A Randomized, Open-label Phase 2 Study of Burosumab (KRN23), an Investigational Fully Human Anti-FGF23 Monoclonal Antibody, in Children with X-linked Hypophosphatemia (XLH)

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Disclosures

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• Drs. Högler, Imel, Boot, Linglart, van’t Hoff, and Portale: travel and/or consulting fees from Ultragenyx Pharmaceuticals Inc.
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XLH Causes Rickets, Skeletal Deformity, and Impaired Growth in Children

Rickets

Bowing of Lower Limbs

Impairment of Growth

XLH, X-linked hypophosphatemia
Excess FGF23 in XLH Pathophysiology


FGF23, Fibroblast growth factor 23; NAPI, sodium/phosphate cotransporter; PHEX, Phosphate Regulating Endopeptidase Homolog, X-Linked.
Burosumab (KRN23), a Monoclonal Antibody, Inhibits Serum FGF23

**Proposed Mechanism of Action of Burosumab, an Investigational Product**

- **PHEX mutation**
- Bone produces FGF23
- Improved mineralization and bone disease expected
- Burosumab Inhibits Serum FGF23
- 1-α hydroxylase
- 1,25(OH)₂D
- Phosphate Absorption
- Phosphate Excretion
- Phosphate Transport
- NaPi-2a/NaPi-2c Cotransporters
- Urine
- Renal Tubule Cell
- α-Klotho
- FGFR
- FGF23
- KRN23
- Serum Phosphate
- Capillary
- Phosphate
Pediatric Phase 2 Study Design (Burosumab-CL201)

**Study Population**
- Children with XLH
- 5-12 years old
- N = 52
- Tanner ≤2

**Study Design**

**SC Burosumab Every 2 Weeks (Q2W) Dose Group**
- Titration Period 16 Weeks
- Treatment Period 48 Weeks

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

**Extension Study**

**Key Endpoints**
- **Pharmacodynamics:** serum phosphorus, TRP, TmP/GFR, and ALP
- **Rickets:** graded by two scoring systems (RGI-C and RSS)
- **Growth velocity**
- **Walking ability:** 6MWT
- **Patient-reported Outcome:** POSNA-PODCI
- **Safety**

- Primary analysis: Week 40 (N = 52)
- Extended analysis: Week 64 (N = 52)
- Pre-specified subgroups based on baseline total rickets severity score ≥ or < 1.5
- Initial doses were 0.1, 0.2, or 0.3 mg/kg Q2W or 0.2, 0.4 or 0.6 mg/kg Q4W

6MWT, 6-minute walk test; POSNA-PODCI, Pediatric Orthopedic Society of North America Patient Outcomes Data Collection Instrument; RGI-C, Radiographic Global Impression of Change; RSS, rickets severity score; SC, subcutaneous; TRP, tubular reabsorption of phosphate
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</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>Severe Worsening</td>
</tr>
<tr>
<td>-2</td>
<td>Moderate Worsening</td>
</tr>
<tr>
<td>-1</td>
<td>Minimal Worsening</td>
</tr>
<tr>
<td>0</td>
<td>No Change</td>
</tr>
<tr>
<td>+1</td>
<td>Minimal Healing</td>
</tr>
<tr>
<td>+2</td>
<td>Substantial Healing</td>
</tr>
<tr>
<td>+3</td>
<td>Complete or Near Complete Healing</td>
</tr>
</tbody>
</table>

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Burosumab Q2W (n = 26)</th>
<th>Burosumab Q4W (n = 26)</th>
<th>Burosumab Overall (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean (SD)</strong></td>
<td>8.7 (1.72)</td>
<td>8.3 (2.04)</td>
<td>8.5 (1.87)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>12 (46.2)</td>
<td>12 (46.2)</td>
<td>24 (46.2)</td>
</tr>
<tr>
<td><strong>White, n (%)</strong></td>
<td>23 (88.5)</td>
<td>23 (88.5)</td>
<td>46 (88.5)</td>
</tr>
<tr>
<td><strong>Weight, kg, median (min, max)</strong></td>
<td>33.05 (17.6, 48.4)</td>
<td>26.15 (14.7, 55.2)</td>
<td>30.50 (14.7, 55.2)</td>
</tr>
<tr>
<td><strong>Height Z score, mean (SD)</strong></td>
<td>-1.72 (1.03)</td>
<td>-2.05 (0.96)</td>
<td>-1.89 (1.00)</td>
</tr>
<tr>
<td><strong>RSS total score, mean (SD) (min, max)</strong></td>
<td>1.92 (1.17) (0.0, 4.5)</td>
<td>1.67 (1.00) (0.0, 3.0)</td>
<td>1.80 (1.09) (0.0, 4.5)</td>
</tr>
<tr>
<td><strong>Received prior oral P / active vitamin D, n (%)</strong></td>
<td>24 (92.3)</td>
<td>26 (100)</td>
<td>50 (96.2)</td>
</tr>
<tr>
<td><strong>Duration of prior oral P / active vitamin D, y, mean</strong></td>
<td>7.02</td>
<td>6.7</td>
<td>6.86</td>
</tr>
</tbody>
</table>

Q2W, every 2 weeks; Q4W, every 4 weeks; P, phosphate; RSS, Thacher Rickets Severity Score; SD, standard deviation
Improvement in Serum Phosphorus, TmP/GFR, and Alkaline Phosphatase

- Mean burosumab doses (SD) at Week 64:
  - **Q2W**:
    - 1.1 (0.5) mg/kg
    - 38.9 (21.9) mg/dose
  - **Q4W**:
    - 1.0 (0.3) mg/kg
    - 32.3 (15.5) mg/dose

- All treatment values were significant compared with baseline
- No hyperphosphatemia in any patient
Rickets Severity Score (RSS)

** p ≤ 0.001 based on the Generalized Estimation Equation for the Week 64 subset
** p < 0.0001 based on the Generalized Estimation Equation for the Week 64 subset; 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 ~10-year-old girl with XLH during burosumab 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 Knee Score</td>
<td>2.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>RGI-C Global Score</td>
<td>+2.3</td>
<td>+2.3</td>
<td>+2.3</td>
</tr>
</tbody>
</table>
Growth Velocity and Standing Height Z-score Change From Baseline

** p ≤ 0.001; * p ≤ 0.01; † p ≤ 0.05 compared with baseline based on one sample t test
## Summary of Safety Measures

<table>
<thead>
<tr>
<th>Patient Incidence, n (%)</th>
<th>Burosumab Q2W (n = 26)</th>
<th>Burosumab Q4W (n = 26)</th>
<th>Burosumab 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>Pain in extremity</td>
<td>9 (35)</td>
<td>12 (46)</td>
<td>21 (40)</td>
</tr>
<tr>
<td>Vitamin D Deficiency</td>
<td>0</td>
<td>3 (12)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (27)</td>
<td>10 (39)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (12)</td>
<td>4 (15)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Any treatment-emergent injection site reaction adverse event</td>
<td>17 (65)</td>
<td>13 (50)</td>
<td>30 (58)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>9 (35)</td>
<td>10 (39)</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>7 (27)</td>
<td>5 (19)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>5 (19)</td>
<td>1 (4)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Injection site rash</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>0</td>
<td>1 (3.8)</td>
<td>1 (1.9)</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>
Summary and Conclusions

• Children with XLH treated with burosumab for up to 64 weeks:
  – Improvement in serum phosphorus, TmP/GFR, and ALP levels
  – 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, with the greatest improvements in patients receiving Q2W dosing
  – At week 64, 77% of all patients with a baseline RSS of ≥1.5 had substantial healing of rickets (RGI-C ≥+2)

• Burosumab improved growth

• Adverse events were predominantly mild to moderate

• No clinically meaningful changes were observed in serum PTH, serum or urine calcium, or renal ultrasounds. Hyperphosphatemia was not observed

• Inhibition of FGF23 by burosumab improved clinical outcomes in children with XLH
Appendix