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# Efficacy and Safety of KRN23 in Adults with X-linked Hypophosphatemia

## Data from a Phase 2 Extension Study

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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 *PHEX,* the phosphate-regulating endopeptidase homolog encoded on the X-chromosome[1]
- 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, and pseudofractures. Other features of the disease include joint pain/stiffness, osteoarthritis, enthesopathy, and dental issues
- KRN23 is a fully human monoclonal antibody designed to bind and thereby inhibit FGF23 action
- 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)[2,3]
- Subjects who participated in the previous studies were eligible to enroll in this long-term extension study
- **The objective of this study was to assess the long-term safety and efficacy, including patient-reported outcomes, of KRN23 therapy in adult subjects with XLH**

## CONCLUSIONS

- 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 48 weeks increased serum phosphorus, renal phosphate reabsorption, serum $1,25(OH)_2D$, and markers of bone turnover
- Sustained decreases in symptoms of pain and stiffness and improved physical function as measured by BPI and WOMAC were observed over 48 weeks
- Clinically meaningful improvements in mobility from baseline to Weeks 24 and 48 were 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

## RESULTS

**Table 1. Baseline characteristics**

| | N = 20 |
|---|---|
| Age (years), mean (SD) | 49.8 (12.9) |
| Female, n (%) | 14 (70) |
| Height (cm), mean (SD) | 147.8 (10.6) |
| Weight (kg), mean (SD) | 78.9 (22.7) |
| BMI ($kg/m^2$), mean (SD) | 36.3 (10.2) |
| Time since first XLH symptoms (years), mean (SD)* | 48 (14) |
| Time since XLH diagnosis (years), mean (SD)* | 41 (16) |
| Serum phosphorus (mmol/L), mean (SD) | 0.61 (0.02) |

Values are 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.

**Table 2. Selected baseline medical history**

| Selected conditions diagnosed in subjects | N = 20<br>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) |
| Osteoarthritis | 15 (75) |
| Excessive cavities | 14 (70) |
| Bowing of upper legs (femur) | 14 (70) |
| Nephrocalcinosis | 4 (20) |

Values are n (%) as indicated.

**Figure 1. Enthesopathy in subjects with XLH**

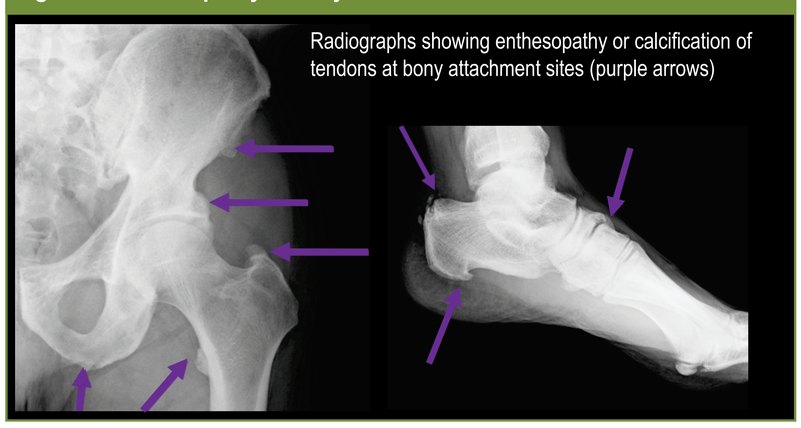
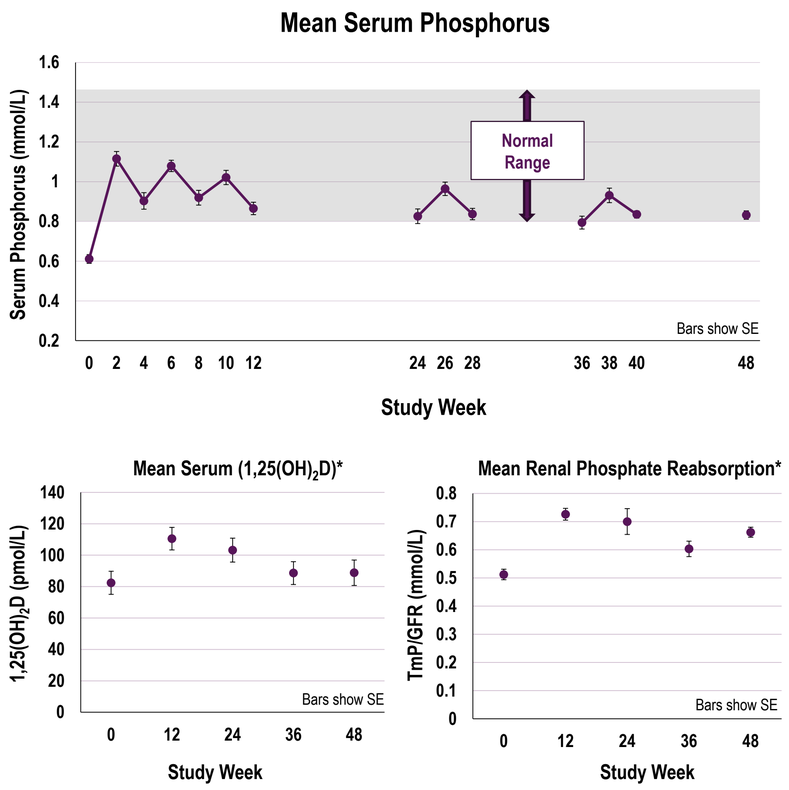


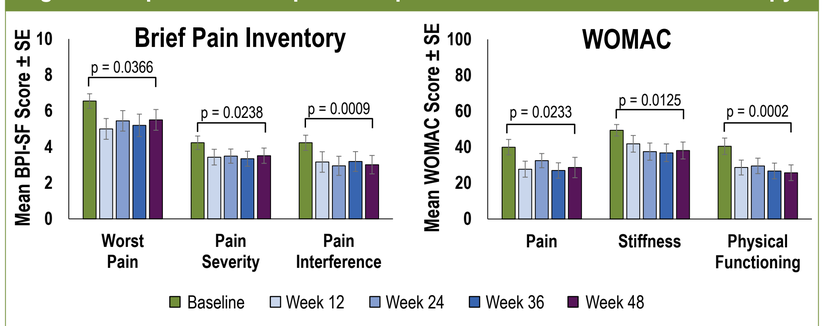

**Figure 2. Improvement in mean serum phosphorus, calcitriol, and TmP/GFR with KRN23 therapy**




* $1,25(OH)_2D$ and TmP/GFR were only measured at expected troughs of KRN23 activity, immediately prior to administration of KRN23.
TmP/GFR, Ratio of Tubular maximum Phosphate reabsorption to Glomerular Filtration Rate.

- Serum phosphorus increased with KRN23 treatment with mean values within the normal range at every post baseline visit (except Week 36) including midpoint and trough measurements
- Serum $1,25(OH)_2D$ and TmP/GFR also increased during the study
- The observed changes reflect the targeted mechanism of action of KRN23 to inhibit FGF23, thereby improving phosphate homeostasis

**Figure 3. Improvement in patient-reported outcomes with KRN23 therapy**



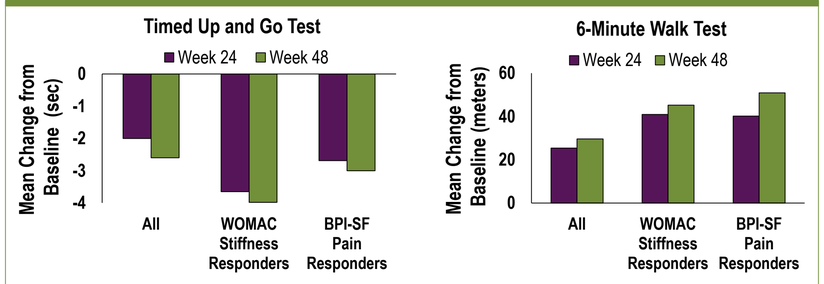

BPI-SF, Brief Pain Inventory – Short Form; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

**Table 4. Improvement in balance, agility, and walking with KRN23 therapy**

| Parameter | Baseline | Week 24 | Mean Change | Week 48 | Mean Change |
|---|---|---|---|---|---|
| Mean Timed Up and Go Test value (sec) | 12.8 | 11.0 | -2.0* | 10.4 | -2.6** |
| 6-Minute Walk Test | | | | | |
| Mean actual distance walked (m) | 322.4 | 347.8 | 25.4* | 352.0 | 29.6 |
| Mean percentage of predicted distance | 48.5 | 52.5 | 4.1* | 53.1 | 4.6* |

* $p < 0.05$; ** $p < 0.0001$.

**Figure 4. Improvement in mobility with reduced pain, stiffness with KRN23**




WOMAC stiffness responders: improvement of ≥10 points; BPI-SF worst pain responders: improvement of ≥2 points.

- Stiffness and pain are major symptoms that contribute to decreased mobility in XLH patients
- WOMAC stiffness responders and BPI-SF worst pain responders demonstrated greater improvement in the TUG and 6MWT than the overall population
- A change from baseline of -1.4 seconds on the TUG test represents a clinically important improvement in function[5]

**Table 3. Markers of bone turnover increased with treatment**

| | Baseline mean (SD) | Week 24 mean (SD) | Week 48 mean (SD) | LS Means Percent Change from Baseline to Week 48 (SE) | p-value* |
|---|---|---|---|---|---|
| CTx (pg/mL) | 732.4 (404.01) | 1093.8 (166.1) | 777.9 (317.11) | +17.6 (7.66) | 0.0214 |
| P1NP (ng/mL) | 76.5 (41.58) | 149.0 (22.9) | 120.9 (50.99) | +72.5 (10.33) | < 0.0001 |

N = 20; CTx, carboxy-terminal cross-linked telopeptide of type I collagen; LS Means, least squares means; P1NP, procollagen type 1 N-terminal propeptide.
*LS Means, SE, and 2-sided p-values calculated from Generalized Estimation Equation (GEE) model.

- The significant increase in bone turnover markers CTx and P1NP with KRN23 therapy is consistent with the impact of normalized serum phosphorus to reconstitute skeletal turnover, needed to heal osteomalacia[4]

**Table 5. Adverse event summary**

| Adverse Events (AE) | Subjects n (%) |
|---|---|
| All AEs | 19 (95) |
| Treatment-related AEs | 9 (45) |
| Serious AEs (SAE) | 6 (30) |
| Serious AEs (treatment-related) | 1 (5) |
| AEs (Grades 3 and 4) | 5 (25) |
| AEs leading to discontinuation | 0 (0) |
| AEs leading to death | 0 (0) |

- The most commonly reported AEs were arthralgia (40.0%), pain in extremity (30.0%), back pain (25.0%), nasopharyngitis (25.0%), fall (20.0%), headache (20.0%), injection site reaction (15.0%), upper respiratory tract infection (15.0%), and vomiting (15.0%)
- 1 subject experienced an SAE of Grade 4 angioedema deemed possibly related to treatment by the investigator
  - This SAE resolved the same day with treatment with diphenhydramine and epinephrine
  - The investigator also considered the event possibly related to concomitant lisinopril
  - Lisinopril was discontinued and KRN23 was continued without further events

## METHODS

- 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
  - 6-Minute Walk Test (6MWT)
    - Distance walked in 6 minutes in meters and percent of predicted normal value vs published normative data
- Analysis of Week 48 data is presented

## REFERENCES AND FINANCIAL DISCLOSURES

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