A Randomized, Open-label Phase 2 Study of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, in 52 Children with X-linked Hypophosphatemia (XLH): 40-Week Results

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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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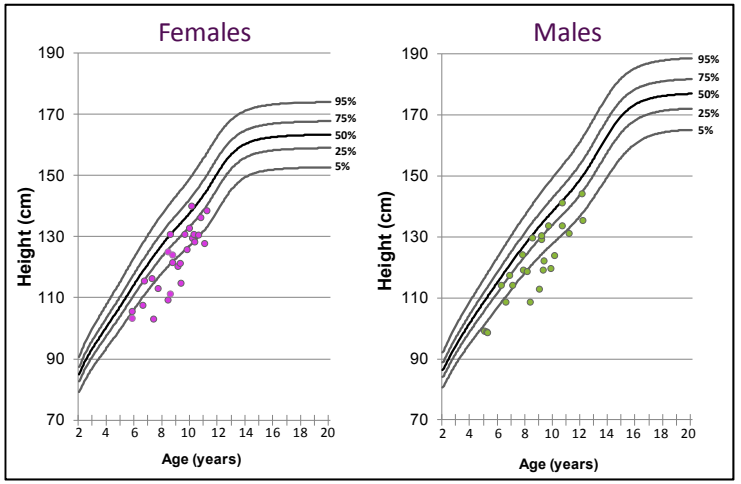
Children with XLH May Have Rickets, Skeletal Deformity, and Impaired Growth

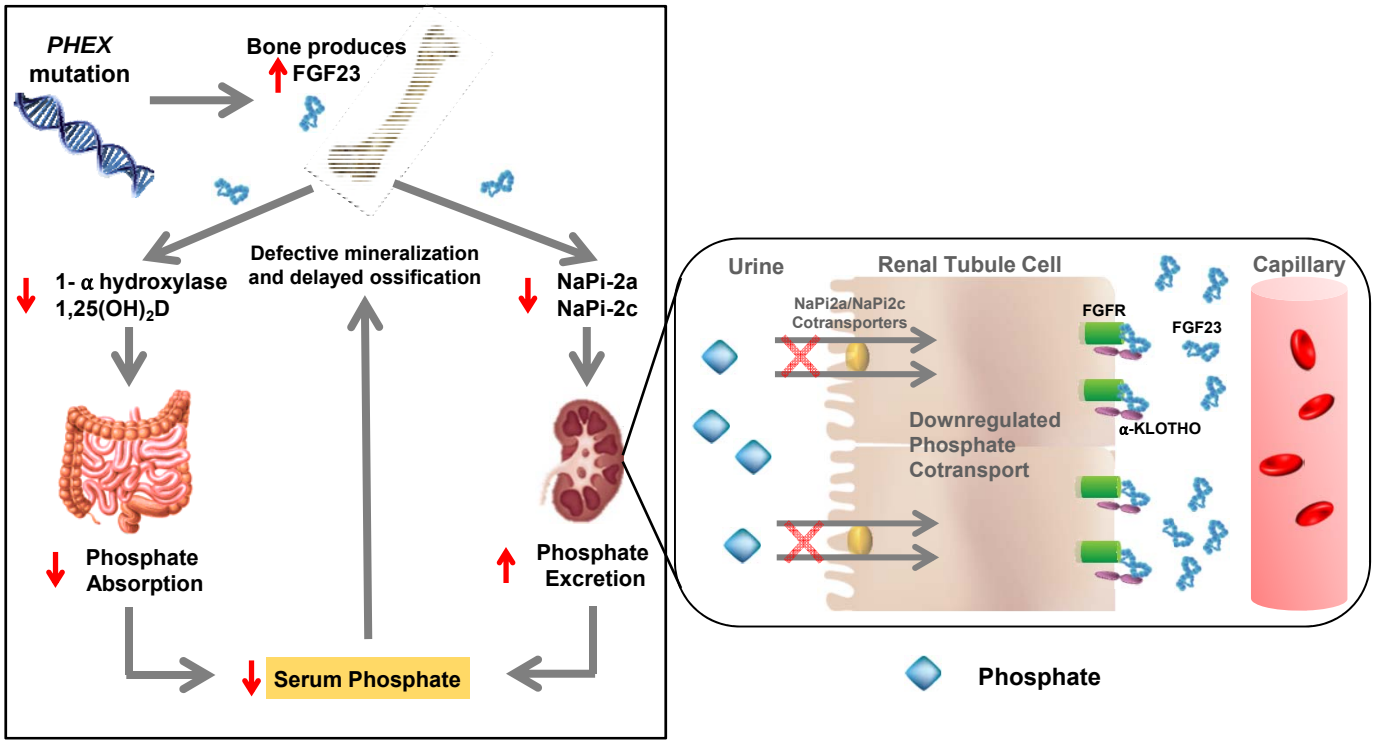
Rickets/Osteomalacia

Bowing of the Leg

Impairment of Linear Growth

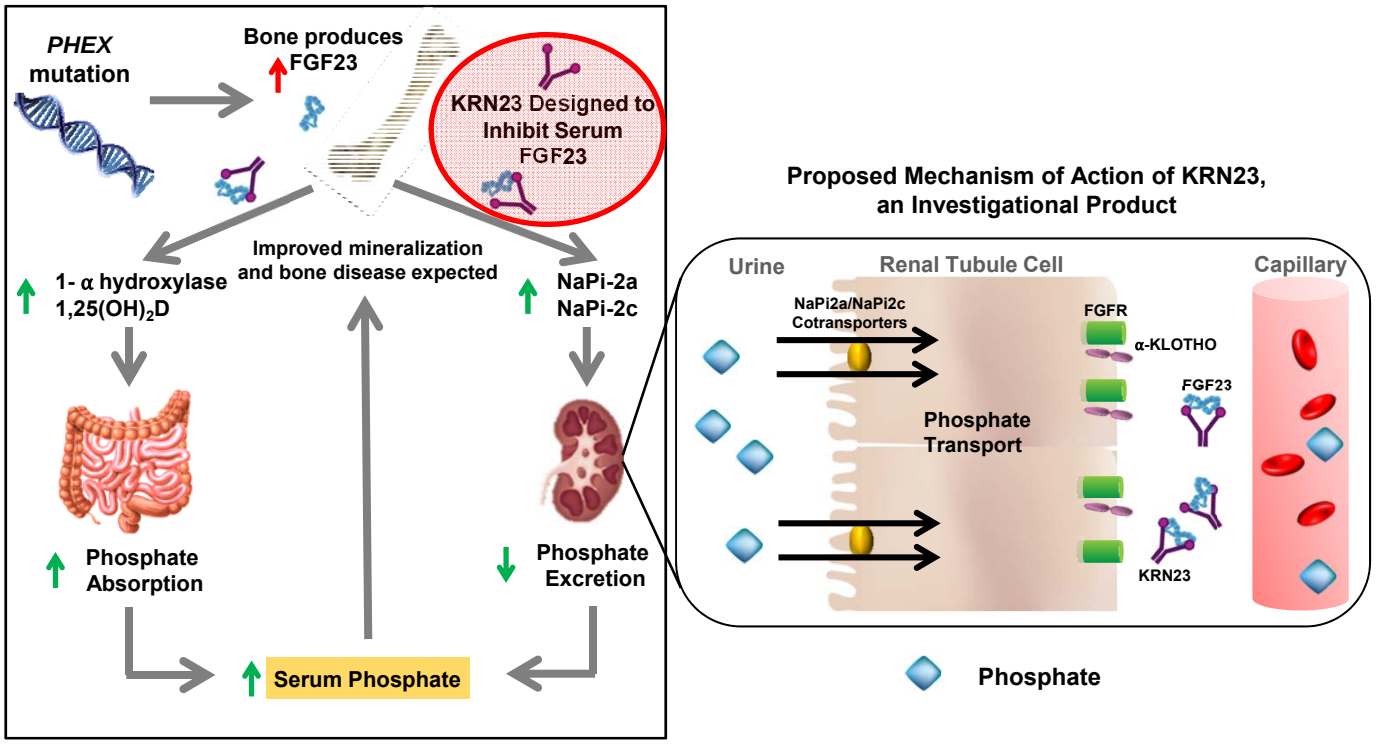


Excess FGF23 in the Pathophysiology of XLH



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

KRN23, a Monoclonal Antibody, Binds and Inhibits FGF23

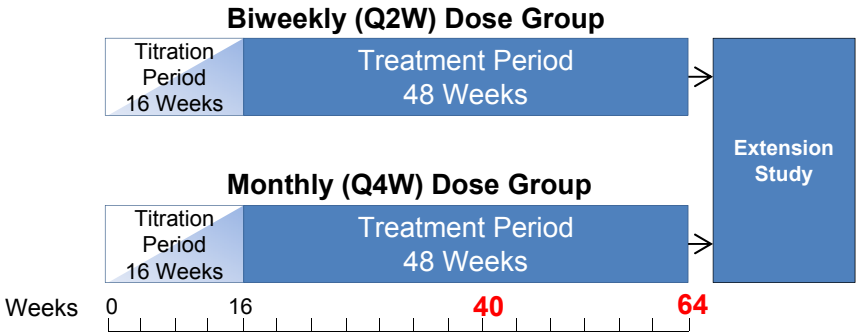


Pediatric Phase 2 Study Design (UX023-CL201)

Study Design

Study Population

Children with XLH
Ages 5-12 yrs
N = 52
Tanner ≤2



- Primary analysis: Week 40 (N=52)
- Extended analysis: Week 64 (N=36)
- Pre-specified subgroups based on baseline total rickets severity score (RSS)
  - Week 40: 34 patients with RSS ≥ 1.5; 18 patients with RSS < 1.5
  - Week 64: 18 patients with RSS ≥ 1.5; 18 patients with RSS < 1.5

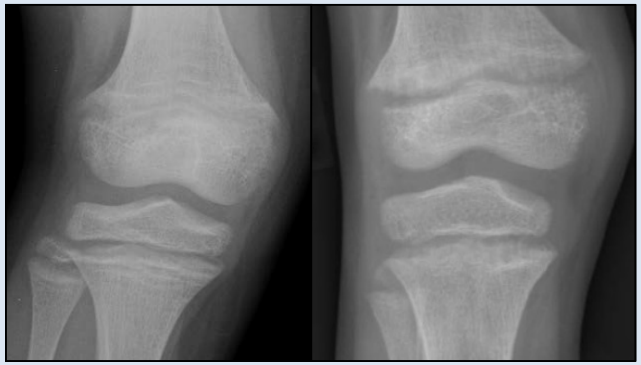
Key Endpoints

- **Pharmacodynamics**: serum P, TRP, TmP/GFR, $1,25(OH)_2D$
- **Rickets --** graded by two scoring systems (RGI-C and RSS)
- **Growth velocity**
- **Walking ability**: 6 minute walk test
- **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

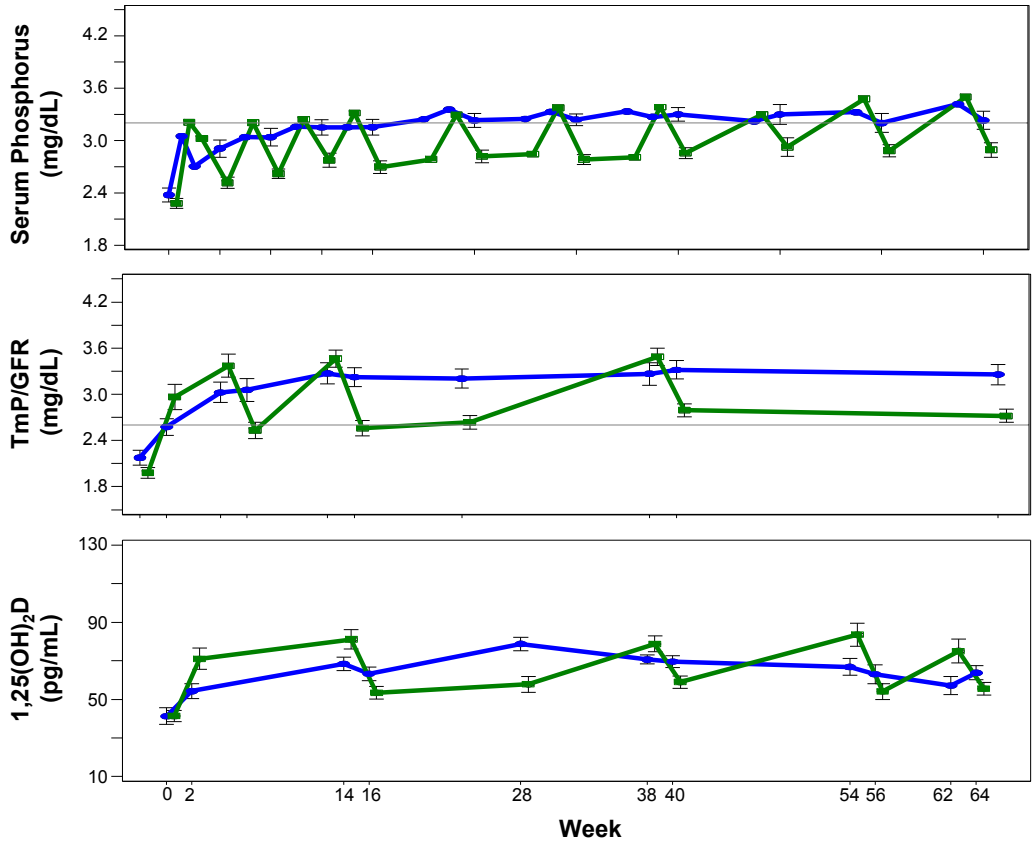
-3	-2	-1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

Baseline Characteristics of the Two Subsets

	Week 40 Subset			Week 64 Subset		
	KRN23 Q2W (N = 26)	KRN23 Q4W (N = 26)	KRN23 Overall (N = 52)	KRN23 Q2W (N = 18)	KRN23 Q4W (N = 18)	KRN23 Overall (N = 36)
Age, yrs	8.7 (1.7)	8.3 (2.0)	8.5 (1.9)	8.3 (1.6)	8.1 (2.1)	8.2 (1.8)
Male	12 (46%)	12 (46%)	24 (46%)	9 (50%)	9 (50%)	18 (50%)
White	23 (89%)	23 (89%)	46 (89%)	16 (89%)	16 (89%)	32 (89%)
Weight, kg	31.9 (7.9)	29.1 (10.7)	30.5 (9.4)	30.1 (7.6)	28.1 (11.2)	29.1 (9.5)
Height Z score	-1.7 (1.0)	-2.1 (1.0)	-1.9 (1.0)	-1.6 (1.0)	-2.2 (1.0)	-1.9 (1.0)
RSS total score **Range**	1.9 (1.2) (0, 4.5)	1.7 (1.0) (0, 3.0)	1.8 (1.1) (0, 4.5)	1.5 (1.1) (0, 3.5)	1.3 (1.0) (0, 3.0)	1.4 (1.0) (0, 3.5)
Received prior oral P / active vitamin D	25 (96%)	24 (92%)	49 (94%)	17 (94%)	17 (94%)	34 (94%)
Duration of prior oral P / active vitamin D, yrs	6.7 (2.5)	6.7 (2.7)	6.7 (2.6)	6.9 (1.9)	6.7 (2.8)	6.8 (2.4)

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

Improvement in Serum Phosphorus, TmP/GFR, and 1,25(OH)$_2$D



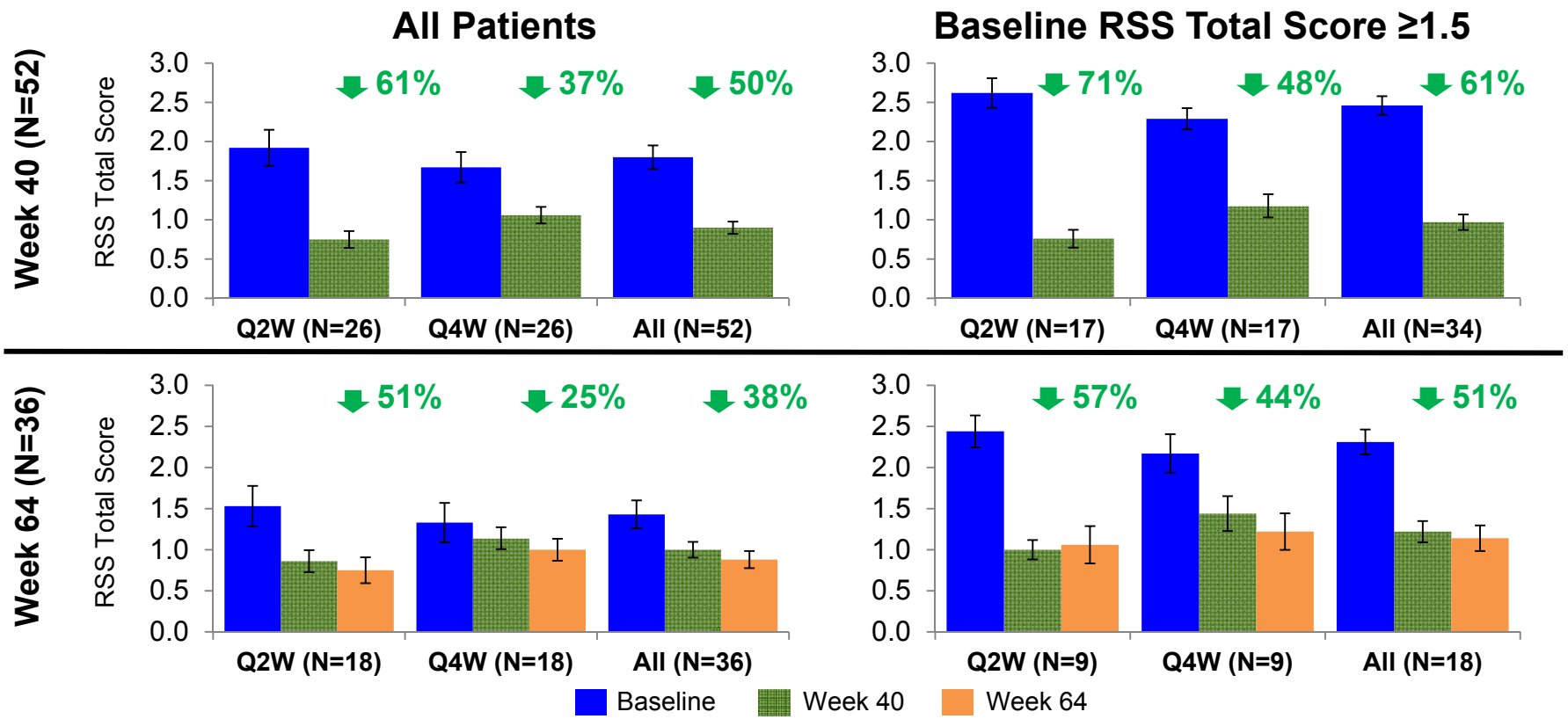
Q2W Q4W

- Mean KRN23 doses (SD) at Week 40:

Q2W:	Q4W:
▪ 1.0 (0.4) mg/kg	▪ 1.5 (0.4) mg/kg
▪ 34.7 (20.5) mg/dose	▪ 45.5 (19.3) mg/dose

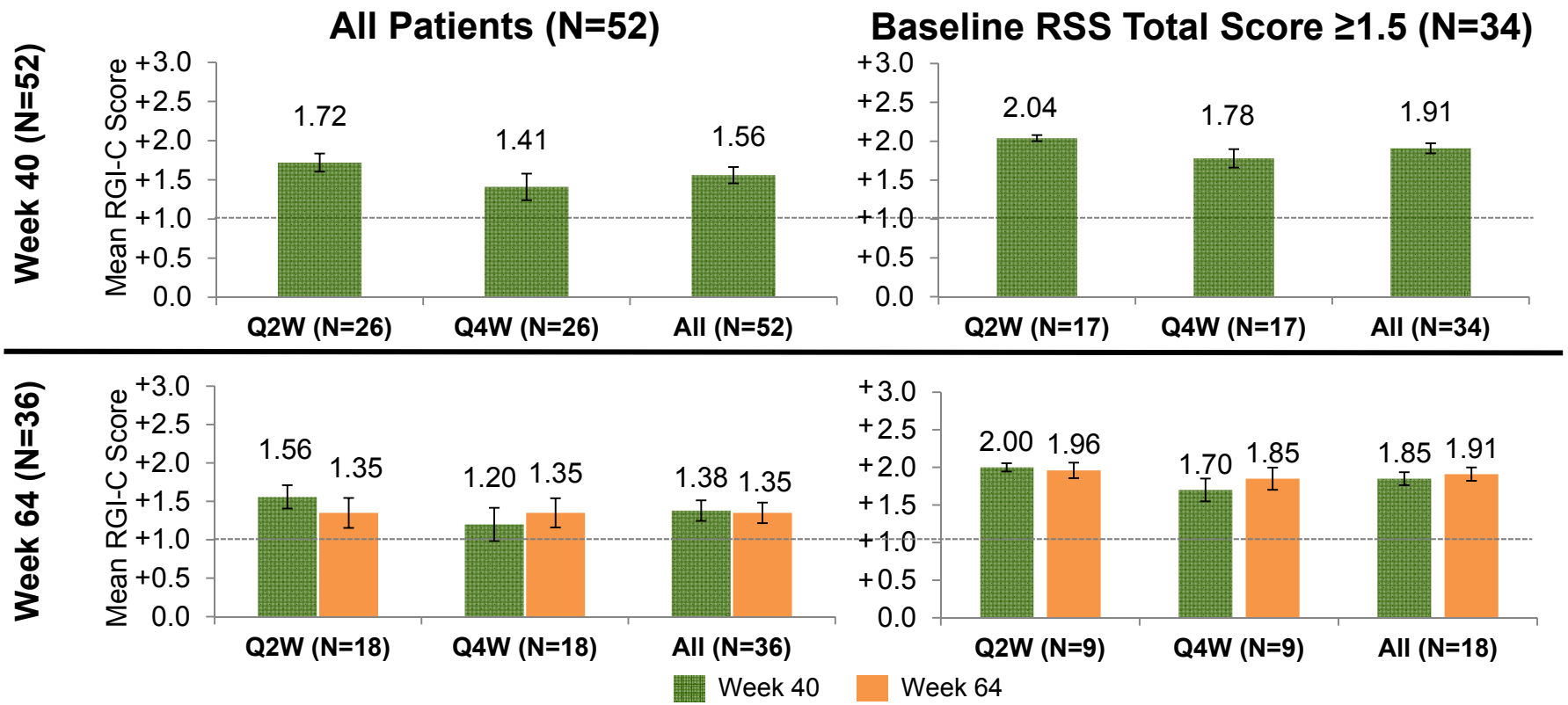
- All treatment values were significant compared with baseline
- No hyperphosphatemia in any patient

Rickets Severity Score (RSS)



Mean values ± SE; $p \leq 0.008$ for all groups based on the Analysis of Covariance (ANOVA) model for the Week 40 subset and the Generalized Estimation Equation (GEE) for the Week 64 subset;

Radiographic Global Impression of Change (RGI-C)



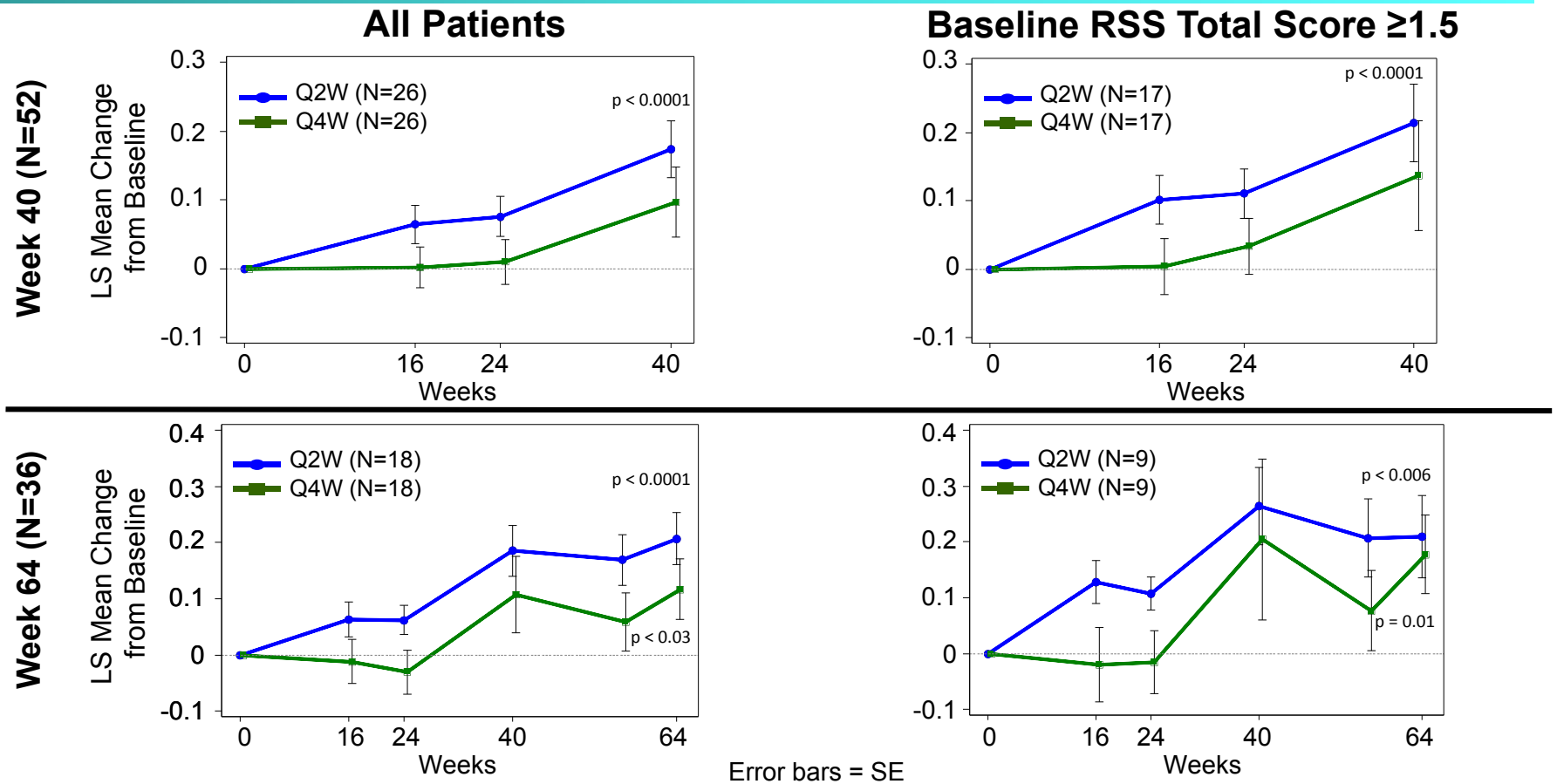
p < 0.0001 for all groups based on the Analysis of Covariance (ANOVA) model for the Week 40 subset and the Generalized Estimation Equation (GEE) for the Week 64 subset; Error bars = SE; RGI-C Scores: +1.0 = minimal healing; +2.0 = substantial healing; +3.0 = complete or near complete healing

Radiographic Appearance of Rickets at Baseline and Follow-up

Knee radiographs in ~11-year-old girl with XLH during KRN23 therapy demonstrate improved rachitic findings at the growth plate

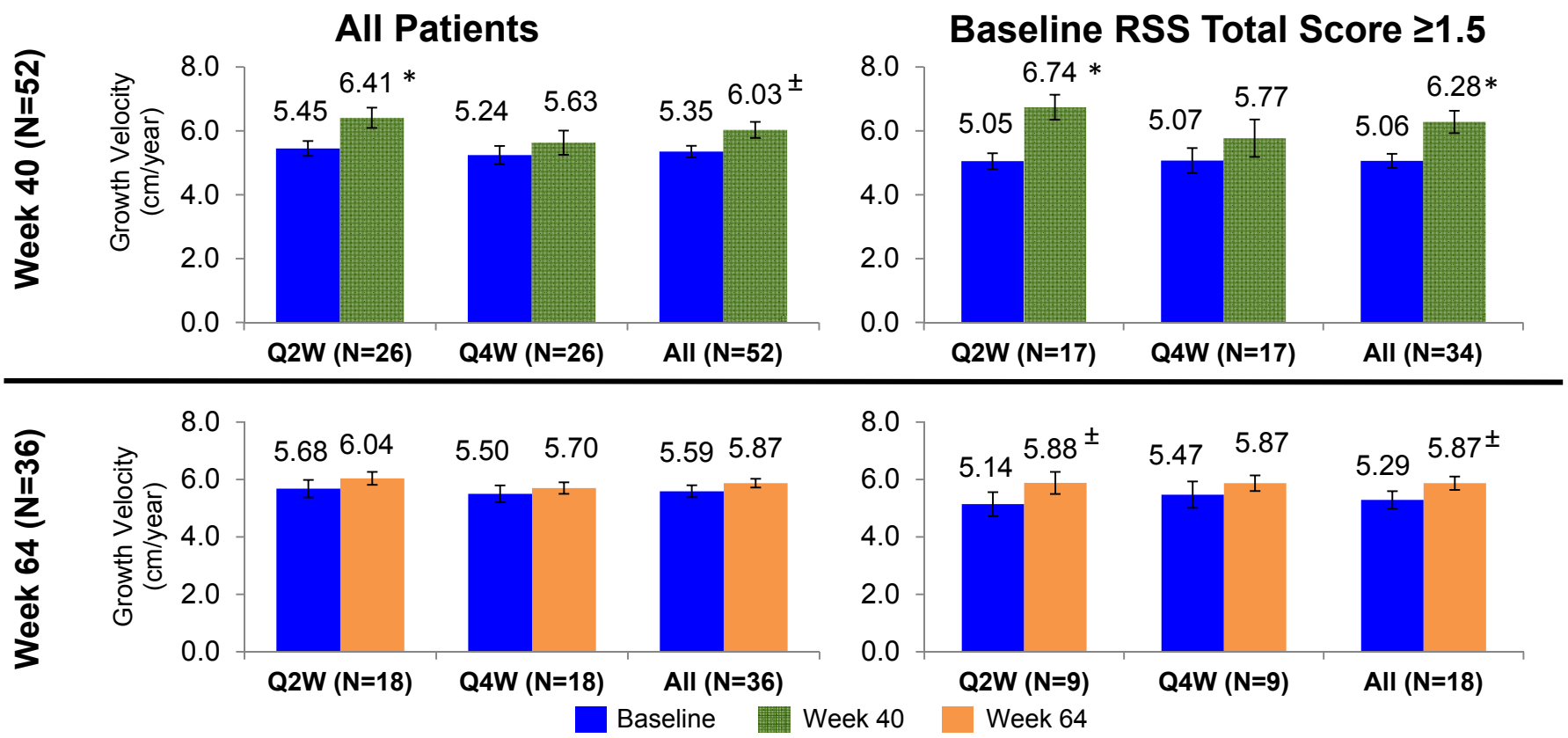
	Baseline	40 weeks	64 weeks
RSS Total Score	3.5	1.0	0.0
RGI-C Global Score		+2.0	+2.3

Standing Height Z-score Change From Baseline



Error bars = SE

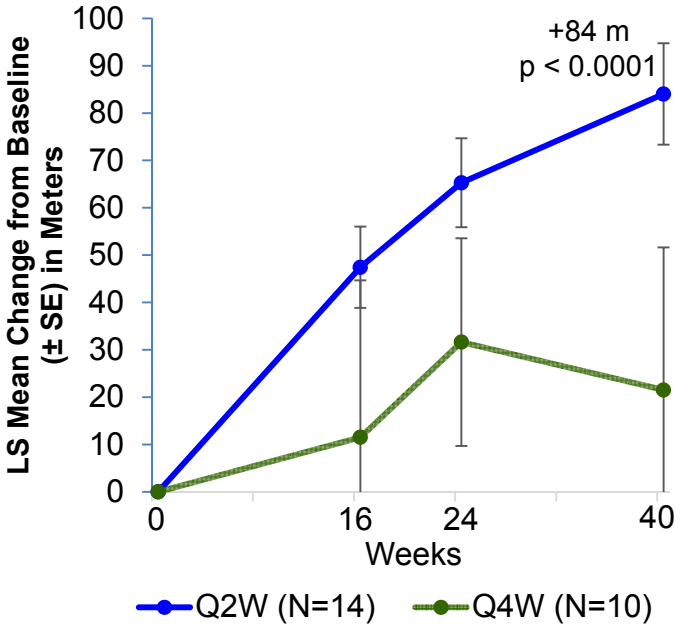
Growth Velocity



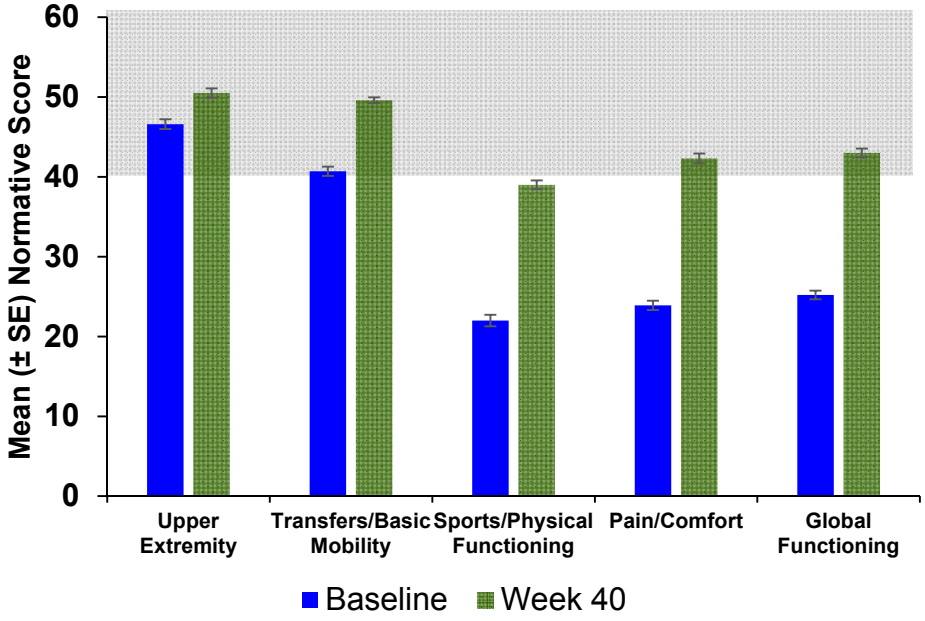
* p ≤ 0.01; ± p ≤ 0.05 compared with baseline based on one sample *t* test; Error bars = SE

6MWT and Functional Ability at Week 40

Patients with Impaired Walking Ability at Baseline (< 80% Predicted; N=24)



Patients with Global Functional Impairment at Baseline (POSNA-PODCI Score <40; N=28)



All treatment values were significant compared with baseline using the generalized estimation equation (GEE) model with the exception of the Q4W group for the 6MWT. POSNA-PODCI – Pediatric Orthopedic Society of North America-Pediatric Outcome Data Collection Instrument

Summary of Safety Measures

Patient Incidence, n (%)	KRN23 Q2W (N=26)	KRN23 Q4W (N=26)	KRN23 Overall (N = 52)
Any adverse events (AEs)	26 (100%)	26 (100%)	52 (100%)
Drug-related AEs*	17 (65%)	18 (69%)	35 (67%)
Injection site reaction	7 (27%)	10 (39%)	17 (33%)
erythema	8 (31%)	5 (19%)	13 (25%)
swelling	4 (15%)	1 (4%)	5 (10%)
rash	2 (8%)	2 (8%)	4 (8%)
Pain in extremity	3 (12%)	2 (8%)	5 (10%)
Vitamin D Deficiency	1 (4%)	4 (15%)	5 (10%)
Arthralgia	2 (8%)	1 (4%)	3 (6%)
Myalgia	1 (4%)	2 (8%)	3 (6%)
Serious AEs	0	1 (4%)	1 (2%)
AEs leading to discontinuation	0	0	0
AEs leading to death	0	0	0

* Assessed by investigator as possibly/probably related to investigational product; most common (≥ 3 patients) drug-related AEs are listed

Summary and Conclusions

- In children with XLH treated with KRN23 for up to 64 weeks:
  - TmP/GFR, serum P, and serum 1,25$(OH)_2$D increased
  - 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 (RSS ≥1.5) receiving Q2W dosing
  - 94% at Week 40 and 89% at Week 64 had substantial healing of rickets
- KRN23 improved growth, walking ability, and functional ability.
- KRN23 was well tolerated
- No clinically meaningful changes were observed in serum PTH, serum or urine calcium, or renal ultrasounds. Hyperphosphatemia was not observed
- Inhibition of FGF23 improves clinical outcomes in children with XLH