

**A Randomized, Open-label Phase 2 Study of  
Burosumab (KRN23), an Investigational  
Fully Human Anti-FGF23 Monoclonal  
Antibody, in Children with X-linked  
Hypophosphatemia (XLH)**

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# Disclosures

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- Dr. Padidela has received consulting fees from Ultragenyx Pharmaceuticals Inc. and Alexion Pharmaceuticals Inc.
- Drs. Högler, Imel, Boot, Linglart, van't Hoff, and Portale: travel and/or consulting fees from Ultragenyx Pharmaceuticals Inc.
- Drs. Mao, Skrinar, and San Martin: employees of Ultragenyx Pharmaceuticals Inc.
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- Dr. Carpenter: grant support, travel fees, and consulting fees from Ultragenyx Pharmaceuticals Inc.
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# XLH Causes Rickets, Skeletal Deformity, and Impaired Growth in Children

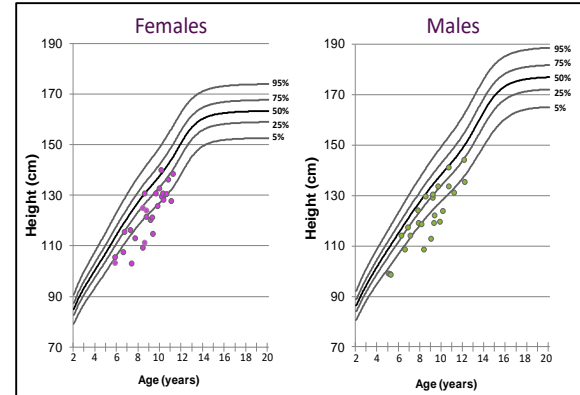
## Rickets



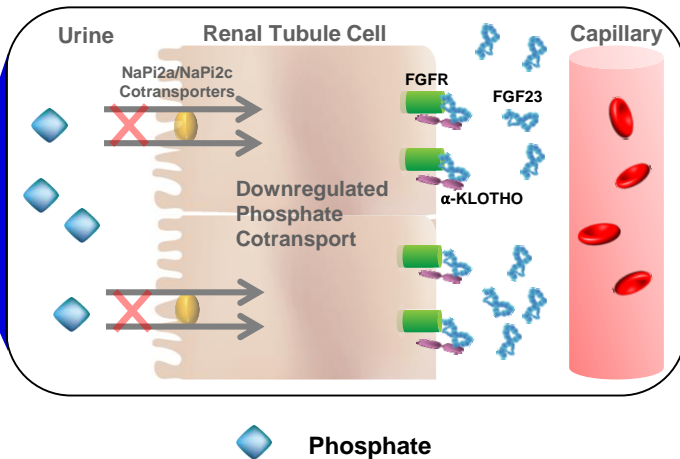
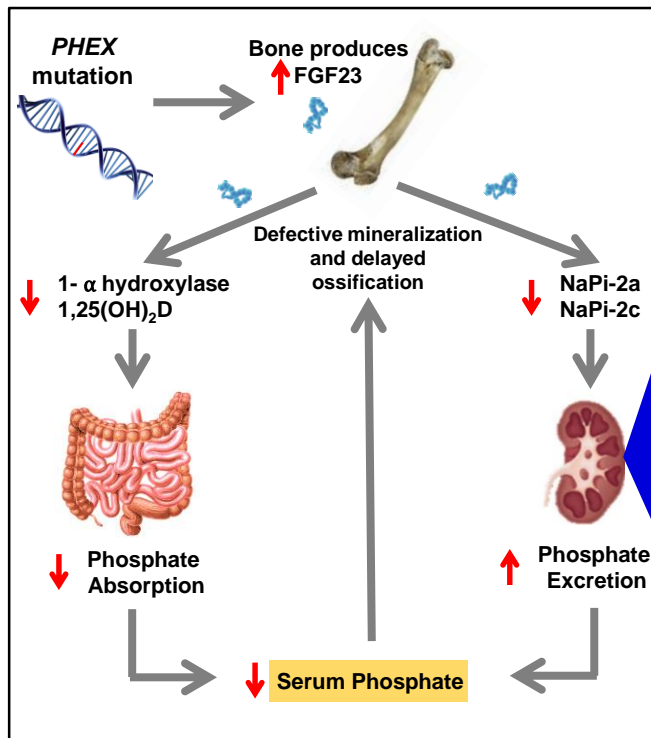
## Bowing of Lower Limbs



## Impairment of Growth

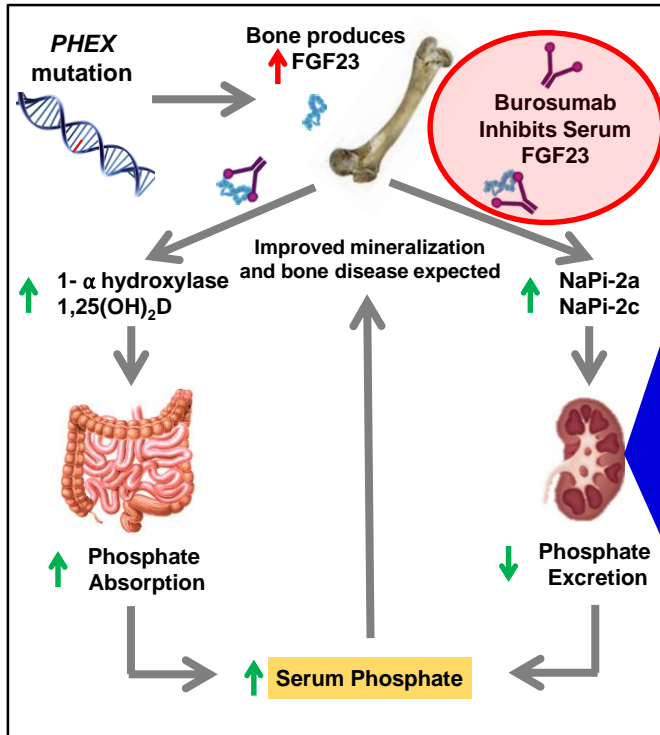


# Excess FGF23 in XLH Pathophysiology

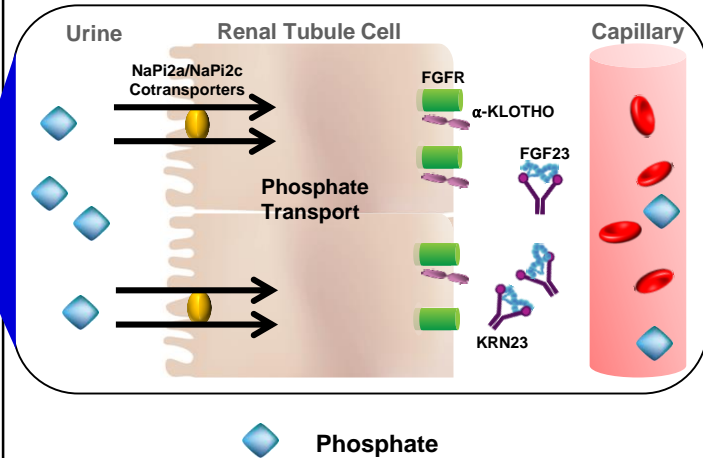


Razaque MS. Nat Rev Endocrinol 2009;5:611-9. Martin A, et al. Physiol Rev 2012;92:131-55.

# Burosumab (KRN23), a Monoclonal Antibody, Inhibits Serum FGF23



Proposed Mechanism of Action of Burosumab, an Investigational Product

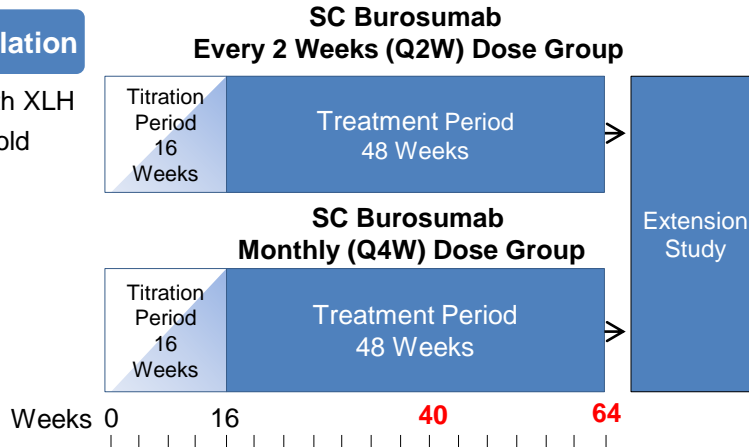


# Pediatric Phase 2 Study Design (Burosumab-CL201)

## Study Design

### Study Population

- Children with XLH
- 5-12 years old
- N = 52
- Tanner  $\leq 2$



- Primary analysis: Week 40 (N = 52)
- Extended analysis: Week 64 (N = 52)
- Pre-specified subgroups based on baseline total rickets severity score  $\geq$  or  $<$  1.5
- Initial doses were 0.1, 0.2, or 0.3 mg/kg Q2W or 0.2, 0.4 or 0.6 mg/kg Q4W

## Key Endpoints

- **Pharmacodynamics:** serum phosphorus, TRP, TmP/GFR, and ALP
- **Rickets:** graded by two scoring systems (RGI-C and RSS)
- **Growth velocity**
- **Walking ability:** 6MWT
- **Patient-reported Outcome:** POSNA-PODCI
- **Safety**

# Two Rickets Scoring Systems

## Thacher Rickets Severity Score (RSS)

- Total 0-10: wrist (0-4) plus knee (0-6)
- Read centrally by an expert blinded to dose and patient



Score 1.0

Score 2.0

**Knee X-ray**

## Radiographic Global Impression of Change (RGI-C)

- 7-point scale describing *changes* at wrist, knee, and leg during treatment
- X-rays read by 3 independent experts blinded to dose

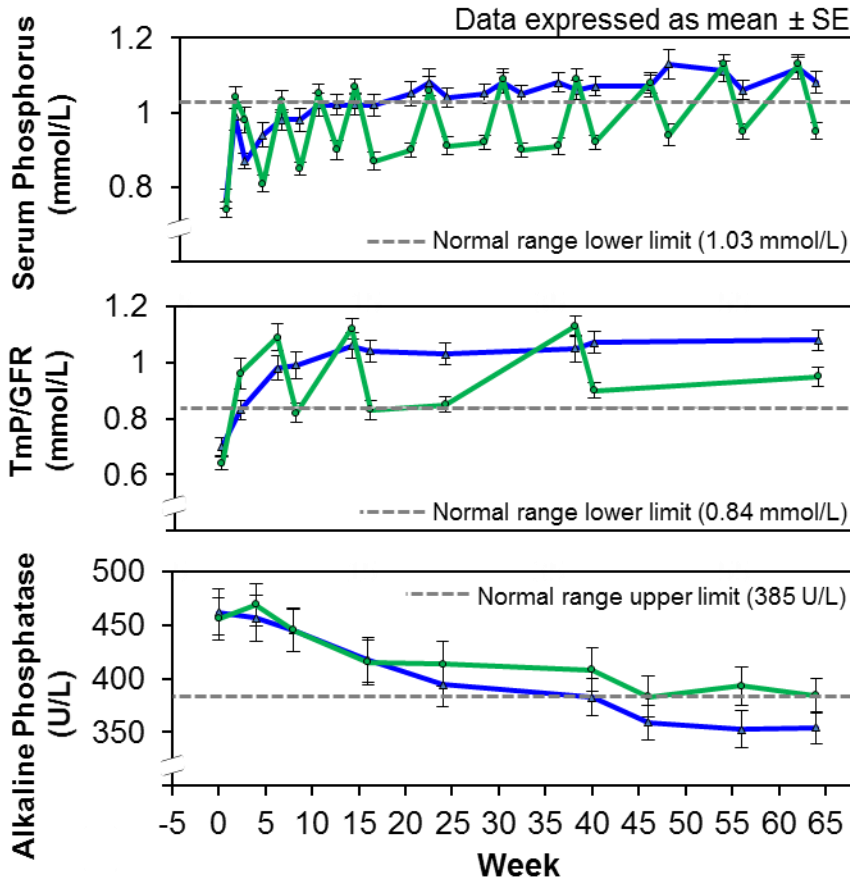
-3	-2	-1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

# Baseline Characteristics

Patient Characteristic	Burosumab Q2W (n = 26)	Burosumab Q4W (n = 26)	Burosumab Overall (N = 52)
<b>Age, y, mean (SD)</b>	8.7 (1.72)	8.3 (2.04)	8.5 (1.87)
<b>Male, n (%)</b>	12 (46.2)	12 (46.2)	24 (46.2)
<b>White, n (%)</b>	23 (88.5)	23 (88.5)	46 (88.5)
<b>Weight, kg, median (min, max)</b>	33.05 (17.6, 48.4)	26.15 (14.7, 55.2)	30.50 (14.7, 55.2)
<b>Height Z score, mean (SD)</b>	-1.72 (1.03)	-2.05 (0.96)	-1.89 (1.00)
<b>RSS total score, mean (SD) (min, max)</b>	1.92 (1.17) (0.0, 4.5)	1.67 (1.00) (0.0, 3.0)	1.80 (1.09) (0.0, 4.5)
<b>Received prior oral P / active vitamin D, n (%)</b>	24 (92.3)	26 (100)	50 (96.2)
<b>Duration of prior oral P / active vitamin D, y, mean</b>	7.02	6.7	6.86



# Improvement in Serum Phosphorus, TmP/GFR, and Alkaline Phosphatase



- Mean burosumab doses (SD) at Week 64:

Q2W:

- 1.1 (0.5) mg/kg
- 38.9 (21.9) mg/dose

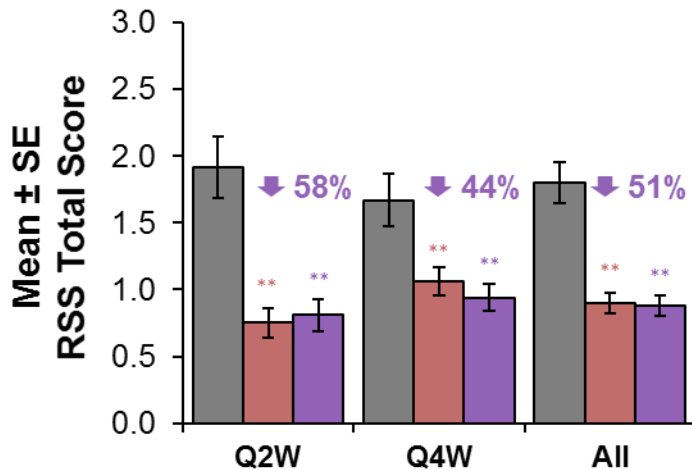
Q4W:

- 1.0 (0.3) mg/kg
- 32.3 (15.5) mg/dose

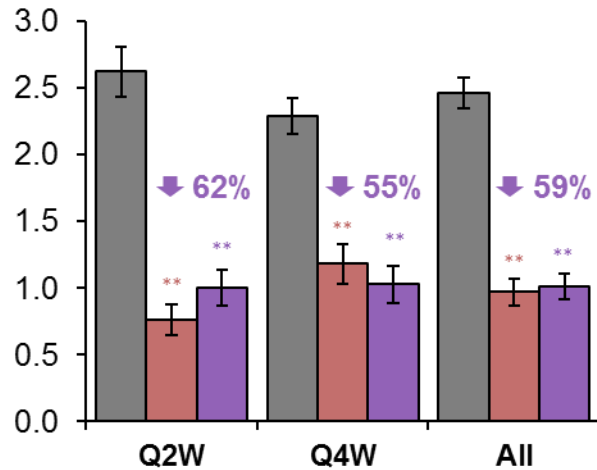
- All treatment values were significant compared with baseline
- No hyperphosphatemia in any patient

# Rickets Severity Score (RSS)

All Patients (N = 52)



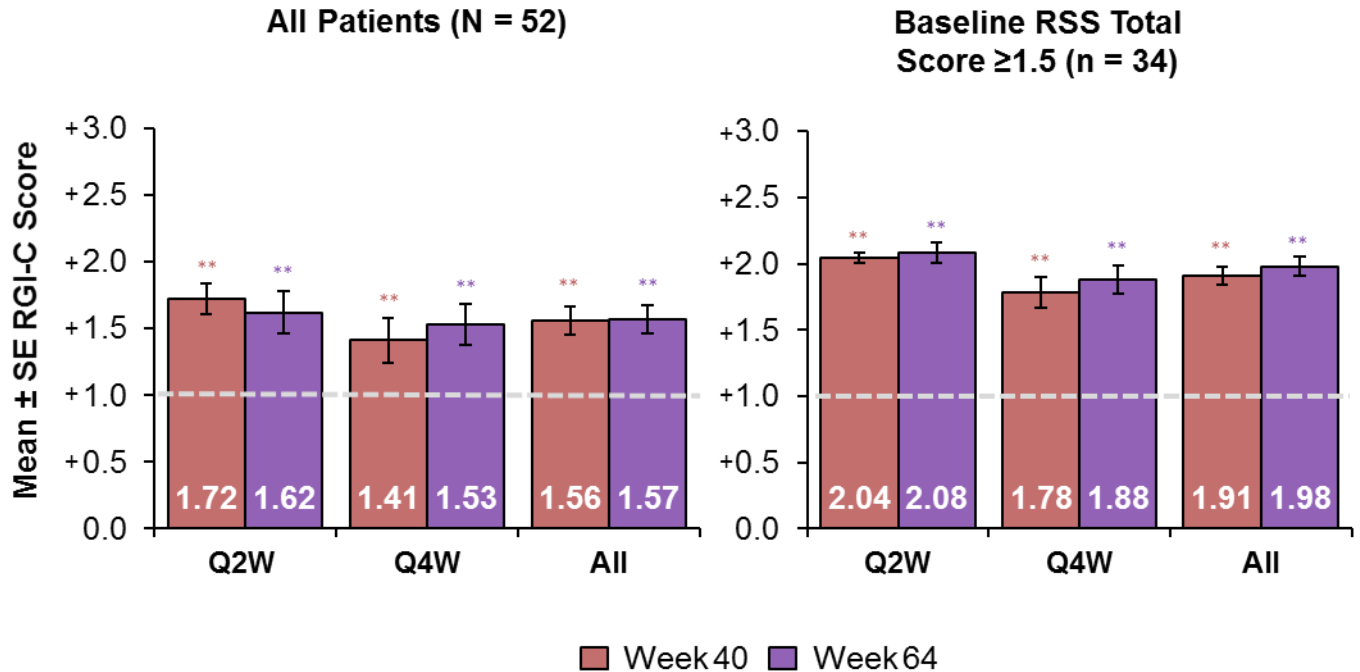
Baseline RSS Total Score  $\geq 1.5$  (n = 34)



■ Baseline ■ Week 40 ■ Week 64

\*\*  $p < 0.001$  based on the Generalized Estimation Equation for the Week 64 subset

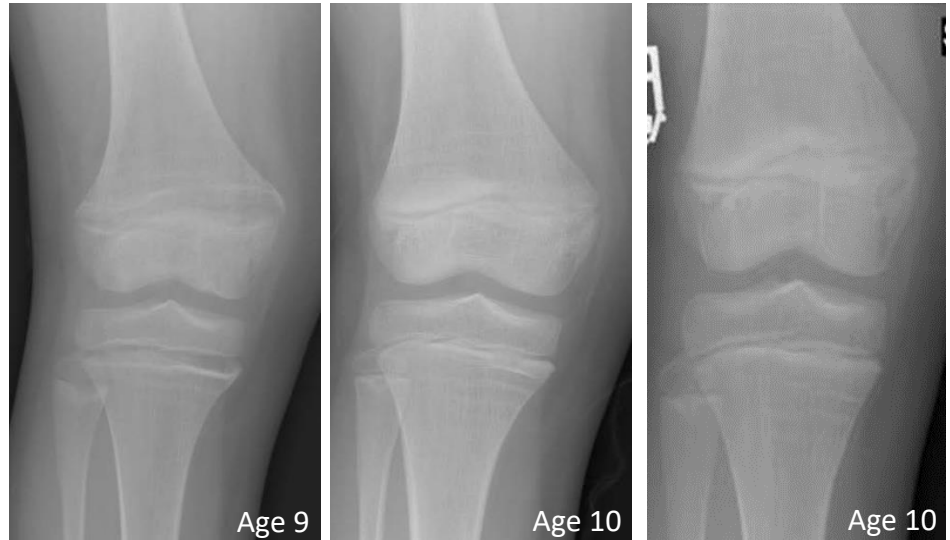
# Radiographic Global Impression of Change (RGI-C)



\*\* p < 0.0001 based on the Generalized Estimation Equation for the Week 64 subset;  
RGI-C Scores: +1.0 = minimal healing; +2.0 = substantial healing; +3.0 = complete or near complete healing

# Radiographic Appearance of Rickets at Baseline and Follow-up

Knee radiographs in ~10-year-old girl with XLH during burosumab therapy demonstrate improved rachitic findings at the growth plate



**Baseline**

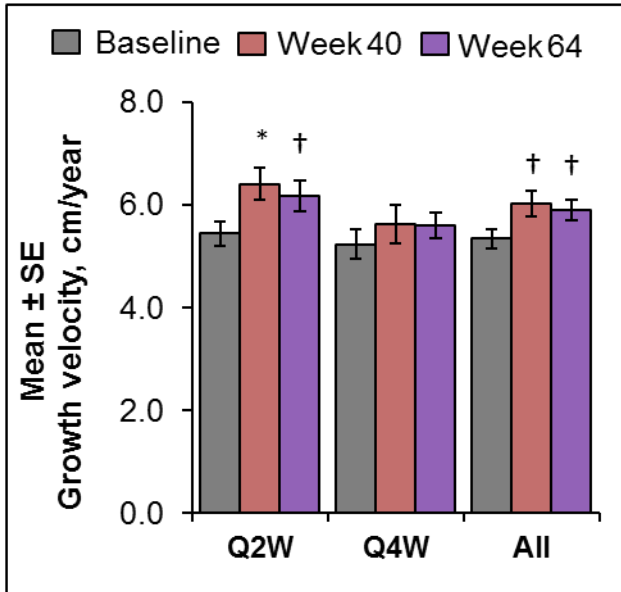
**40 weeks**

**64 weeks**

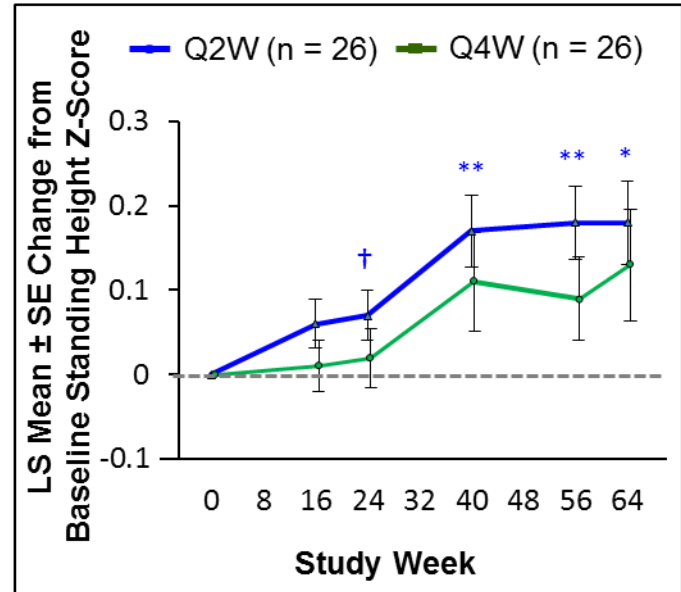
<b>RSS Knee Score</b>	<b>2.0</b>	<b>0.0</b>	<b>0.0</b>
<b>RGI-C Global Score</b>		<b>+2.3</b>	<b>+2.3</b>

# Growth Velocity and Standing Height Z-score Change From Baseline

All Patients (N = 52)



All Patients (N = 52)



\*\*  $p \leq 0.001$ ; \*  $p \leq 0.01$ ; †  $p \leq 0.05$  compared with baseline based on one sample  $t$  test

# Summary of Safety Measures

Patient Incidence, n (%)	Burosumab Q2W (n = 26)	Burosumab Q4W (n = 26)	Burosumab Overall (N = 52)
Any adverse events (AEs)	26 (100)	26 (100)	52 (100)
Pain in extremity	9 (35)	12 (46)	21 (40)
Vitamin D Deficiency	0	3 (12)	3 (6)
Arthralgia	7 (27)	10 (39)	17 (33)
Myalgia	3 (12)	4 (15)	7 (14)
Any treatment-emergent injection site reaction adverse event	17 (65)	13 (50)	30 (58)
Injection site reaction	9 (35)	10 (39)	19 (37)
Injection site erythema	7 (27)	5 (19)	12 (23)
Injection site swelling	5 (19)	1 (4)	6 (12)
Injection site rash	2 (8)	2 (8)	4 (8)
Serious AEs	0	1 (3.8)	1 (1.9)
AEs leading to discontinuation	0	0	0
AEs leading to death	0	0	0

# Summary and Conclusions

- Children with XLH treated with burosumab for up to 64 weeks:
  - Improvement in serum phosphorus, TmP/GFR, and ALP levels
  - Rickets improved significantly despite previous conventional treatment for a mean of ~7 years
- Improvements in rickets scores were greater in patients with more severe baseline rickets, with the greatest improvements in patients receiving Q2W dosing
  - At week 64, 77% of all patients with a baseline RSS of  $\geq 1.5$  had substantial healing of rickets (RGI-C  $\geq +2$ )
- Burosumab improved growth
- Adverse events were predominantly mild to moderate
- No clinically meaningful changes were observed in serum PTH, serum or urine calcium, or renal ultrasounds. Hyperphosphatemia was not observed
- Inhibition of FGF23 by burosumab improved clinical outcomes in children with XLH

# Appendix

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