MO0319

Clinical and Radiographic Characteristics of Adult X-linked Hypophosphatemia (XLH) in a Cohort of Patients Treated with KRN23, an Antibody to FGF23

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INTRODUCTION

- X-linked hypophosphatemia (XLH) is a rare, serious, and chronically debilitating genetic disorder caused by excess circulating fibroblast growth factor 23 (FGF23), resulting from mutations in the phosphate-regulating endopeptidase homolog, X-linked (*PHEX*) gene (Carpenter et al. 2011)
- Excess FGF23 produces hypophosphatemia through two actions:
  - Inhibition of phosphate reabsorption by kidney proximal tubular cells
  - Inhibition of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) synthesis leading to decreased intestinal absorption of phosphate
- Low serum phosphorus levels in XLH lead to defects in bone mineralization, rickets and/or osteomalacia, skeletal abnormalities, pseudofractures, joint pain/stiffness, osteoarthritis, enthesopathy, and dental issues
- KRN23 is a fully human monoclonal antibody designed to bind and thereby inhibit FGF23
- In previous phase 1/2 studies, XLH patients treated with KRN23 for up to 17 months showed improvements in serum phosphorus levels, $1,25(OH)_2D$ levels, and the ratio of tubular maximal reabsorption of phosphate to glomerular filtration rate (TmP/GFR) (Carpenter et al. 2014, Imel et al. 2015)
- Subjects who participated in the previous studies were eligible to enroll in this long-term extension study

OBJECTIVE

To assess the long-term safety and efficacy, including patient-reported outcomes, of KRN23 in adult subjects with XLH

METHODS

Study Design

- Phase 2b, open-label, long-term extension study of KRN23 in adult subjects who had previously participated in study KRN23-INT-001 or KRN23-INT-002
  - 20 of 28 subjects in the original cohort enrolled
    - 3 subjects who participated only in KRN23-INT-001
    - 17 subjects who participated in both KRN23-INT-001 and KRN23-INT-002
  - For all subjects, the last dose of KRN23 received was >12 months before extension study enrollment
  - Some subjects (65%) had resumed oral phosphate and pharmacologic vitamin D therapy in the interim between trials
- Eligibility criteria:
  - Received at least 2 doses of KRN23 during participation in previous study
  - 21-day washout of oral phosphate/pharmacologic vitamin D therapy
  - Estimated glomerular filtration rate (eGFR) ≥60 mL/min
  - Excluded based on severe nephrocalcinosis on renal ultrasound
  - Subjects discontinued from the previous studies due to a treatment-emergent adverse event were eligible, depending on the investigator's judgement
- Subjects received subcutaneous KRN23 every 4 weeks at doses of 0.3, 0.6, or 1.0 mg/kg
  - Starting dose was based on the subject's final dose in the previous studies
  - Dose could be titrated upward (through Week 12) or downward based on serum phosphorus levels
- Pharmacodynamic endpoints
  - Serum phosphorus
  - TmP/GFR
  - Serum $1,25(OH)_2D$
  - Biochemical markers of bone turnover
- Patient-reported outcomes
  - Brief Pain Inventory – Short Form (BPI-SF)
    - Assesses pain severity and interference of pain with daily function
  - Disability – Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index
    - Assesses joint pain, stiffness, and impairment in physical function
- Assessment of physical function
  - Timed Up and Go (TUG) test
    - Time required to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down
  - Six-Minute Walk Test (6MWT)
    - Distance walked in 6 minutes in meters and percent of predicted normal value vs published normative data
- Analysis of Week 24 data is presented

RESULTS

Baseline and Clinical Characteristics

Characteristics	N = 20
Age (years), mean (SD)	49.8 (12.9)
Female, n (%)	14 (70)
BMI (kg/m^2), mean (SD)	36.61 (9.87)
Time since first XLH symptoms (years), mean (SD)*	48 (14)
Time since XLH diagnosis (years), mean (SD)*	41(16)
Baseline serum phosphorus concentration (mg/dL), mean (SD)	1.89 (0.30)

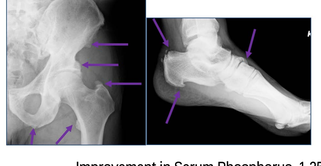
Values as or mean (SD) or n (%), as indicated. SD, standard deviation; XLH, X-linked hypophosphatemia.
One subject had a screening GFR of 58 mL/min and one subject received only one dose of KRN23 in study KRN23-INT-001 because of possible nephrocalcinosis that was subsequently ruled out by CT scan after the subject discontinued KRN23 treatment in that study; the sponsor granted permission to include these subjects in the study.
- N=17 subjects; the date was unknown for 3 subjects in each category

Selected Medical History at Baseline

Condition	N = 20
Selected conditions diagnosed in subjects, n (%)	
Short stature	19 (95)
Bowing of lower legs (shin)	19 (95)
Unusual gait or way of walking/running	17 (85)
Dental abscesses	17 (85)
Calcium deposits on bone and/or bone spurs	17 (85)
Excessive cavities	14 (70)
Bowing of upper legs (femur)	14 (70)
Osteoarthritis	14 (70)
Nephrocalcinosis	4 (20)

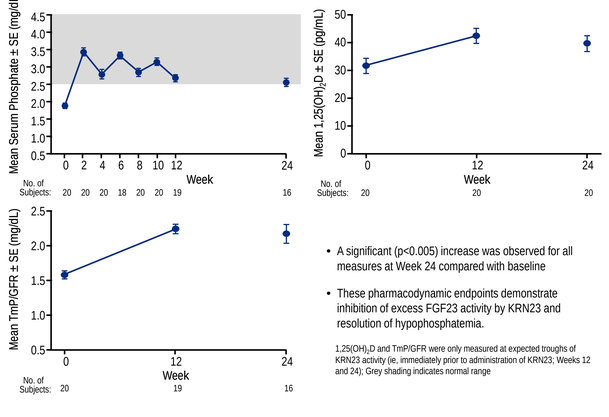
Values are n (%) as indicated.

Enthesopathy Observed at Baseline



Radiographic images from two subjects showing a number of sites of enthesopathy or calcification of tendons near the attachment with the bones (purple arrows)

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



- A significant (p<0.005) increase was observed for all measures at Week 24 compared with baseline
- These pharmacodynamic endpoints demonstrate inhibition of excess FGF23 activity by KRN23 and resolution of hypophosphatemia.

1,25(OH)$_2$D and TmP/GFR were only measured at expected troughs of KRN23 activity (ie, immediately prior to administration of KRN23; Weeks 12 and 24); Grey shading indicates normal range

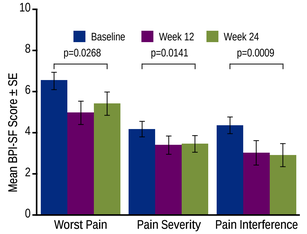
Bone Turnover Markers Increased With Treatment

	Baseline	Week 24	Percent Change from Baseline	P value
ALP (U/L)	131.1 (11.3)	145.8 (13.5)	11.4 (3.8)	0.0080
BALP (mcg/L)	31.3 (4.1)	36.2 (5.4)*	11.8 (6.1)	0.0681
CTx (pg/mL)	732.4 (90.3)	1093.8 (166.1)*	46.9 (11.8)	0.0010
P1NP (ng/mL)	76.5 (9.3)	149.0 (22.9)	102.3 (15.4)	<0.0001

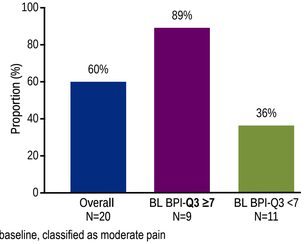
Values are mean (SE). N = 20, except *N = 18. ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase; CTx, carboxy-terminal cross-linked telopeptide of type I collagen; P1NP, procollagen type 1 N-terminal propeptide; SE, standard error

- The significant increase in bone turnover markers, particularly in CTx and P1NP, is consistent with the impact of normalized serum phosphorus to reconstitute skeletal turnover that is necessary to heal osteomalacia (Ros et al. 2005)

Improvement in Brief Pain Inventory Short Form Scores Overall

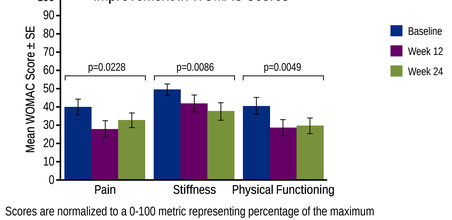


BPI-Q3 Worst Pain Responder Analysis: Proportion of Subjects With ≥2 Point Decrease in Worst Pain at Any Time Point



- 19 of 20 subjects had baseline worst pain scores ≥4 at baseline, classified as moderate pain
- 9 subjects (45.0%) reported worst pain scores ≥7 at baseline, classified as severe pain

Improvement in WOMAC Scores



Scores are normalized to a 0-100 metric representing percentage of the maximum score, where 0 indicates best health and 100 indicates worst.

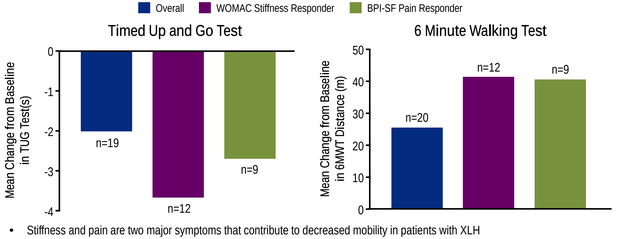
Improvement in Balance and Agility (TUG test) and Walking Ability (6MWT)

Parameter	Baseline	Week 24	Mean Change	P value
Mean TUG test value, seconds (range)	12.8 (6.2-24.9)	11.0 (6.3-18.6)	-2.0	0.04
6MWT				
Mean actual distance walked, meters (range)	322 (80-639)	348 (160-592)	+25	0.05
Mean percentage of predicted distance, % (range)	49 (13-97)	53 (25-90)	+4	0.04

Values as mean (range) as indicated. 6MWT, 6 Minute Walk Test; TUG, Timed Up and Go

- Baseline impairment in TUG was similar to that reported previously for patients with ankylosing spondylitis (Çınar et al. 2016)
- At baseline, nearly all subjects (19/20; 95%) walked <80% of predicted normative values (based on age, gender, and height), indicating impairment in mobility
- Significant improvements in both the time required to complete the TUG test and 6MWT distance walked were observed at Week 24 of KRN23 treatment

Improvements in Stiffness and Pain Were Related to Improvement in Mobility



- Stiffness and pain are two major symptoms that contribute to decreased mobility in patients with XLH
- WOMAC stiffness responders (improvement of ≥ 10 points) and BPI-SF worst pain responders (improvement of ≥2 points) demonstrated greater improvement in the TUG and 6MWT than the overall population
- A change from baseline of -1.4 s on the TUG test represents a clinically important improvement in function (Wright et al. 2011)

Overall Summary of Adverse Events

Event	Events, n	Subjects, n (%)
All adverse events	132	19 (95)
Treatment-related adverse events	30	8 (40)
Serious adverse events	4	4 (20)
Serious adverse events (treatment-related)	0	0 (0)
Adverse events (grades 3 and 4)	4	3 (15)
Adverse events leading to discontinuation	0	0 (0)
Adverse events leading to death	0	0 (0)

- The most common adverse events were arthralgia (30%), nasopharyngitis (25%), back pain (20%), injection site reaction (20%), and pain in extremity (20%)
- The only treatment-related adverse events reported for more than one subject were injection site reaction (3/20; 15%) and arthralgia (2/20; 10%)

SUMMARY

- The substantial burden of disease observed in these subjects highlights the chronicity of XLH in adults and the need for effective, ongoing treatment
- KRN23 treatment for 24 weeks increased serum phosphorus, renal phosphate reabsorption, serum $1,25(OH)_2D$, and markers of bone turnover
- More than half of patients overall and 89% of subjects with severe pain at baseline had a clinically meaningful reduction in worst pain during the study
- Approximately half the subjects had clinically meaningful improvements in stiffness from baseline to Week 24.
- Clinically meaningful improvement in mobility from baseline to Week 24 was also observed, particularly among subjects with the greatest improvement in pain and stiffness.
- KRN23 had an acceptable safety profile, similar to previous studies
- These preliminary data are promising and support the need for continued development of KRN23 for the treatment of XLH in adults

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DISCLOSURES

This study was sponsored and funded by Ultragenyx Pharmaceuticals Inc. in partnership with Kyowa Hakko Kirin Co., Ltd
MR, MP, TW, AP, KI, EI, and TC are investigators for the study; TW, EI, and TC have received research grants and/or travel support from Ultragenyx; AP is an advisory board member for Ultragenyx
DL, AS, MM, and JSM are employees of Ultragenyx
Holly Zoog (Ultragenyx) and Chu Kong Liew (ProScribe) provided medical writing support.