

# **Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody for X-linked Hypophosphatemia (XLH): Final 64-Week Results of a Randomized, Open-label, Phase 2 Study of 52 Children**

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# Disclosures

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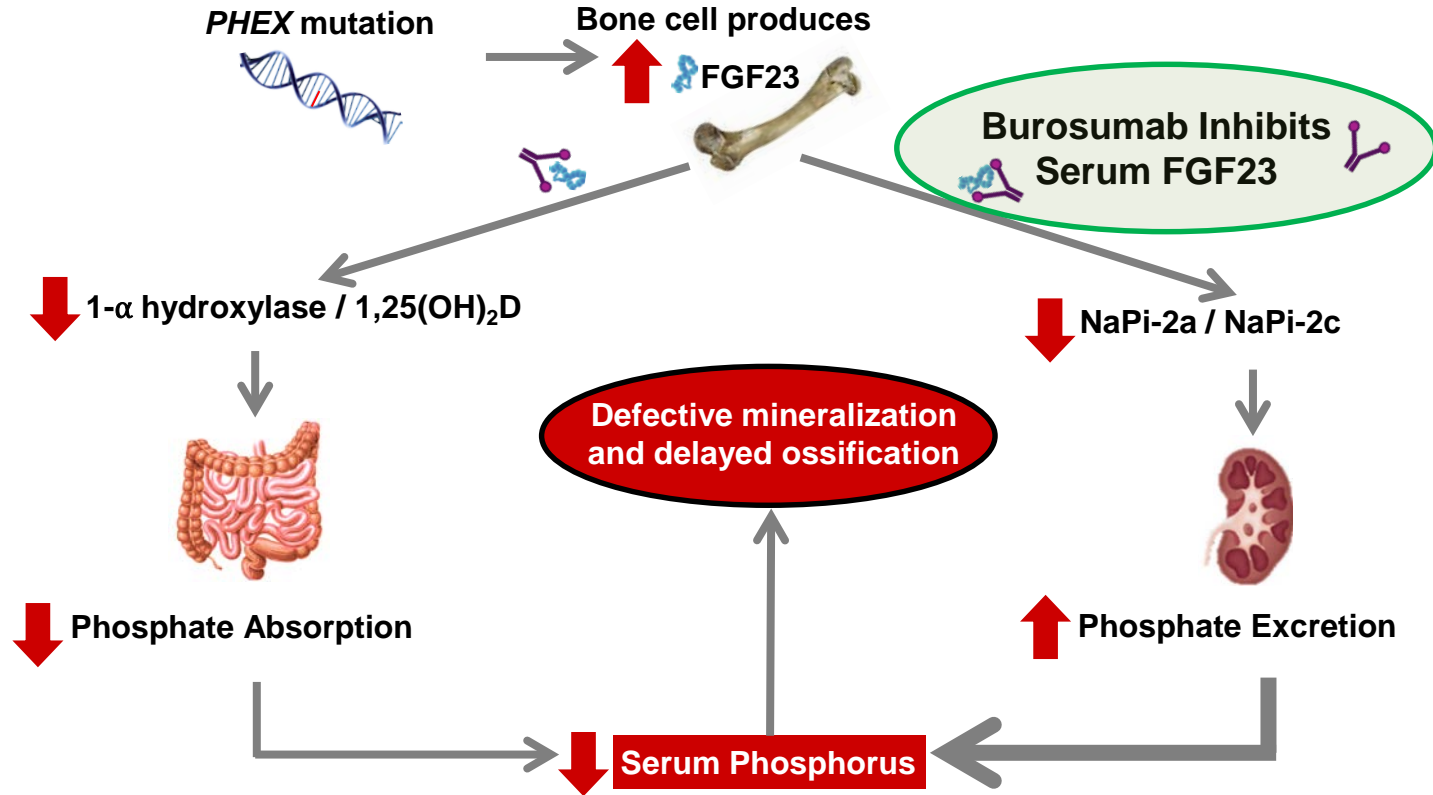
- Dr. Whyte: research grant support, honoraria, and travel from Ultragenyx, Alexion Pharmaceutical Inc, and Merck Inc
- Drs. Carpenter, Imel, Boot, Högler, Linglart, van't Hoff, and Portale: research support, travel, and/or consulting fees from Ultragenyx Pharmaceutical Inc.
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- Drs. Kakkis, Mao, Skrinar, and San Martin: employees of Ultragenyx Pharmaceutical Inc.
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# X-Linked Hypophosphatemia (XLH)

- Most prevalent genetic rickets/osteomalacia (~1:25,000)
- Affects all ethnicities
- 1937: Fuller Albright et al, “Vitamin D Resistant Rickets”
- 1958: X-linked inheritance identified
- 1972: Key pathogenic factors:
  - Renal phosphate wasting
  - Inappropriately normal/low circulating 1,25-dihydroxyvitamin D
- 1980: Rx: Phosphate and Calcitriol Supplementation
- 1995: Loss-of-function mutations in *PHEX*
- 2002: ↑ Phosphaturic factor FGF23



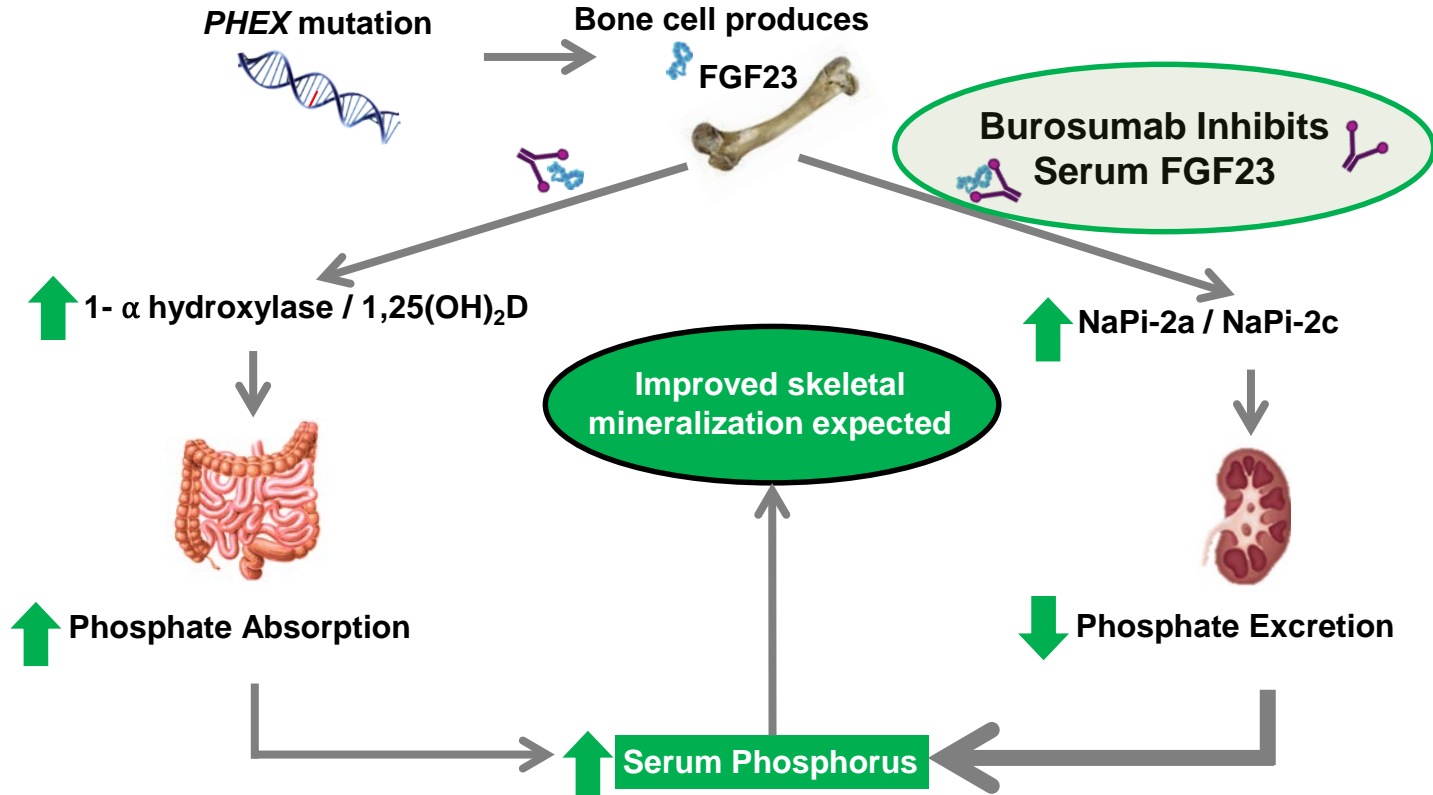
# Excess FGF23 in XLH Pathophysiology



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

FGF23, Fibroblast growth factor 23; NAPI, sodium/phosphate cotransporter; PHEX, Phosphate Regulating Endopeptidase Homolog, X-Linked.

# Excess FGF23 in XLH Pathophysiology



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# Objectives

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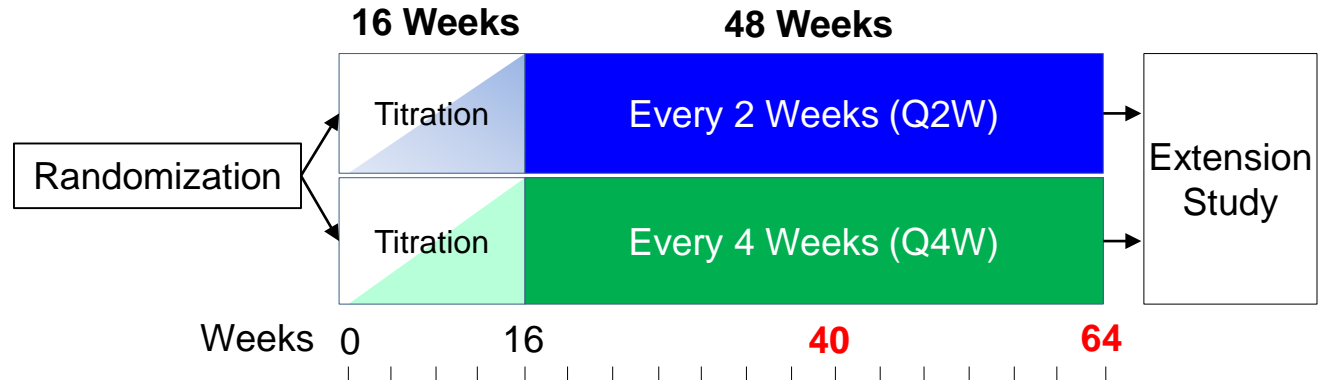
For Children with XLH:

- Identify a dose/dosing regimen for burosumab based on safety and pharmacodynamic (PD) effects
- Assess the clinical effects of burosumab on:
  - 1) Rickets, growth, and leg deformities
  - 2) Patient reported outcomes including pain, disability, and quality-of-life
- Safety

# Study Design

## Study Population

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



# Key Endpoints

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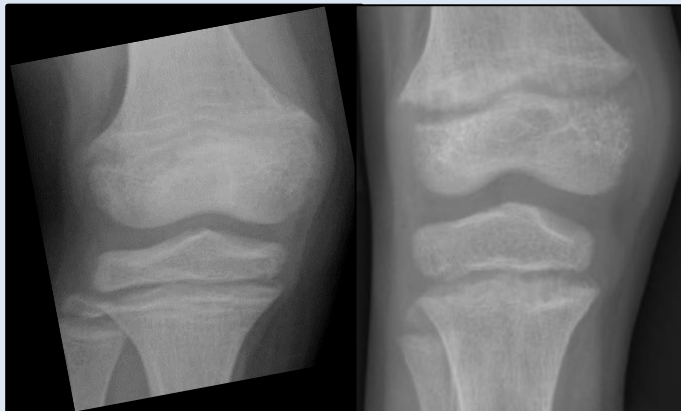
- **Primary:** Rickets Severity Scales
  - RSS, Thacher Rickets Severity Score
  - RGI-C, Radiographic Global Impression of Change
- **Secondary:**
  - Serum phosphorus
  - TmP/GFR, Maximum rate of tubular phosphate reabsorption to the GFR
  - ALP, Alkaline phosphatase
  - Growth: Standing height z-score
  - 6MWT, 6-minute walk test
  - Patient-reported Outcome, POSNA-PODCI Scale
  - Safety



## Two Rickets Scoring Systems

### Thacher Rickets Severity Score (RSS)

- Range: 0–10 (10 worst)
- Total 10: wrist (0-4) and knee (0-6)
- X-rays read by 1 expert blinded to dose and patient



Score 1.0

Score 2.0

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

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

← Worsening
Improving →

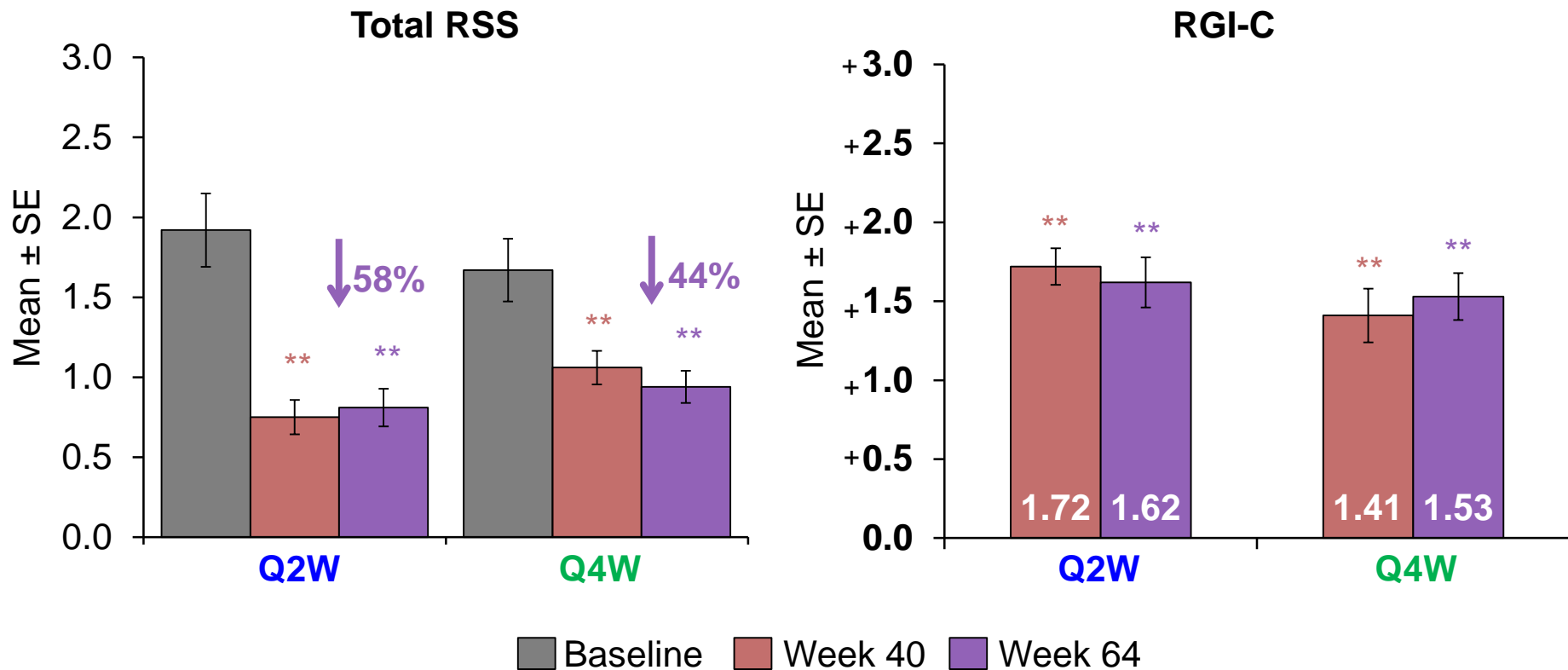
-3	-2	-1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

# Results:

## Baseline Characteristics

Patient Characteristic	Burosumab Q2W (n = 26)	Burosumab Q4W (n = 26)	Burosumab Combined (N = 52)
Age, y, mean (SD)	8.7 (1.7)	8.3 (2.0)	8.5 (1.9)
Male, n (%)	12 (46.2)	12 (46.2)	24 (46.2)
White, n (%)	23 (88.5)	23 (88.5)	46 (88.5)
Weight, kg, median (min, max)	33.1 (17.6, 48.4)	26.2 (14.7, 55.2)	30.5 (14.7, 55.2)
Height Z score, mean (SD)	-1.72 (1.03)	-2.05 (0.96)	-1.89 (1.00)
RSS total score, mean (SD) (min, max)	1.9 (1.2) (0.0, 4.5)	1.8 (1.0) (0.0, 3.0)	1.8 (1.09) (0.0, 4.5)
Received prior oral P / active vitamin D, n (%)	24 (92.3)	26 (100)	50 (96.2)
Duration of prior oral P / active vitamin D, y, mean	7.0	6.7	6.9
Q2W, every 2 weeks; Q4W, every 4 weeks; P, phosphate; RSS, Thacher Rickets Severity Score; SD, standard deviation			

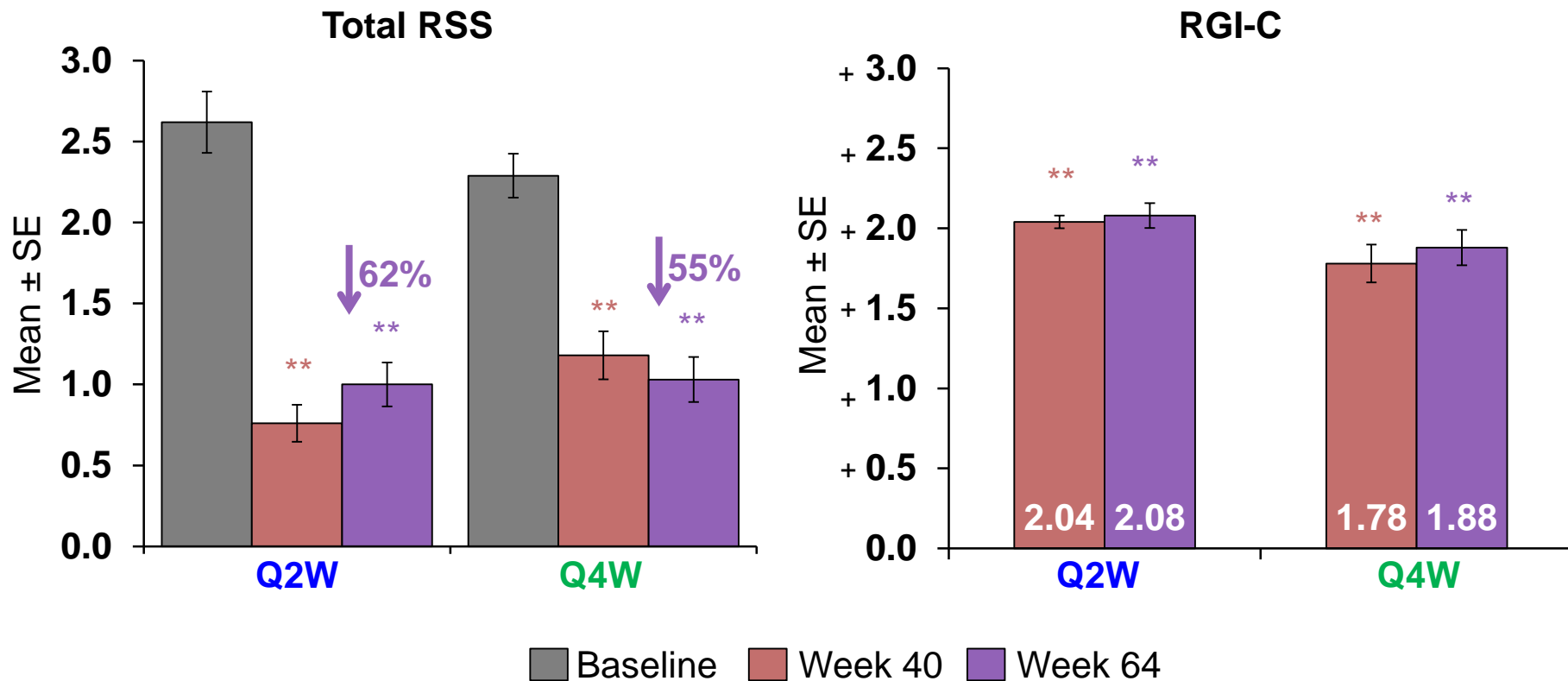
# RSS and RGI-C for All 52 Patients



\*\*p ≤ 0.0001 based on the Generalized Estimation Equation (GEE) model for the Week 64 subset.

RGI-C Scores: +1.0 = minimal healing; +2.0 = substantial healing; +3.0 = complete or near complete healing

# RSS and RGI-C in the 34 Patients with High Rickets Severity at Baseline (RSS $\geq 1.5$ )



\*\*p  $\leq 0.0001$  based on the Generalized Estimation Equation (GEE) model for the Week 64 subset.

RGI-C Scores: +1.0 = minimal healing; +2.0 = substantial healing; +3.0 = complete or near complete healing

# Change in Rickets During Burosumab Treatment

Improved rickets  
in a girl with XLH



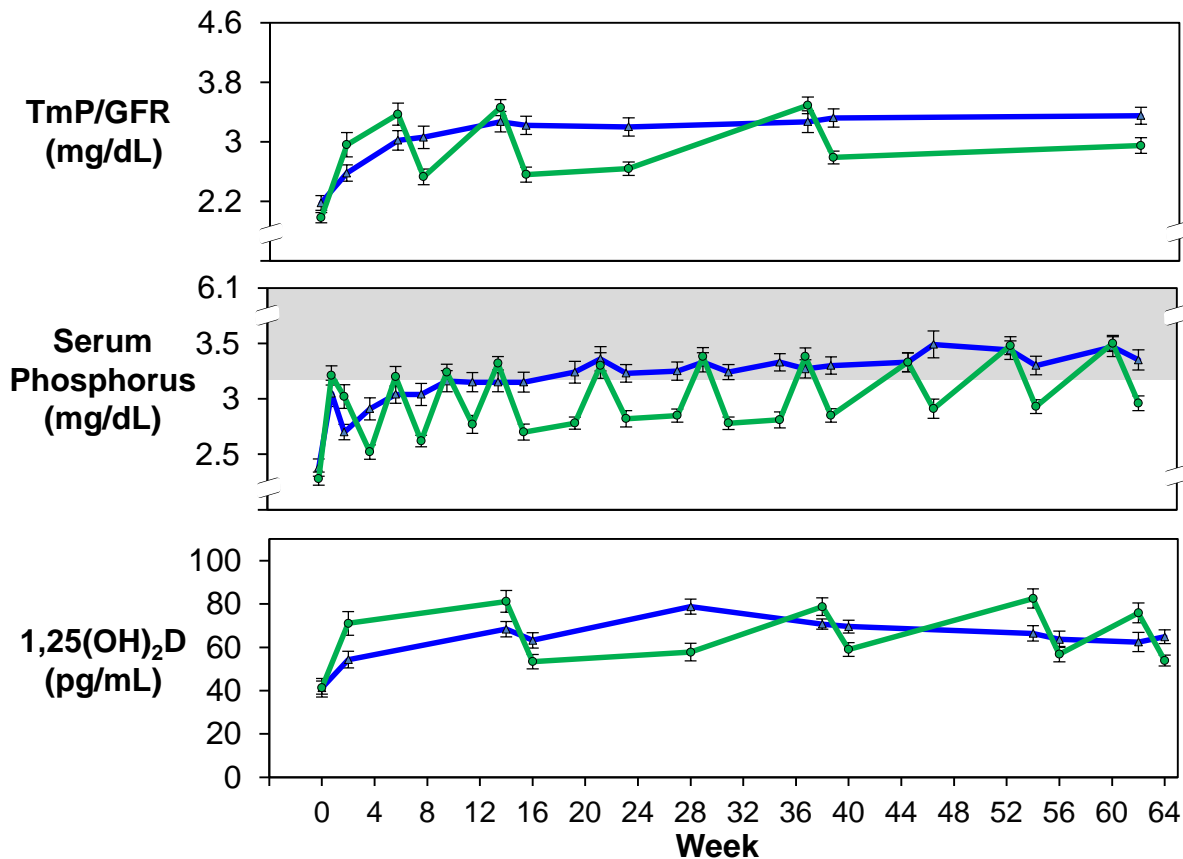
**Baseline**

**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>

# TmP/GFR, Serum Phosphorus, and Serum 1,25(OH)<sub>2</sub>D

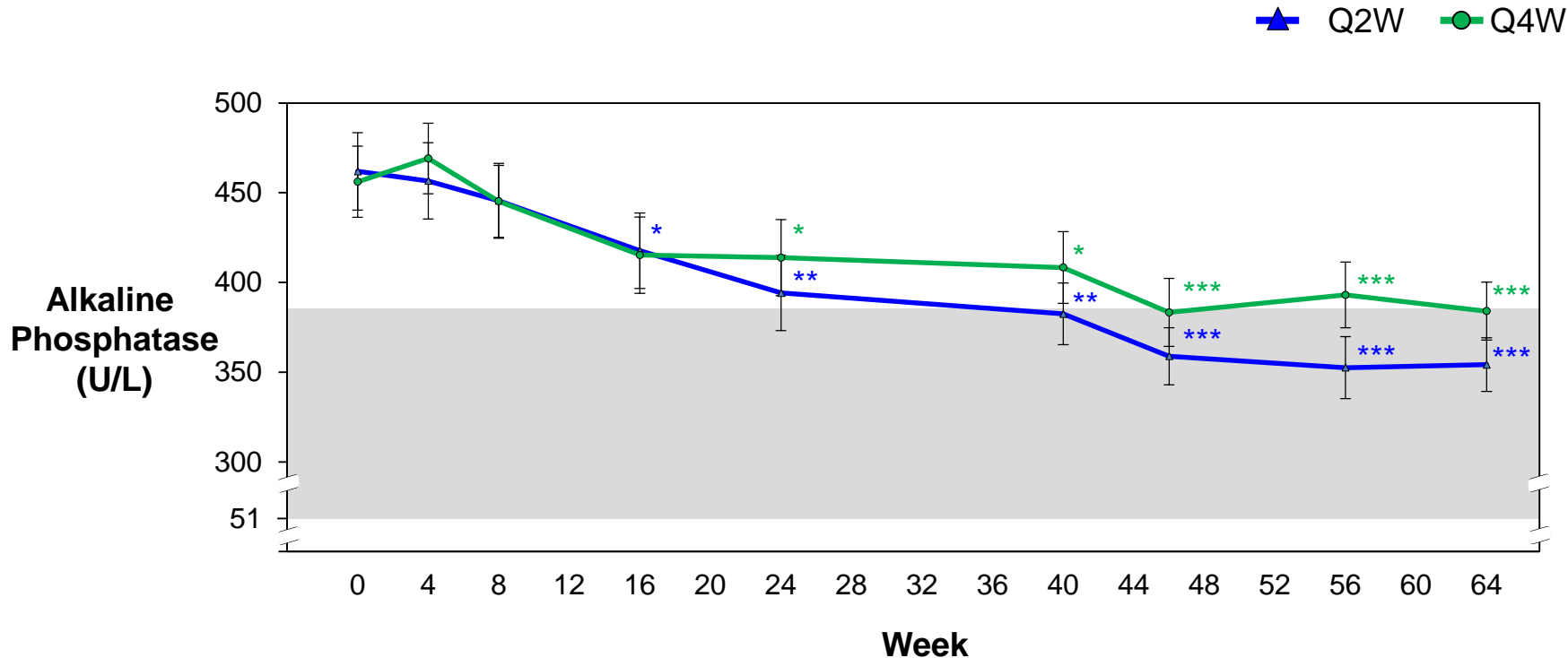


▲ Q2W ● Q4W

- All treatment values significantly improved (t-test)
- No hyperphosphatemia in any patient

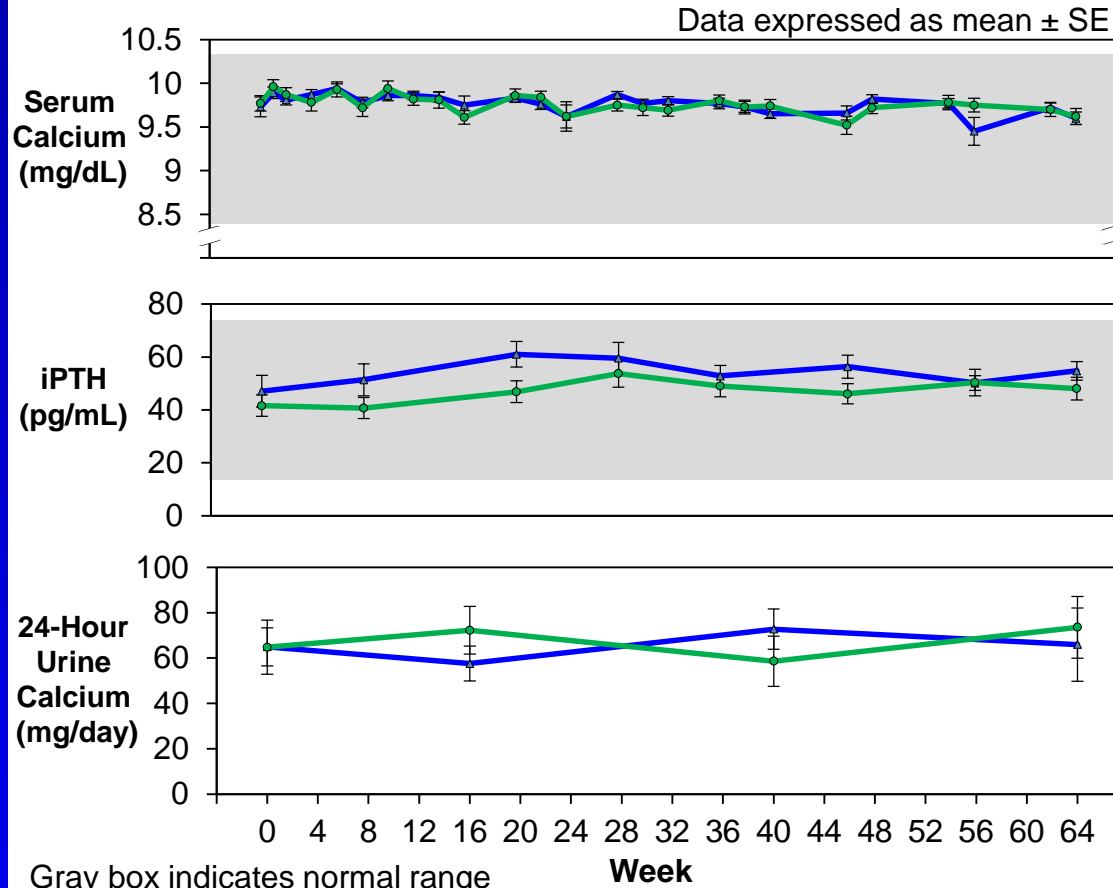
Mean ± SE. Gray box indicates normal range.

# Serum Alkaline Phosphatase



Mean  $\pm$  SE; Gray box indicates normal range. \*\*\* $p \leq 0.0001$  \*\* $p \leq 0.001$ ; \* $p \leq 0.01$ ; versus baseline (p-values are presented as nominal p-values, no adjustment on multiplicity)

# Serum Calcium, iPTH, and Urine Calcium



▲ Q2W ● Q4W

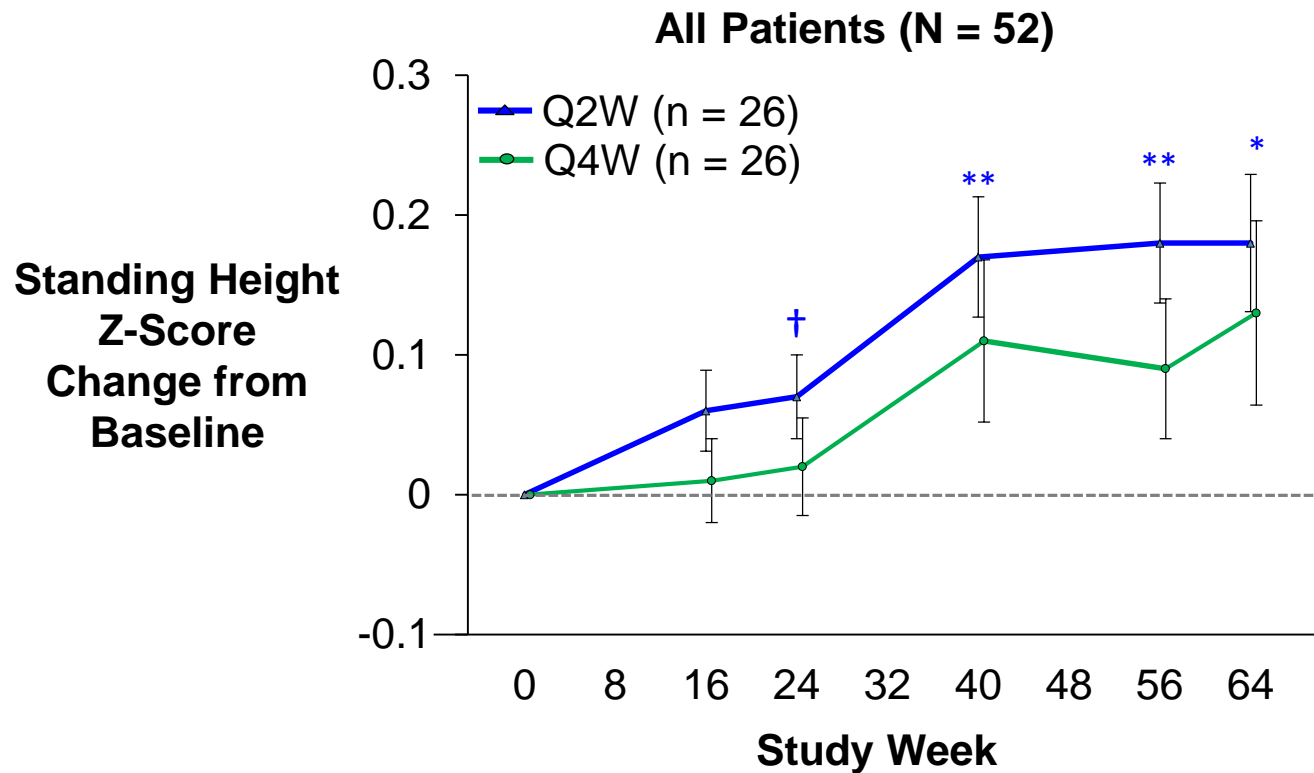
- For renal ultrasound scores (0 [normal] to 4 [stone formation]), no subject had a change >1 point

Change from Baseline to Week 64 in Nephrocalcinosis Score	Number of Subjects (n = 50)
No Change	21 Q2W; 21 Q4W
Decreased: 1→0	1 Q2W; 1 Q4W
Increased: 0→1, 1→2, or 2→3	3 Q2W; 3 Q4W

- Renal function remained normal
- No evidence of ectopic mineralization of the myocardium



# Standing Height Z-Score



Data expressed as least squares mean  $\pm$  SE. \*\* $p \leq 0.001$ ; \* $p \leq 0.01$ ; † $p \leq 0.05$  versus baseline (GEE model; p-values are presented as nominal p-values, no adjustment on multiplicity)

# 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

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- In children with XLH, 64 weeks of burosumab treatment:
  - Improved serum phosphorus and TmP/GFR
  - Improved rickets despite previous conventional treatment for a mean of ~7 years
    - Normalized serum ALP
    - Especially in patients with more severe baseline rickets, and for the patients receiving Q2W dosing
- Adverse events were predominantly mild to moderate and expected for a pediatric population
- No clinically concerning changes were observed in serum PTH, serum or urine calcium, or renal ultrasonography. No Hyperphosphatemia

**With its favorable benefit:risk profile, burosumab holds promise for improvement in the long term outcomes for these boys and girls**

# Thank you

We thank all clinical investigators,  
study site personnel, and the patients  
and their families