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**

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### Graphs

- **Females**
- **Males**

- Height (cm)
- Age (years)
Excess FGF23 in the Pathophysiology of XLH

KRN23, a Monoclonal Antibody, Binds and Inhibits FGF23
Pediatric Phase 2 Study Design (UX023-CL201)

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

**Study Design**

- **Biweekly (Q2W) Dose Group**
  - Titration Period: 16 Weeks
  - Treatment Period: 48 Weeks

- **Monthly (Q4W) Dose Group**
  - Titration Period: 16 Weeks
  - Treatment Period: 48 Weeks

- **Extension Study**

**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**

- **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
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

<table>
<thead>
<tr>
<th>Score 1.0</th>
<th>Score 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee X-ray</td>
<td>Knee X-ray</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Worsening</td>
<td>Moderate Worsening</td>
<td>Minimal Worsening</td>
<td>No Change</td>
<td>Minimal Healing</td>
<td>Substantial Healing</td>
<td>Complete or Near Complete Healing</td>
</tr>
</tbody>
</table>
## Baseline Characteristics of the Two Subsets

<table>
<thead>
<tr>
<th></th>
<th>Week 40 Subset</th>
<th></th>
<th>Week 64 Subset</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KRN23 Q2W (N = 26)</td>
<td>KRN23 Q4W (N = 26)</td>
<td>KRN23 Overall (N = 52)</td>
<td>KRN23 Q2W (N = 18)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>8.7 (1.7)</td>
<td>8.3 (2.0)</td>
<td>8.5 (1.9)</td>
<td>8.3 (1.6)</td>
</tr>
<tr>
<td>Male</td>
<td>12 (46%)</td>
<td>12 (46%)</td>
<td>24 (46%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>White</td>
<td>23 (89%)</td>
<td>23 (89%)</td>
<td>46 (89%)</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>31.9 (7.9)</td>
<td>29.1 (10.7)</td>
<td>30.5 (9.4)</td>
<td>30.1 (7.6)</td>
</tr>
<tr>
<td>Height Z score</td>
<td>-1.7 (1.0)</td>
<td>-2.1 (1.0)</td>
<td>-1.9 (1.0)</td>
<td>-1.6 (1.0)</td>
</tr>
<tr>
<td>RSS total score</td>
<td>1.9 (1.2)</td>
<td>1.7 (1.0)</td>
<td>1.8 (1.1)</td>
<td>1.5 (1.1)</td>
</tr>
<tr>
<td>Range</td>
<td>(0, 4.5)</td>
<td>(0, 3.0)</td>
<td>(0, 4.5)</td>
<td>(0, 3.5)</td>
</tr>
<tr>
<td>Received prior oral P / active vitamin D</td>
<td>25 (96%)</td>
<td>24 (92%)</td>
<td>49 (94%)</td>
<td>17 (94%)</td>
</tr>
<tr>
<td>Duration of prior oral P / active vitamin D, yrs</td>
<td>6.7 (2.5)</td>
<td>6.7 (2.7)</td>
<td>6.7 (2.6)</td>
<td>6.9 (1.9)</td>
</tr>
</tbody>
</table>

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)₂D

- 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
Rickets Severity Score (RSS)

Week 40 (N=52)

All Patients

Week 64 (N=36)

Baseline RSS Total Score ≥1.5

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)

**All Patients (N=52)**

- Week 40 (N=52)
  - Mean RGI-C Score: 1.72, 1.41, 1.56
- Week 64 (N=36)
  - Mean RGI-C Score: 2.00, 1.96, 1.85

**Baseline RSS Total Score ≥1.5 (N=34)**

- Week 40 (N=34)
  - Mean RGI-C Score: 2.04, 1.78, 1.91
- Week 64 (N=18)
  - Mean RGI-C Score: 1.85, 1.91

*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.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>40 weeks</th>
<th>64 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSS Total Score</td>
<td>3.5</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>RGI-C Global Score</td>
<td>+2.0</td>
<td>+2.3</td>
<td></td>
</tr>
</tbody>
</table>
Standing Height Z-score Change From Baseline

**All Patients**

- **Week 40 (N=52)**
  - LS Mean Change from Baseline
  - Error bars = SE

- **Week 64 (N=36)**
  - LS Mean Change from Baseline
  - Error bars = SE

**Baseline RSS Total Score ≥1.5**

- **Week 40 (N=36)**
  - LS Mean Change from Baseline
  - Error bars = SE

- **Week 64 (N=36)**
  - LS Mean Change from Baseline
  - Error bars = SE

*Significance levels:
- p < 0.0001
- p < 0.006
- p = 0.01
- p < 0.03
Growth Velocity

Week 40 (N=52)

- **All Patients**
  - Q2W (N=26): 5.45 ± 0.24
  - Q4W (N=26): 5.63 ± 0.35
  - All (N=52): 5.06 ± 0.63

- **Baseline RSS Total Score ≥1.5**
  - Q2W (N=17): 6.41 ± 0.74
  - Q4W (N=17): 5.77 ± 0.87
  - All (N=34): 5.06 ± 0.87

Week 64 (N=36)

- **All Patients**
  - Q2W (N=18): 5.68 ± 0.50
  - Q4W (N=18): 5.70 ± 0.59
  - All (N=36): 5.59 ± 0.87

- **Baseline Week 40**
  - Q2W (N=9): 5.14 ± 0.58
  - Q4W (N=9): 5.47 ± 0.87
  - All (N=18): 5.29 ± 0.87

* 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

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

* 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