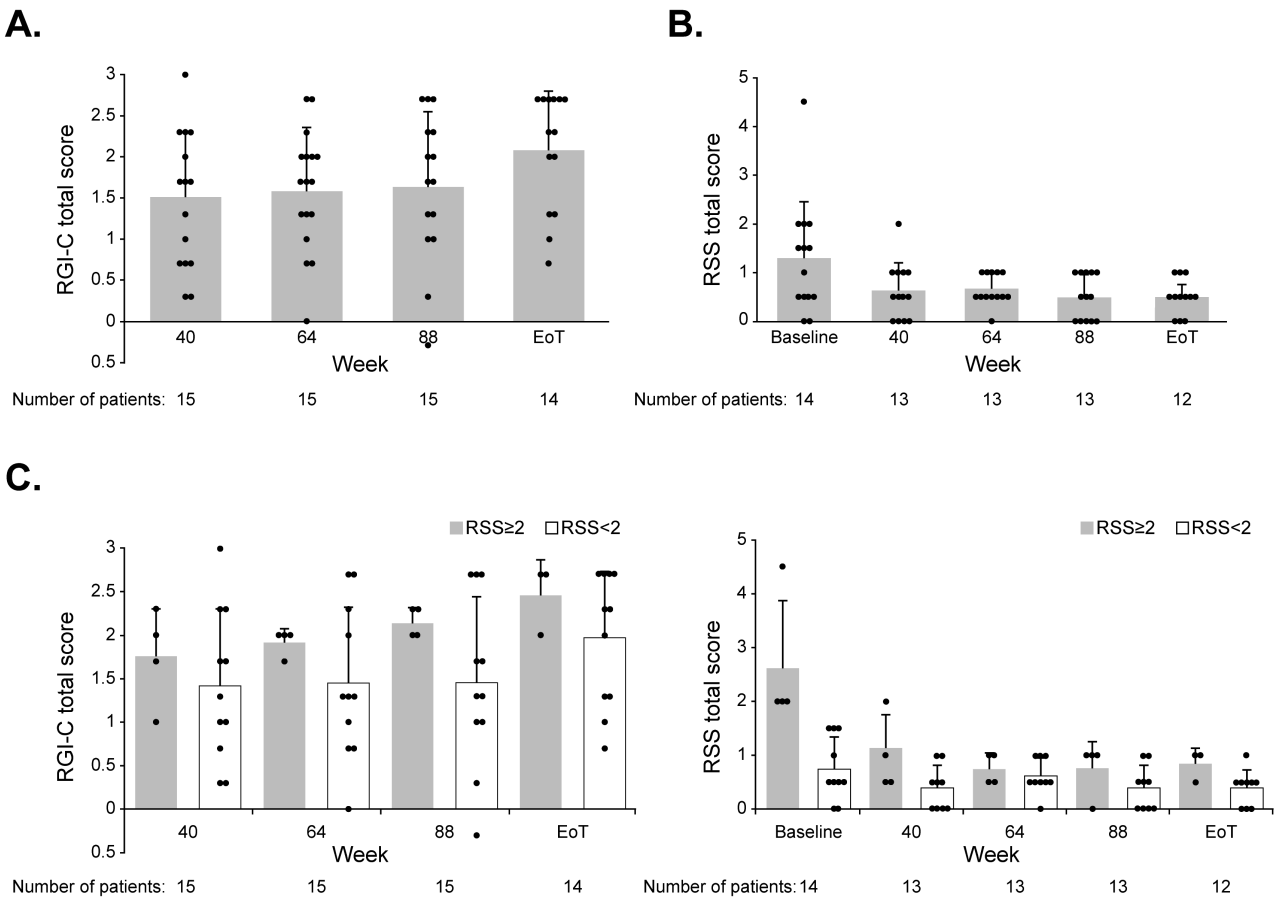


Figure 3. Mean + SD changes in biomarkers from baseline (full analysis set). **A**, Serum phosphorus. **B**, Serum 1,25(OH)$_2$D. **C**, Serum alkaline phosphatase. **D**, Urinary tubular reabsorption of phosphate. **E**, Urinary TmP/GFR. [a]15 for Weeks 0, 1, and 2. [b]Alkaline phosphatase was measured and changes were calculated using the methods of the Japan Society of Clinical Chemistry (JSCC) [43]. Values according to the International Federation of Clinical Chemistry and Laboratory Medicine measurement methods can be estimated as approximately 0.35 × the JSCC values. Normative values of alkaline phosphatase by age are available [41-43]. Abbreviations: 1,25(OH)$_2$D, 1,25 dihydroxyvitamin D; EoT, end of treatment; TmP/GFR, ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate.

Efficacy Outcomes

Biomarker data are shown in Fig. 3. Serum phosphorus concentration was increased from baseline at the earliest time point evaluated. This elevation was maintained during the study period (Fig. 3A). A similar trend was observed for 1,25(OH)$_2$D (Fig. 3B). ALP decreased continuously from the start of burosumab treatment (Fig. 3C). Both TRP and TmP/GFR increased until Week 8 and remained constant thereafter (Fig. 3D and Fig. 3E).

The mean RGI-C total score at Week 40 was 1.5 ± 0.8. Symptoms in the study population continued to improve over the course of the study, with mean RGI-C scores of 1.7 ± 0.9



	Baseline	Week 40	Week 64	Week 88	EoT
RSS	2	0.5	0.5	0	0.5
RGI-C	-	2.3	2	2.3	2.7

Figure 4. Mean + SD changes in clinical signs of rickets (full analysis set). **A**, RGI-C total score. An increase indicates an improvement in rickets. **B**, RSS total score. A decrease indicates an improvement in rickets. **C**, Improvement in RGI-C score (left) and RSS (right) according to baseline disease severity. **D**, Radiographs showing improvement in rickets with corresponding RGI-C score and RSS in a 7-year-old girl treated with burosumab. Abbreviations: EoT, end of treatment; RGI-C, Radiographic Global Impression of Change; RSS, Thacher Rickets Severity Score.

at Week 88 and 2.1 ± 0.7 at the end of treatment (Fig. 4A). The RSS also decreased, suggesting an improvement in rickets symptoms (Fig. 4B). Notably, the degree of improvement according to increased RGI-C scores and decreased RSS was greater in patients with higher RSS (indicating more severe symptoms) at baseline (RSS ≥ 2.0; Fig. 4C). Improvement in RSS was also seen in patients with RSS < 2.0 (milder symptoms) at baseline. Radiographs showing improvement in

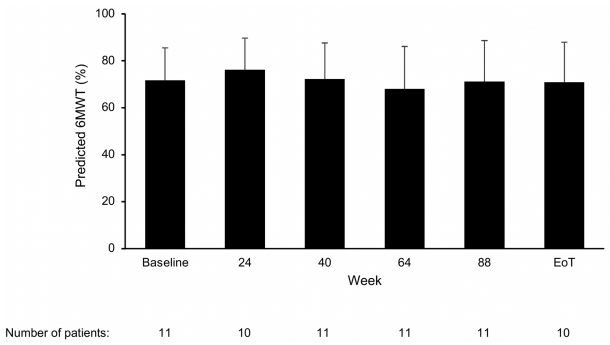


Figure 5. Summary of percentage of predicted 6MWT (meters walked) at each time point (full analysis set). Abbreviations: 6MWT, six-minute walk test; EoT, end of treatment.

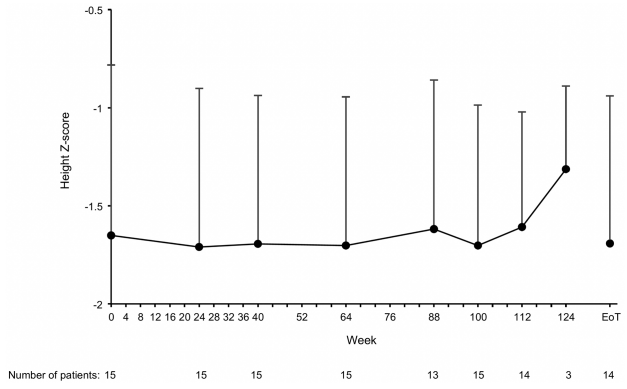


Figure 6. Mean + SD changes in height Z-score over time (full analysis set). Abbreviation: EoT, end of treatment.

rickets with corresponding RGI-C scores and RSS in a 7-year-old girl treated with burosumab are shown in Fig. 4D.

At baseline, the mean 6MWT distance was 425.0 ± 81.3 m. After the start of burosumab treatment, the 6MWT distance increased to 461.1 ± 58.2 m at Week 24 and was also increased at Week 40 (437.6 ± 77.3 m), Week 88 (444.1 ± 96.6 m), and the end of treatment (453.1 ± 97.3 m), but not at Week 64, when it decreased to 419.5 ± 102.8 m. The percentages of predicted 6MWT were 71.7% ± 13.9%, 76.2% ± 13.5%, 72.2% ± 15.4%, 68.0% ± 18.1%, 71.2% ± 17.4%, and 70.9% ± 17.0% at baseline, Week 24, Week 40, Week 64, Week 88, and the end of treatment, respectively (Fig. 5).

No apparent changes in growth rate, according to height Z-scores, were observed during the study (Fig. 6).

Discussion

This was a clinical study of burosumab in a population of Japanese pediatric patients aged 1 to 12 years with XLH. Compared with a previous phase 3 study [34], the study inclusion criteria allowed for the enrollment of patients with milder symptoms at baseline, making this study more generalizable to the wider clinical population. The duration of treatment with burosumab in this single-country trial is one of the longest reported to date in a pediatric population. No new safety concerns were reported, and the efficacy data were consistent with previous studies in pediatric XLH patients [32-34], providing further confirmation that the benefits of burosumab are relevant for different ethnic populations.

Many of the baseline clinical characteristics of patients in this study were broadly similar to those reported in previous pediatric studies of burosumab [32-34]. These similarities may be attributable to the broad inclusion criteria, allowing for the enrollment of children with a wide range of symptoms at baseline; serum phosphorus values were slightly higher than those reported in previous phase 2 and 3 trials, and the mean RSS was lower. The dose of burosumab was increased in several patients, particularly in those who had higher RSS at baseline, a trend that warrants further examination in future studies.

There were no new safety concerns during the study, and no differences in safety outcomes were observed in patients who received a dose increase. Although there were individual changes in levels of serum calcium and iPTH, no distinct or clinically relevant trends were reported.

Improvements in phosphorus homeostasis and rickets scores were consistent with previously published pediatric data [34]. These improvements were observed in all patients, regardless of baseline RSS, and the degree of improvement was greater in patients with higher baseline RSS. However, these data also demonstrated improvements in patients with lower baseline RSS whose rickets symptoms were not fully resolved despite treatment with conventional therapy and who had not previously been evaluated under trial conditions. This finding suggests that burosumab may represent a suitable treatment option for this patient population. Although the degree of improvement in RGI-C scores and RSS in the overall population was slightly weaker than in the previous trial [34], this is likely due to the inclusion of patients with lower baseline RSS who had less scope for improvement. We suggest that early treatment of all patients across the XLH clinical spectrum is key to improving the physical and laboratory symptoms of XLH by ameliorating the effects of excess FGF23 and normalizing musculoskeletal development from early childhood.

In this study, we observed a trend toward increased 6MWT, which is consistent with a previous international phase 3 study [34]. The 6MWT was included in our study as a surrogate marker for the evaluation of muscle strength; however, it must be noted that this measure is not specific for XLH or for muscle. Patients with XLH have a range of complex, interconnecting symptoms that can affect motor function, and a specific tool dedicated to measuring muscle strength in XLH would be a valuable addition for future clinical analyses.

In a previous international phase 3 study, height Z-score significantly ($P < 0.05$) improved following burosumab treatment in patients with XLH [34]. In the present study, a trend toward increased height Z-score was observed at Week 124; however, patients that completed the Week 124 visit ($n = 3$) had higher height Z-scores at the beginning of the study. Studies with longer observational periods and larger sample sizes may provide higher sensitivity to detect height improvements.

Overall, the results from this trial confirm that burosumab is an effective treatment with an acceptable safety profile for pediatric patients with XLH across the disease severity spectrum. Limitations of the study were predominantly related to the design; this was a single-arm, open-label study with no comparative control group. In addition, because of the small size of the target population, only 15 patients were enrolled in

this single-nation study to receive burosumab, compared with 61 patients included in the multi-country phase 3 study [34]. However, in Japan, around 50 babies are born with XLH per year [8]; thus, we can estimate that the potential Japanese target population aged between 1 and 12 years consists of approximately 600 patients, in which case the 15 children included in our study would comprise around 2.5% of the total XLH population. Therefore, we consider that the patients in our study are representative of the pediatric XLH population and that the results are likely to be generalizable to other patients with this disorder.

In conclusion, the results of this phase 3/4, multicenter, open-label study confirm the safety and efficacy of burosumab for up to 124 weeks when administered every 2 weeks to pediatric patients with XLH.

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Author Contributions

Study design: K.O., Y.S., M.Ka., and H.K.; study conduct: N.N., T.K., K.M., and H.T.; data analysis: M.Ko. and S.O.; drafting manuscript: N.N. and M.Ka.; reviewing manuscript content: K.O., Y.S., H.K., T.K., K.M., and H.T. Approving final version of manuscript: All authors. All authors accept responsibility for the integrity of the data analysis.

Disclosures

N.N., T.K., Y.S., and K.O. have received consulting fees from Kyowa Kirin Co., Ltd.

M.Ka., MKo., S.O., and H.K. are employed by Kyowa Kirin Co., Ltd, Tokyo, Japan.

K.M. and H.T. have nothing to declare.

Clinical Trial Information

ClinicalTrials.gov registration no. NCT03233126.

Data Availability

Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. On request, the corresponding author will detail the restrictions and any conditions under which access to some data may be provided.

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