Randomized, Open-label, Dose-finding, Phase 2 Study of KRN23, a Human Monoclonal Anti-FGF23 Antibody, in Children with X-linked Hypophosphatemia (XLH)

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Disclosures

- Dr. Carpenter: grant support and travel fees from Ultragenyx Pharmaceuticals Inc. (Ultragenyx)
- Drs. Imel, Boot, Linglart, Högler, van't Hoff, and Portale: travel and/or consulting fees from Ultragenyx. Dr. Padidela has received consulting fees from Ultragenyx and Alexion Pharmaceuticals Inc.
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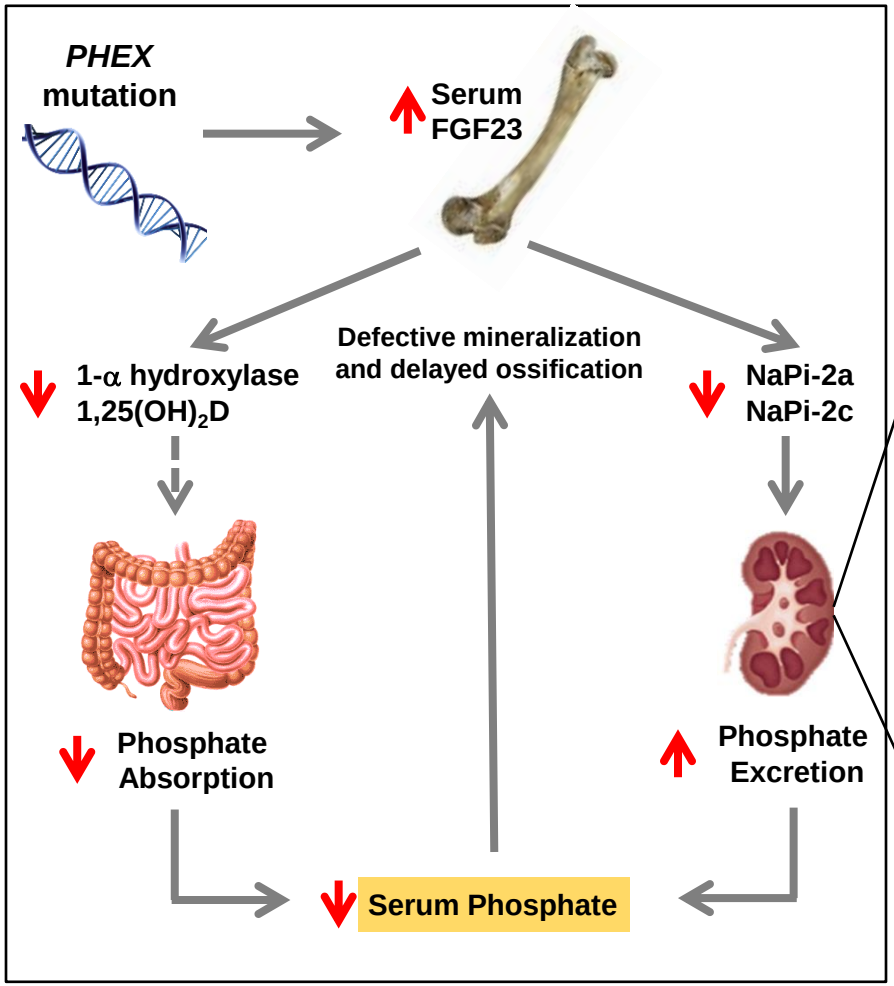
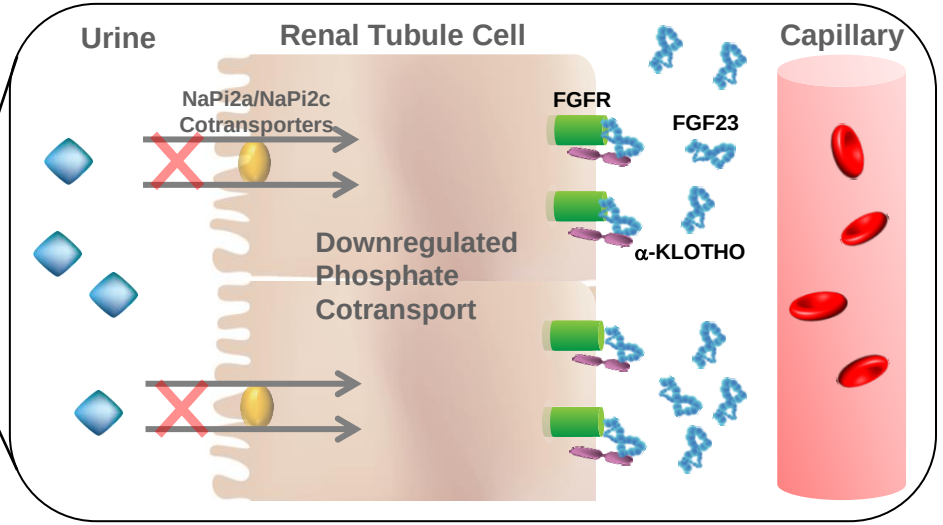
Excess FGF23 in XLH Leads to Phosphate Wasting and Chronic Hypophosphatemia

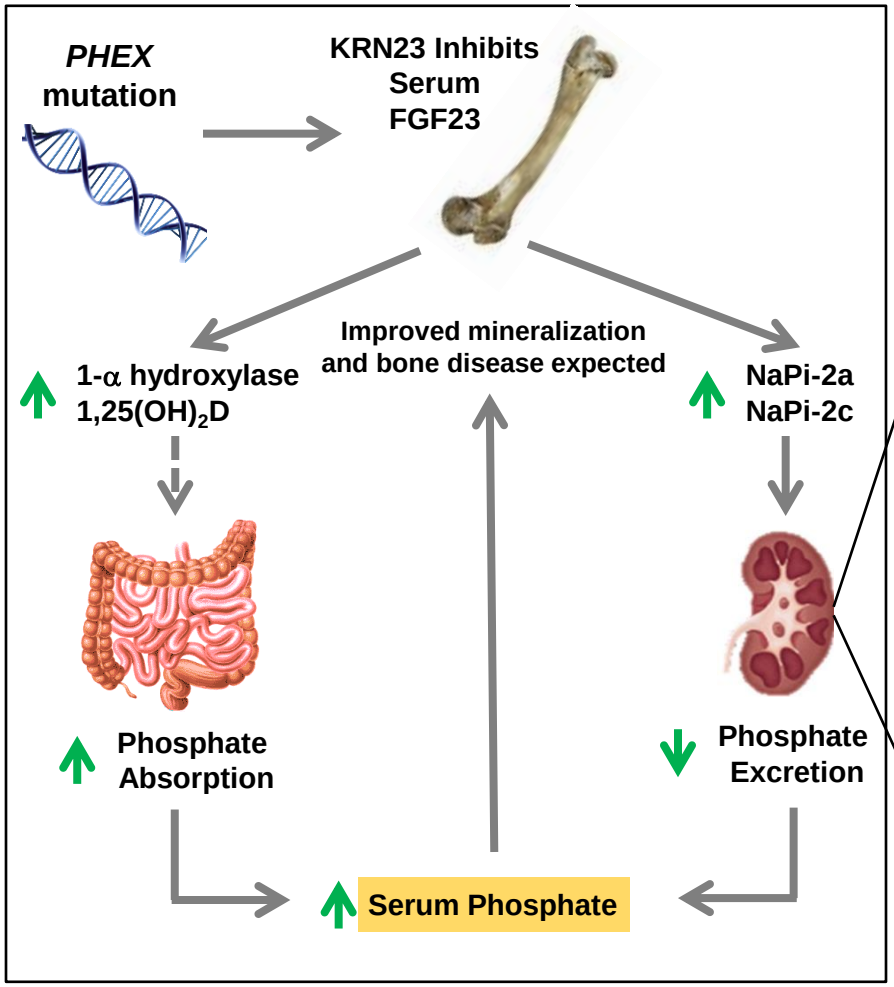




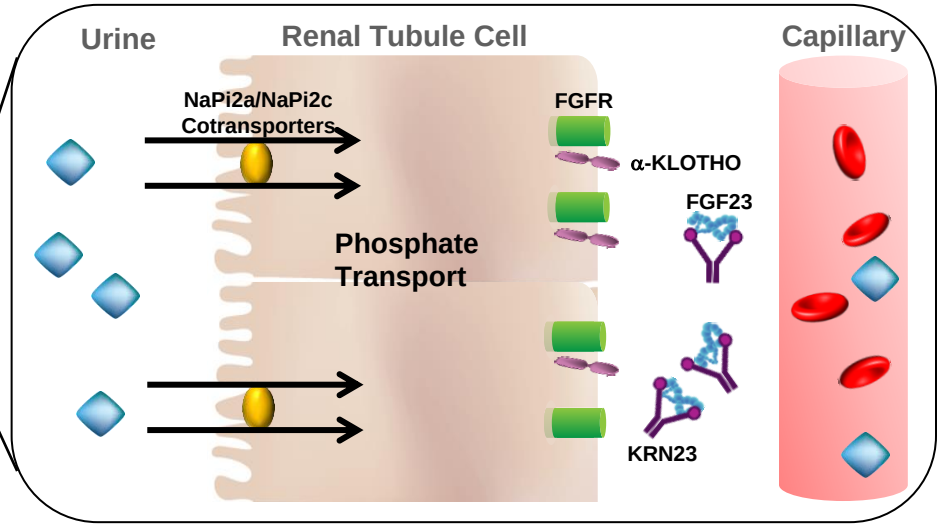
Phosphate

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

KRN23 Is Designed to Inhibit FGF23 to Improve Phosphate Homeostasis

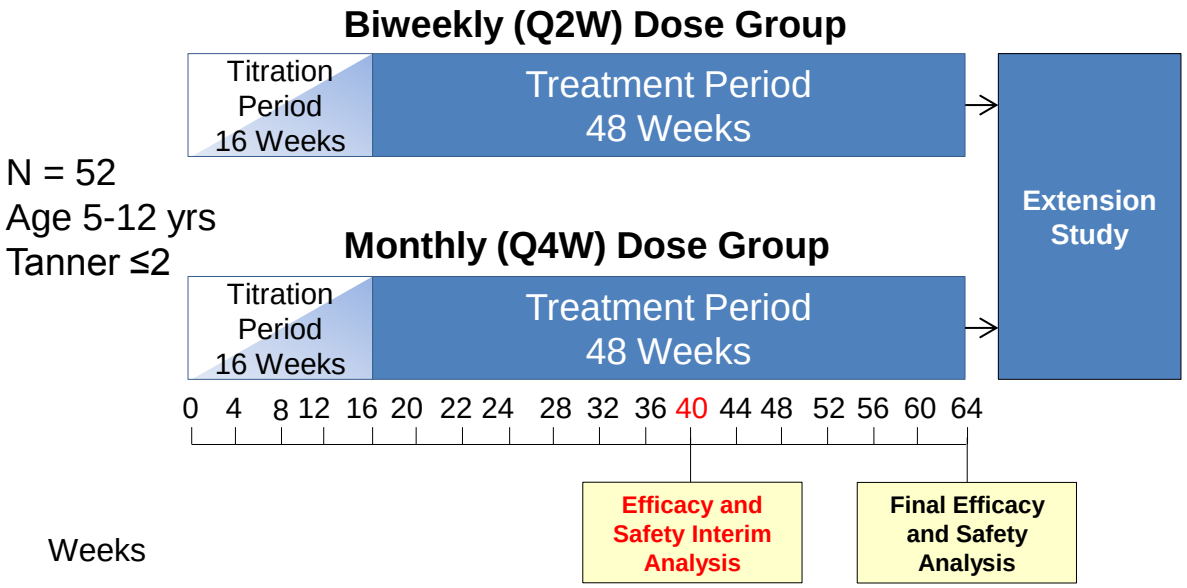


Proposed KRN23 Mechanism of Action



Pediatric Phase 2 Study Design (UX023-CL201)

Study Design



Key Endpoints

- **Pharmacodynamics**: serum P,1,25$(OH)_2$D, TmP/GFR
- **Rickets --** graded by two scoring systems (RGI-C and RSS)
- **Serum alkaline phosphatase**
- **Safety**

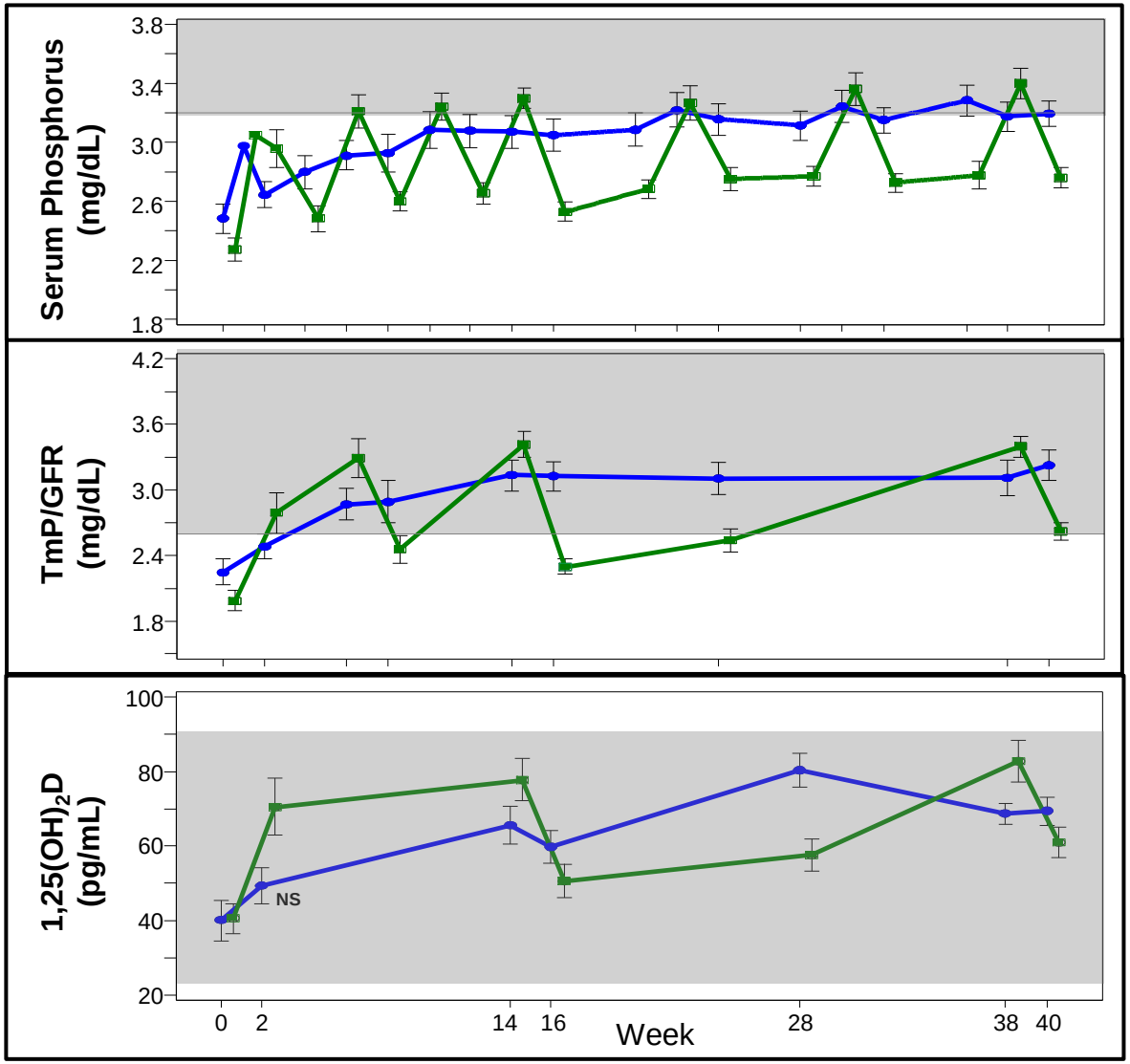
- **Data available for first 36 subjects through 40 weeks**
  - Pre-specified subgroups: 18 subjects with baseline rickets severity total score [RSS] ≥1.5 and 18 subjects with RSS < 1.5

Baseline Demographics and Characteristics

	KRN23 Q2W (N = 18)	KRN23 Q4W (N = 18)	KRN23 Overall (N = 36)
Age, yrs	8.3 (1.6)	8.1 (2.1)	8.2 (1.8)
Male	9 (50%)	9 (50%)	18 (50%)
White	16 (89%)	16 (89%)	32 (89%)
Weight, kg	31.5 (17.6, 47.2)	24.4 (14.7, 55.2)	28.8 (14.7, 55.2)
Height Z score	-1.6 (1.0)	-2.2 (1.0)	-1.9 (1.0)
RSS total score	1.53 (1.05)	1.33 (1.02)	1.43 (1.02)
Received Oral P / Active Vitamin D	17 (94%)	18 (100%)	35 (97%)
Duration of Oral P / Active Vitamin D	6.9 (1.9)	6.3 (3.1)	6.6 (2.6)

Values as mean (SD), median (min, max), or n (%) as indicated. Q2W, biweekly; Q4W, monthly; P, phosphorus; RSS, Thacher Rickets Severity Score; SD, standard deviation

Improvement in Serum Phosphate, TmP/GFR, and $1,25(OH)_2D$

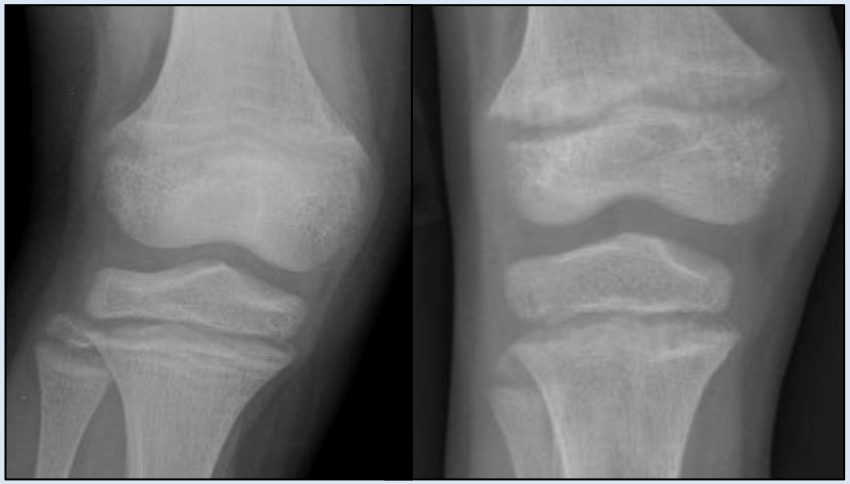


- All post-baseline values were significant ($p<0.05$) compared with baseline unless denoted as not significant (NS)
- Mean dose (SD) at Week 40:
  - Q2W:
    - 0.8 (0.3) mg/kg
    - 25.8 (10.8) mg total dose
  - Q4W:
    - 1.3 (0.4) mg/kg
    - 39.2 (17.7) mg total dose

Two Rickets Scoring Systems Utilized

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

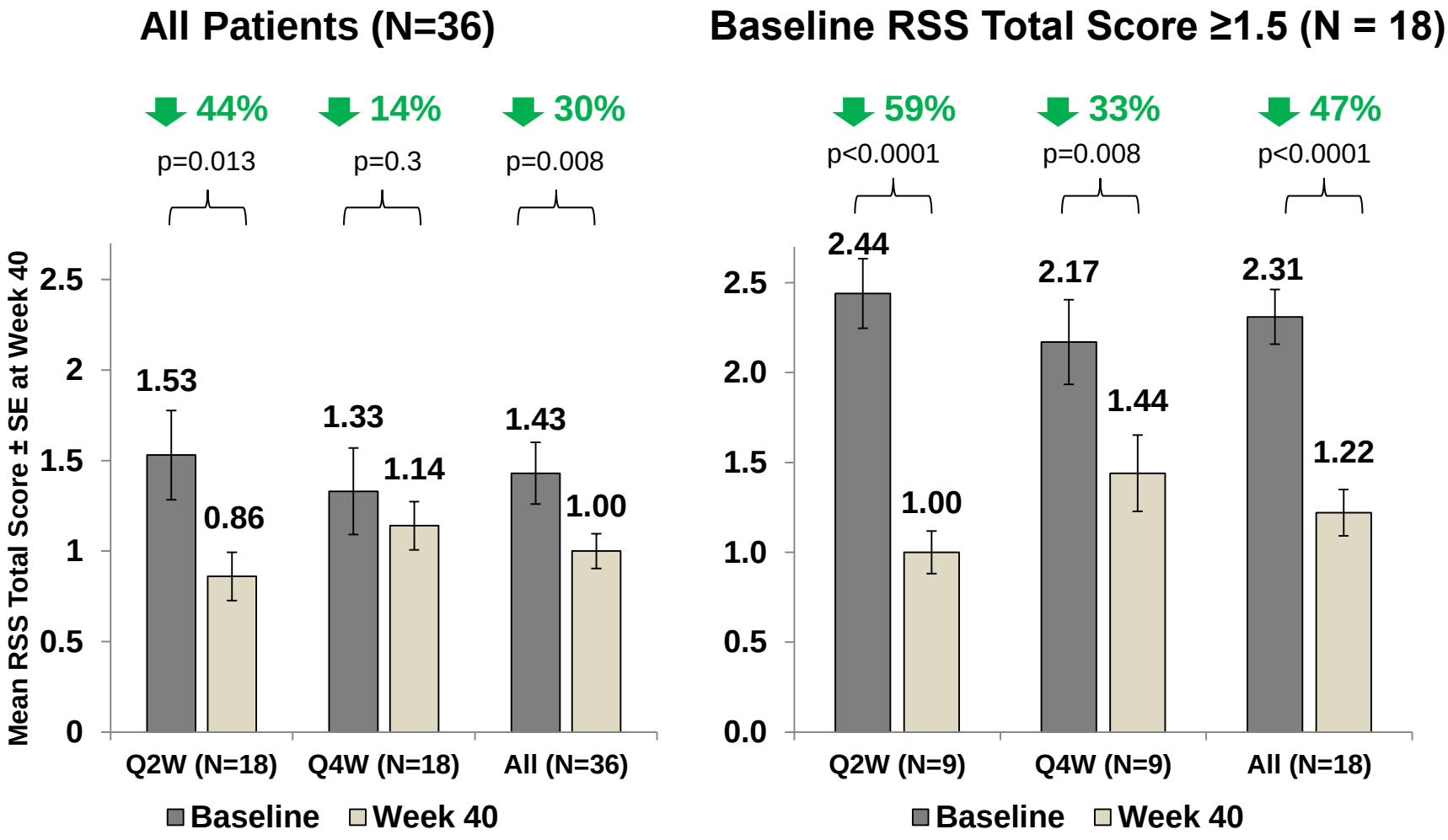
Knee X-Ray

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

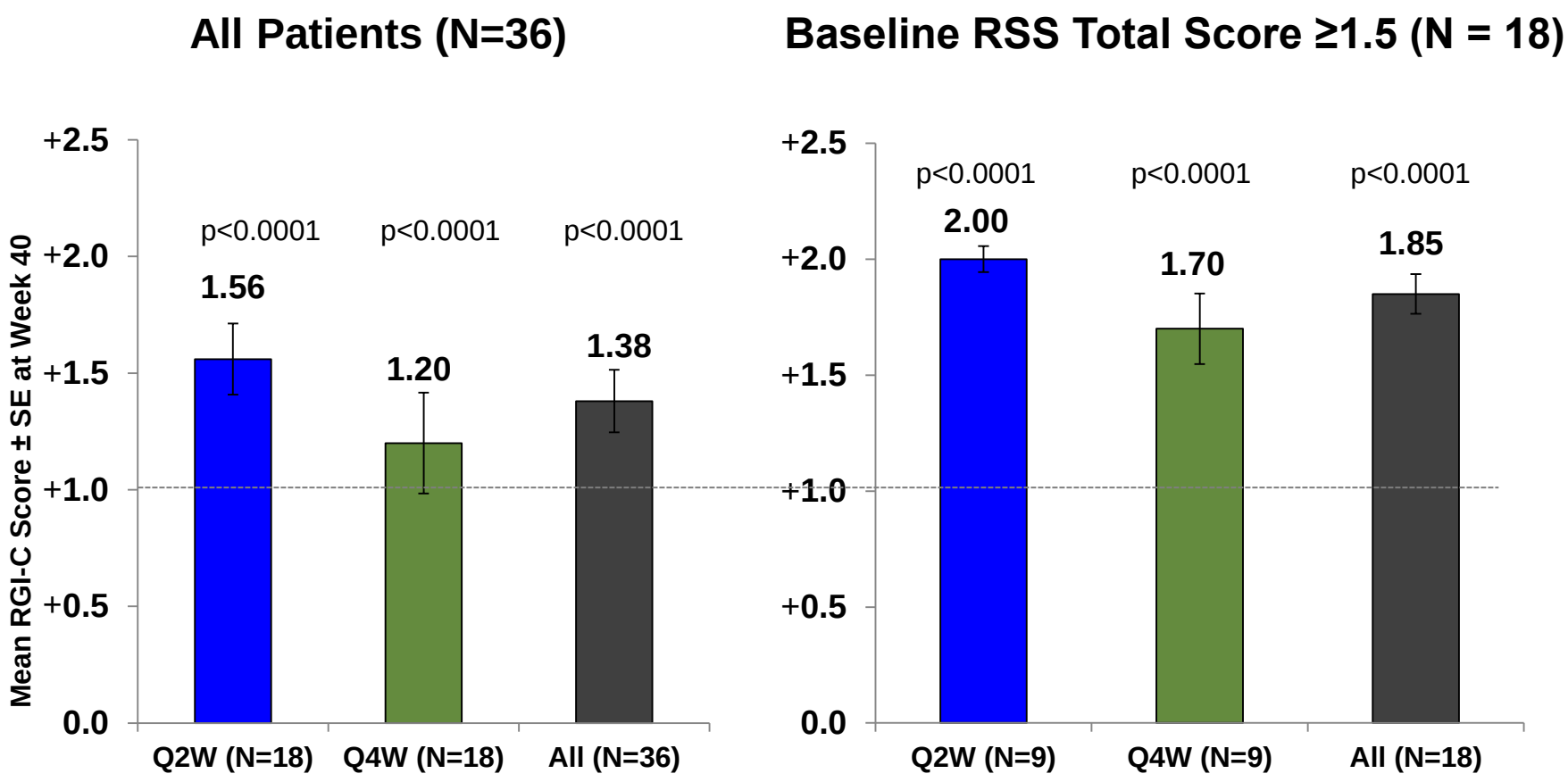
-3	-2	-1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

Mean Change from Baseline to Week 40 in RSS



p value based on paired t test

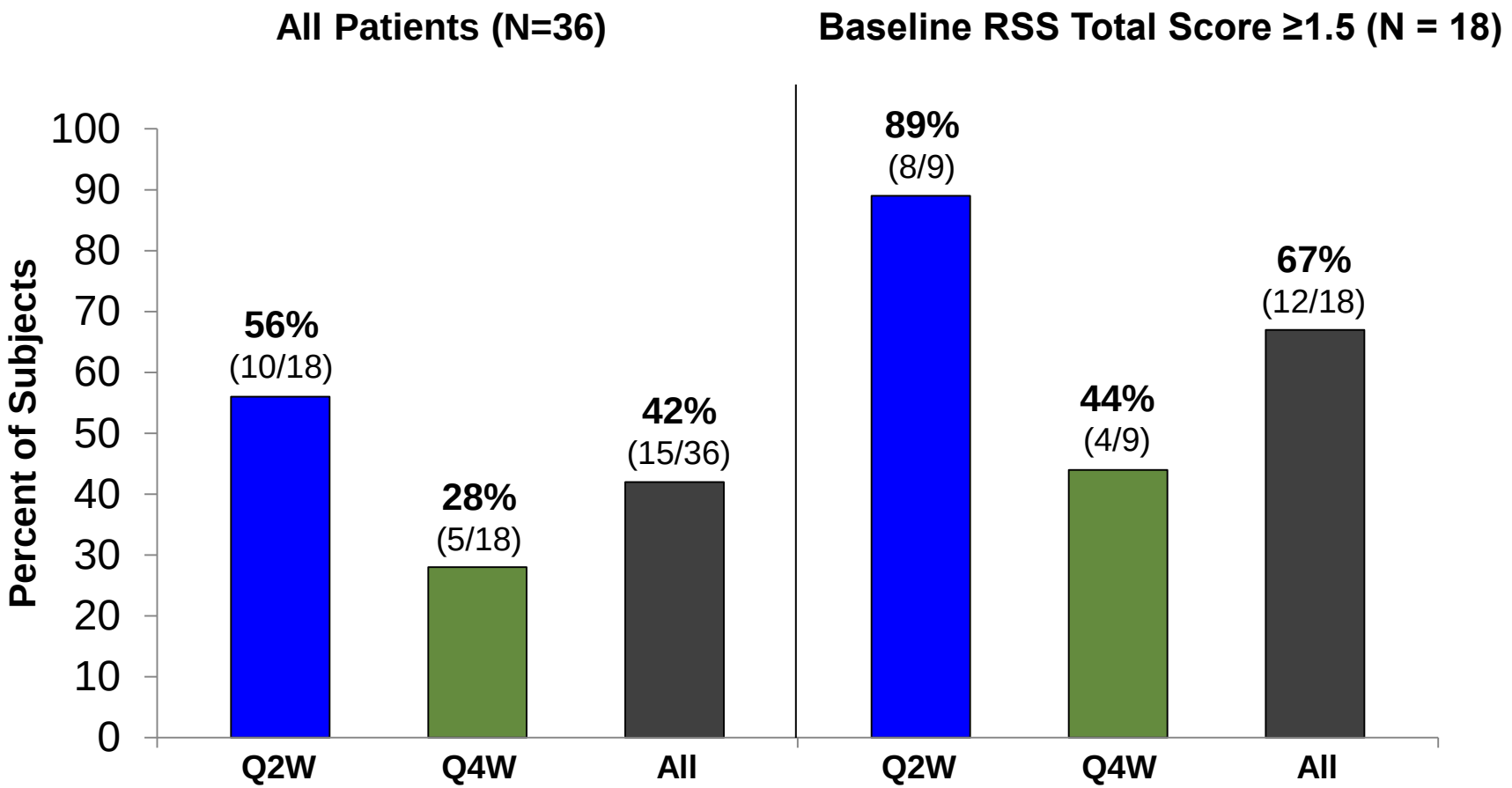
Mean RGI-C Global Score at Week 40



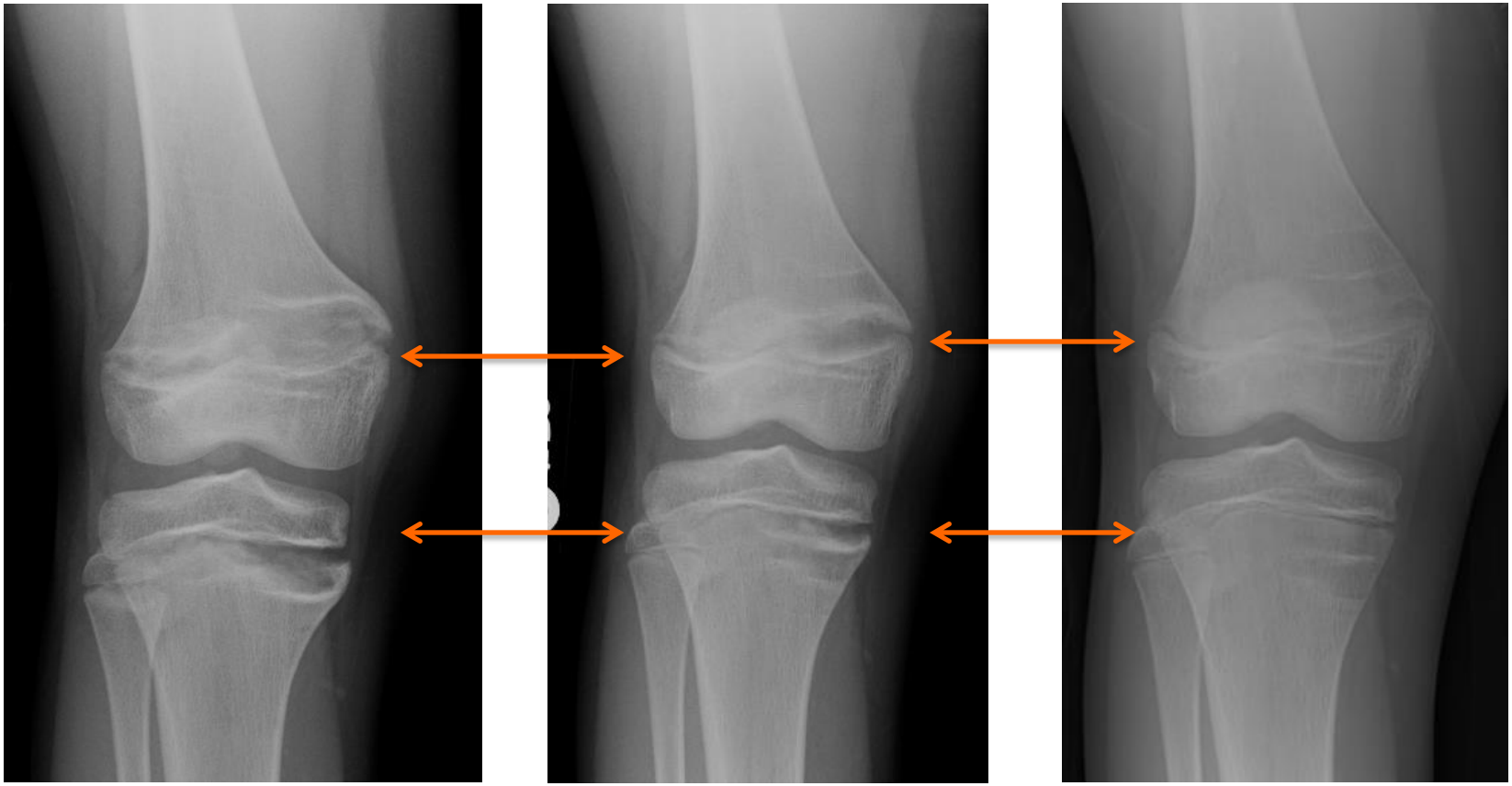
P value is based on one sample t test

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

Proportion of Subjects with Substantial Healing (RGI-C Global Score ≥2.0) at Week 40

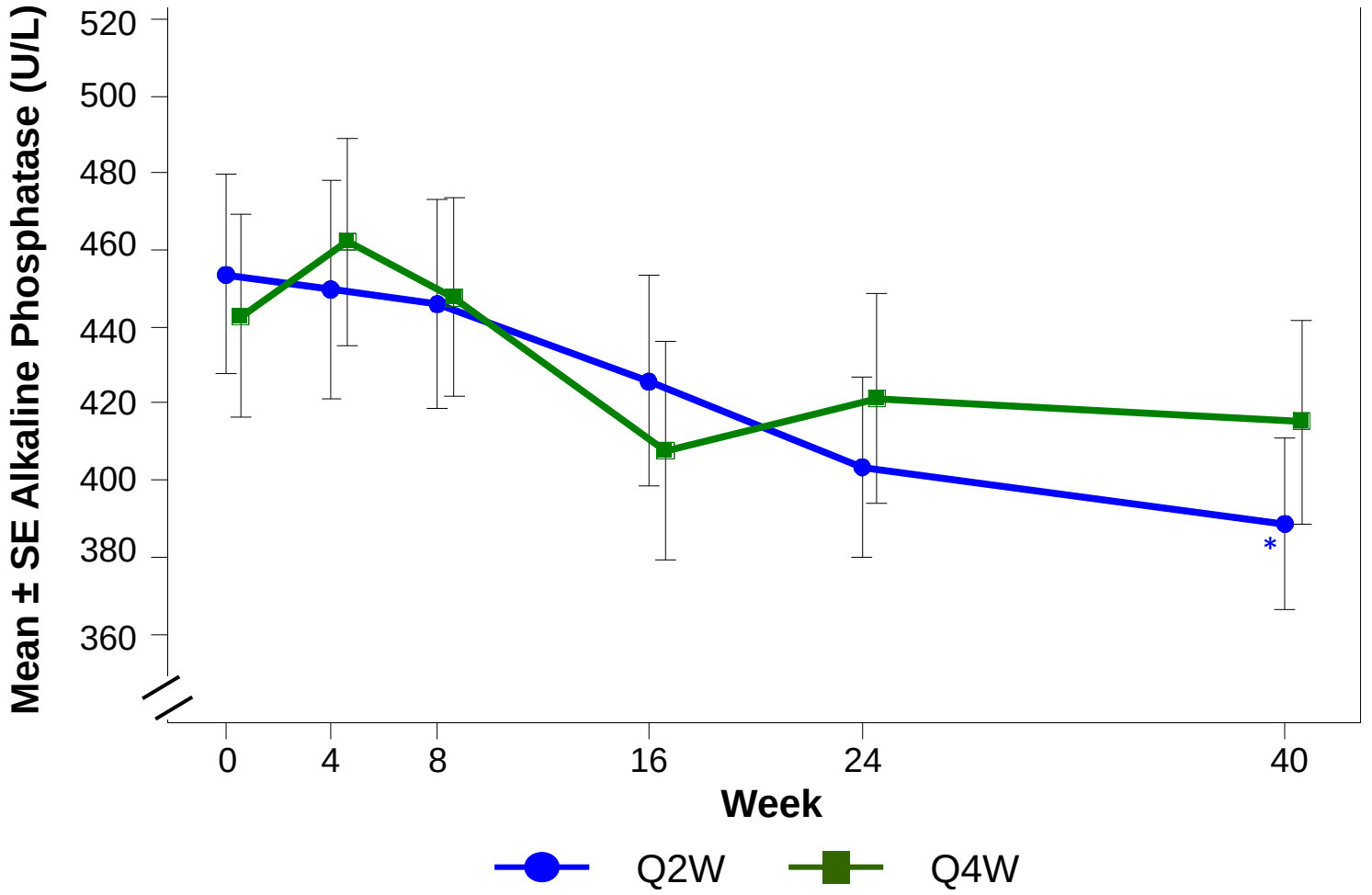


Radiographic Appearance of Rickets at Baseline and Follow-up



Knee X-rays in 12 yr-old girl before (left) and after 40 wks (center) and 64 wks (right) of KRN23 therapy for XLH. Noted the improved rachtic findings at the growth plate.

Change in Serum Alkaline Phosphatase



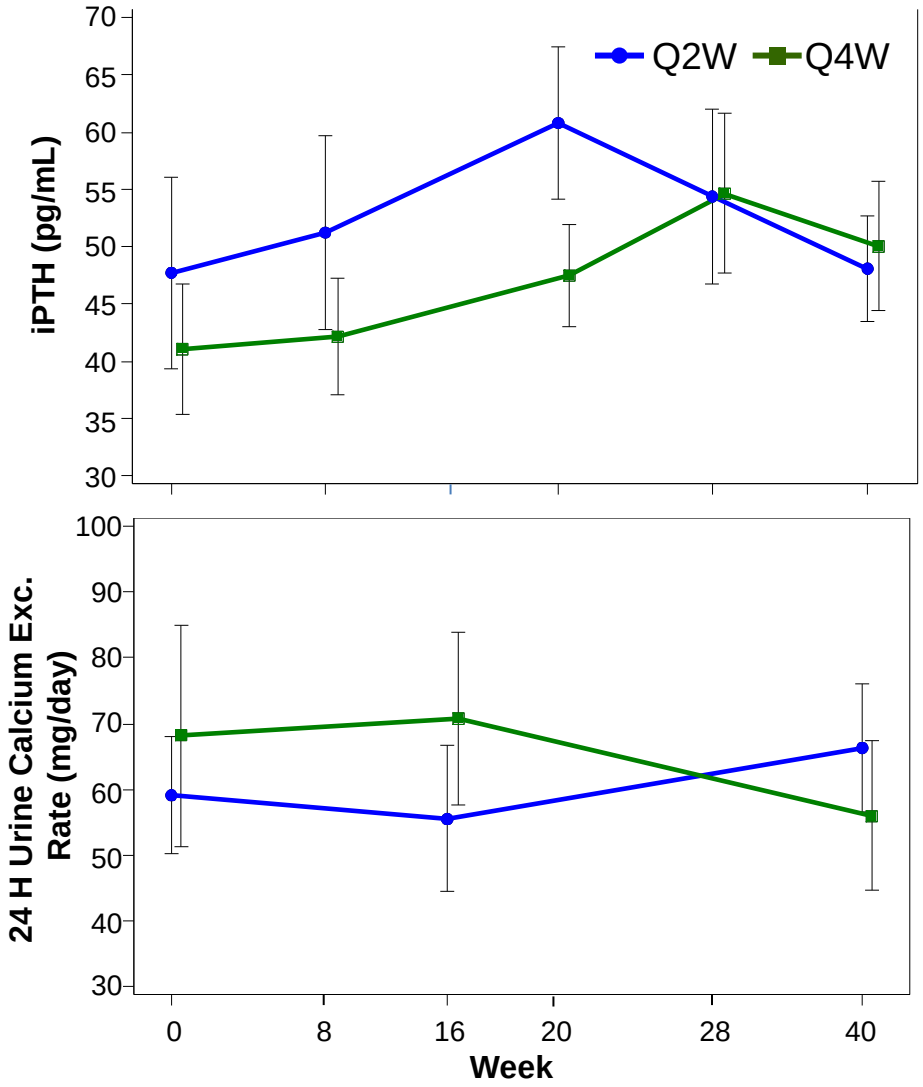
* p=0.01; p value calculated from paired t test based on baseline and Week 40 value

Summary of Safety Measures

Subject Incidence (%)	KRN23 Q2W (N = 18)	KRN23 Q4W (N = 18)	KRN23 Overall (N = 36)
Any Adverse Events (AEs)	18 (100%)	18 (100%)	36 (100%)
Drug-related AEs*	13 (72%)	13 (72%)	26 (72%)
Injection Site Reaction	7 (39%)	7 (39%)	14 (39%)
Erythema	4 (22%)	3 (17%)	7 (19%)
Swelling	3 (17 %)	1 (6 %)	4 (11%)
Rash	1 (6%)	2 (11%)	3 (8%)
Pain in Extremity	2 (11%)	2 (11%)	4 (11%)
Arthralgia	2 (11%)	1 (6%)	3 (8%)
Serious AEs	0	1 (6%)	1 (3%)
AEs leading to discontinuation	0	0	0
AEs leading to death	0	0	0

* Assessed by the investigator as possibly or probably related to investigational product; the most common (≥ 3 subjects) drug-related AEs are listed by preferred terms

PTH and Urine Calcium



- No meaningful increases in serum PTH levels
- No increases in serum or urinary calcium levels were observed

Summary

- KRN23, an investigational product, improved P homeostasis and rickets in children with XLH previously treated for a mean of 6.6 years
- Greater improvement in rickets scores occurred with Q2W dosing and in subjects with more severe baseline rickets (RSS total score ≥1.5)
- KRN23 was well-tolerated and no subject became hyperphosphatemic
- No clinically meaningful changes in serum PTH, serum or urine calcium, or renal ultrasound were observed
- Inhibition of FGF23 has the potential to improve clinical outcomes in children with XLH