Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody for X-linked Hypophosphatemia (XLH): Final 64-Week Results of a Randomized, Open-label, Phase 2 Study of 52 Children

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X-Linked Hypophosphatemia (XLH)

- Most prevalent genetic rickets/osteomalacia (~1:25,000)
- Affects all ethnicities
- 1937: Fuller Albright et al, “Vitamin D Resistant Rickets”
- 1958: X-linked inheritance identified
- 1972: Key pathogenic factors:
  - Renal phosphate wasting
  - Inappropriately normal/low circulating 1,25-dihydroxyvitamin D
- 1980: Rx: Phosphate and Calcitriol Supplementation
- 1995: Loss-of-function mutations in PHEX
- 2002: Phosphaturic factor FGF23
Excess FGF23 in XLH Pathophysiology

PHEX mutation → Bone cell produces FGF23 → Burosumab Inhibits Serum FGF23

↓ 1-α hydroxylase / 1,25(OH)2D

↓ Phosphate Absorption

↓ Phosphate Excretion

Defective mineralization and delayed ossification


FGF23, Fibroblast growth factor 23; NAPi, sodium/phosphate cotransporter; PHEX, Phosphate Regulating Endopeptidase Homolog, X-Linked.
Excess FGF23 in XLH Pathophysiology

- PHEX mutation
- Bone cell produces FGF23
- Burosumab Inhibits Serum FGF23

1-α hydroxylase / 1,25(OH)2D

- NaPi-2a / NaPi-2c

Improved skeletal mineralization expected

- Phosphate Absorption
- Serum Phosphorus

Phosphate Excretion


FGF23, Fibroblast growth factor 23; NAPi, sodium/phosphate cotransporter; PHEX, Phosphate Regulating Endopeptidase Homolog, X-Linked.
Objectives

For Children with XLH:

- Identify a dose/dosing regimen for burosumab based on safety and pharmacodynamic (PD) effects

- Assess the clinical effects of burosumab on:
  1) Rickets, growth, and leg deformities
  2) Patient reported outcomes including pain, disability, and quality-of-life

- Safety
Study Design

Study Population

- Children 5-12 years old with XLH
- Tanner \( \leq 2 \)

Study Titration

- Every 4 Weeks (Q4W)
- Every 2 Weeks (Q2W)

Randomization

- 16 Weeks
- 48 Weeks

Extension Study

- 0 16 40 64 Weeks
Key Endpoints

• **Primary:** Rickets Severity Scales
  - RSS, Thacher Rickets Severity Score
  - RGI-C, Radiographic Global Impression of Change

• **Secondary:**
  - Serum phosphorus
  - TmP/GFR, Maximum rate of tubular phosphate reabsorption to the GFR
  - ALP, Alkaline phosphatase
  - Growth: Standing height z-score
  - 6MWT, 6-minute walk test
  - Patient-reported Outcome, POSNA-PODCI Scale
  - Safety
Two Rickets Scoring Systems

Thacher Rickets Severity Score (RSS)
- Range: 0–10 (10 worst)
- Total 10: wrist (0-4) and knee (0-6)
- X-rays read by 1 expert blinded to dose and patient

Radiographic Global Impression of Change (RGI-C)
- 7-point scale describing temporal changes at wrist, knee, and leg
- X-rays read by 3 independent experts blinded to dose and patient

<table>
<thead>
<tr>
<th>Worsening</th>
<th>Improving</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>-2</td>
</tr>
<tr>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>+1</td>
<td>+2</td>
</tr>
<tr>
<td>+3</td>
<td></td>
</tr>
</tbody>
</table>

-3 -2 -1 0 +1 +2 +3
Severe Worsening Moderate Worsening Minimal Worsening No Change Minimal Healing Substantial Healing Complete or Near Complete Healing

Score 1.0 Score 2.0

# Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Burosumab Q2W (n = 26)</th>
<th>Burosumab Q4W (n = 26)</th>
<th>Burosumab Combined (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>8.7 (1.7)</td>
<td>8.3 (2.0)</td>
<td>8.5 (1.9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (46.2)</td>
<td>12 (46.2)</td>
<td>24 (46.2)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>23 (88.5)</td>
<td>23 (88.5)</td>
<td>46 (88.5)</td>
</tr>
<tr>
<td>Weight, kg, median (min, max)</td>
<td>33.1 (17.6, 48.4)</td>
<td>26.2 (14.7, 55.2)</td>
<td>30.5 (14.7, 55.2)</td>
</tr>
<tr>
<td>Height Z score, mean (SD)</td>
<td>-1.72 (1.03)</td>
<td>-2.05 (0.96)</td>
<td>-1.89 (1.00)</td>
</tr>
<tr>
<td>RSS total score, mean (SD)</td>
<td>1.9 (1.2)</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.09)</td>
</tr>
<tr>
<td>(min, max)</td>
<td>(0.0, 4.5)</td>
<td>(0.0, 3.0)</td>
<td>(0.0, 4.5)</td>
</tr>
<tr>
<td>Received prior oral P / active vitamin D, n (%)</td>
<td>24 (92.3)</td>
<td>26 (100)</td>
<td>50 (96.2)</td>
</tr>
<tr>
<td>Duration of prior oral P / active vitamin D, y, mean</td>
<td>7.0</td>
<td>6.7</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Q2W, every 2 weeks; Q4W, every 4 weeks; P, phosphate; RSS, Thacher Rickets Severity Score; SD, standard deviation
**p ≤ 0.0001 based on the Generalized Estimation Equation (GEE) model for the Week 64 subset.

RGI-C Scores: +1.0 = minimal healing; +2.0 = substantial healing; +3.0 = complete or near complete healing.
RSS and RGI-C in the 34 Patients with High Rickets Severity at Baseline (RSS ≥1.5)

**p ≤ 0.0001 based on the Generalized Estimation Equation (GEE) model for the Week 64 subset.**

RGI-C Scores: +1.0 = minimal healing; +2.0 = substantial healing; +3.0 = complete or near complete healing
Change in Rickets During Burosumab Treatment

Improved rickets in a girl with XLH

<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></td>
<td>+2.3</td>
</tr>
</tbody>
</table>
TmP/GFR, Serum Phosphorus, and Serum 1,25(OH)₂D

- All treatment values significantly improved (t-test)
- No hyperphosphatemia in any patient

Mean ± SE. Gray box indicates normal range.
Serum Alkaline Phosphatase

Mean ± SE; Gray box indicates normal range. ***p ≤ 0.0001 **p ≤ 0.001; *p ≤ 0.01; versus baseline (p-values are presented as nominal p-values, no adjustment on multiplicity)
Serum Calcium, iPTH, and Urine Calcium

- For renal ultrasound scores (0 [normal] to 4 [stone formation]), no subject had a change >1 point
- Renal function remained normal
- No evidence of ectopic mineralization of the myocardium

Change from Baseline to Week 64 in Nephrocalcinosis Score

<table>
<thead>
<tr>
<th>Number of Subjects (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Change</td>
</tr>
<tr>
<td>21 Q2W; 21 Q4W</td>
</tr>
<tr>
<td>Decreased: 1→0</td>
</tr>
<tr>
<td>1 Q2W; 1 Q4W</td>
</tr>
<tr>
<td>Increased: 0→1, 1→2, or 2→3</td>
</tr>
<tr>
<td>3 Q2W; 3 Q4W</td>
</tr>
</tbody>
</table>
Standing Height Z-Score

Data expressed as least squares mean ± SE. **p ≤ 0.001; *p ≤ 0.01; †p ≤ 0.05 versus baseline (GEE model; p-values are presented as nominal p-values, no adjustment on multiplicity)
## 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

• In children with XLH, 64 weeks of burosumab treatment:
  – Improved serum phosphorus and TmP/GFR
  – Improved rickets despite previous conventional treatment for a mean of ~7 years
    • Normalized serum ALP
    • Especially in patients with more severe baseline rickets, and for the patients receiving Q2W dosing
  • Adverse events were predominantly mild to moderate and expected for a pediatric population
  • No clinically concerning changes were observed in serum PTH, serum or urine calcium, or renal ultrasonography. No Hyperphosphatemia

With its favorable benefit:risk profile, burosumab holds promise for improvement in the long term outcomes for these boys and girls
Thank you

We thank all clinical investigators, study site personnel, and the patients and their families