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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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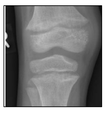
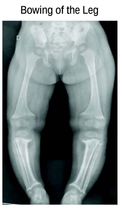
INTRODUCTION

- X-linked hypophosphatemia (XLH) is a rare, lifelong, chronically debilitating, and deformative bone disease mediated by high circulating fibroblast growth factor-23 (FGF23) (Carpenter et al, 2011; Linglart et al, 2014).
- The resulting skeletal abnormalities, including rickets and bowing of the legs, can significantly impair gross motor function, growth, and quality of life in childhood or adulthood.

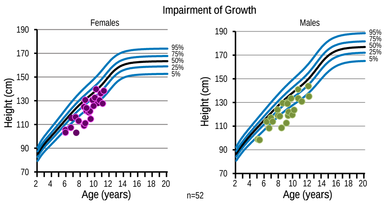
Rickets/Osteomalacia



Bowing of the Leg

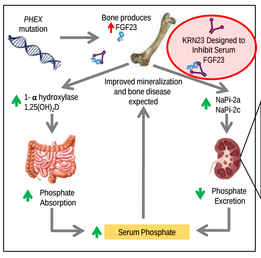


Impairment of Growth

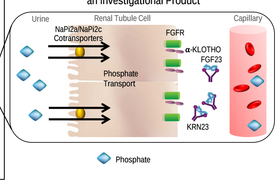


Excess FGF23 in the Pathophysiology of XLH

- KRN23 is an investigational fully human IgG1 monoclonal antibody designed to specifically bind to and inhibit excess FGF23.



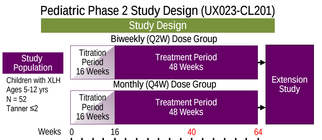
Proposed Mechanism of Action of KRN23, an Investigational Product



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

METHODS

Pediatric Phase 2 Study Design (UX023-CL201)



- 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

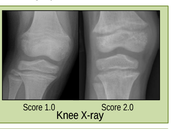
Key Endpoints

- Pharmacodynamics: serum P, TRP, TmP/GFR, 1,25(OH)$_2$D
- Rickets: graded by two scoring systems (RGI-C and RSS)
- Growth velocity
- Walking ability: Six-Minute Walk Test (6MWT)
  - Distance walked in 6 minutes, corrected for age, height, and weight
- 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



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

RESULTS

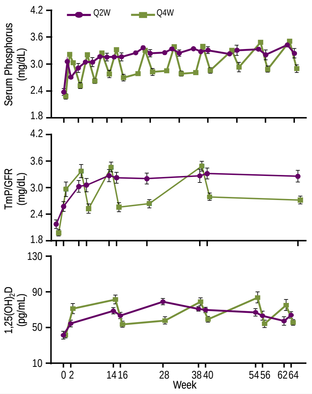
Baseline Characteristics of the Two Subsets

	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

- Baseline characteristics for the full patient population (N=52) used in the Week 40 analysis and the first 36 enrolled patients (N=36) used in the Week 64 analysis were similar. Both subsets had short statures and persistent rickets despite almost 7 years of treatment with oral phosphate and active vitamin D.

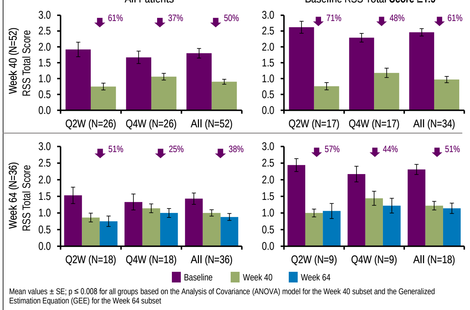
Improvement in Serum Phosphorus, TmP/GFR, and 1,25(OH)$_2$D



- Mean KRN23 doses (SD) at Week 40:
  - Q2W:
    - 1.0 (0.4) mg/kg
    - 34.7 (20.5) mg/dose
  - Q4W:
    - 1.5 (0.4) mg/kg
    - 45.5 (19.3) mg/dose
- All treatment values were significant compared with baseline
- No hyperphosphatemia in any patient
- KRN23 reversed renal phosphate wasting; serum phosphorus levels and TmP/GFR increased from baseline in all patients and were sustained through Week 64. Mean levels were close to or at the low end of the normal range.
- Serum 1,25(OH)$_2$D levels also increased indicating that KRN23 treatment restores 25-hydroxyvitamin D 1-alpha hydroxylase activity.

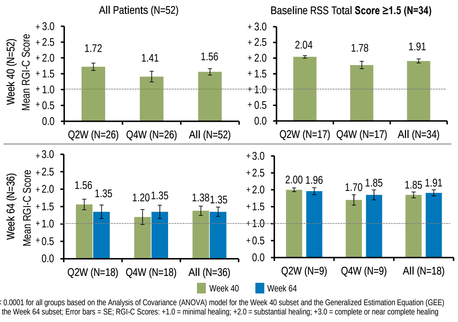
Improvement in Rickets

Rickets Severity Score (RSS)



Mean values ± SE; p ≤ 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

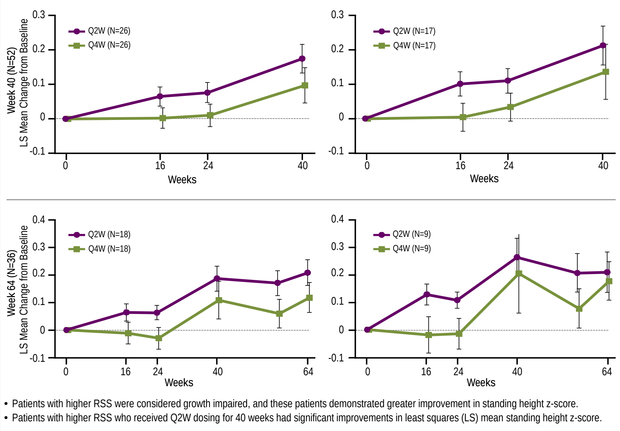
Radiographic Global Impression of Change (RGI-C)



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

- KRN23 significantly improved rickets in all groups at Week 40, with sustained efficacy through Week 64, as assessed by the RSS and RGI-C
  - The greatest improvements were in patients with higher baseline rickets severity (RSS total score ≥1.5; higher RSS) who received Q2W dosing.
  - Subjects in the Q2W group with higher RSS had substantial healing of rickets (RGI-C score of ≥+2.0) after 40 and 64 weeks of KRN23 treatment.
  - The Week 40 analysis subset included all 52 patients in the study, 34 with higher RSS subgroup and 18 with lower baseline rickets severity (RSS total score <1.5; lower RSS subgroup). The Week 64 analysis subset only included the first 36 enrolled patients, 18 with higher RSS and 18 with lower RSS.

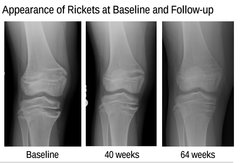
Standing Height Z-score Change from Baseline



- Patients with higher RSS were considered growth impaired, and these patients demonstrated greater improvement in standing height z-score.
- Patients with higher RSS who received Q2W dosing for 40 weeks had significant improvements in least squares (LS) mean standing height z-score.

Radiographic Appearance of Rickets at Baseline and Follow-up

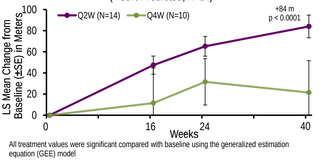
Knee radiographs in ~11-year-old girl with XLH during KRN23 therapy demonstrate improved rachitic findings at the growth plate



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

6MWT at Week 40

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



All treatment values were significant compared with baseline using the generalized estimation equation (GEE) model

- 6MWT
  - Patients in the bi-weekly dosing group showed an increase in meters walked in the 6MWT of 33 meters (p<0.001) at 40 weeks (n=26), and 49 meters (p<0.001) at 64 weeks (n=18).
  - Patients with walking impairment at baseline (defined by < 80% predicted normal walk distance in 6MWT) in the bi-weekly dosing group achieved a mean increase of 84 meters (p<0.001) at 40 weeks (n=14), and 97 meters (p<0.001) at 64 weeks (n=7).

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

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 and walking 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

DISCLOSURES

- Drs. Linglart, Imel, Boot, 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.
- Dr. Carpenter: grant support and travel fees from Ultragenyx Pharmaceuticals Inc. (Ultragenyx)
- Drs. Mao, Skrinar, Kakkis, and San Martin: employees of Ultragenyx
- Dr. Whyte: research grant support, honoraria, and travel from Ultragenyx and Alexion Pharmaceuticals Inc.
- This study was sponsored and funded by Ultragenyx in partnership with Kyowa Hakko Kirin Co., Ltd.
- Ting Chang, PhD, from Ultragenyx provided medical writing support