Burosumab (KRN23): Effects on Phosphate and Vitamin D Dysregulation in Children < 5 Years Old with X-linked Hypophosphatemia (XLH)

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XLH Causes Rickets, Skeletal Deformity, and Impaired Growth in Children

Bowing of the Lower Limbs

Growth Impairment

- Skeletal deformity and growth impairment begin in early childhood, and some studies suggest earlier initiation of treatment with phosphate and active vitamin D may lead to better height outcomes.
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)_{2}D
- Phosphate Absorption
- Phosphate Excretion
- Serum Phosphate

**Bone produces FGF23**

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

- **NaPi-2a NaPi-2c**
- **Phosphate Transport**
- **Urine**
- **Renal Tubule Cell**
- **Capillary**
- **FGFR**
- **α-KLOTHO**
- **FGF23**
- **KRN23**

**Bone produces FGF23**

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- **FGF23**
- **KRN23**
Pediatric Phase 2 Study Design (Burosumab-CL205)

Population
- N = 13
- Children with XLH
- 1-4 years old
- A RSS at the knee of ≥ 1.5 required in ≥ 5 patients

7-day Wash-out
Vitamin D metabolites/analogs, Oral phosphate

Treatment Period*
Open-Label SC Burosumab
0.8 mg/kg Q2W

Weeks 0 24 40 64

Extension Study

Interim Analysis

Final Analysis

Endpoints
- Pharmacodynamics: serum phosphorus (primary), serum 1,25(OH)₂D, serum alkaline phosphatase
- Rickets and lower extremity skeletal abnormalities (RSS and RGI-C at week 40 and 64)
- Height (cm, height-for-age z-scores, and percentiles)
- Safety

Week 20 biochemistry data and week 24 safety data for all 13 subjects

*Dose was increased to 1.2 mg/kg if serum phosphorus increased by < 0.16 mmol/L (0.5 mg/dL) from baseline or 2 consecutive measurements were below normal range. Only 2 patients had dose increases from 0.8 to 1.2 mg/kg at week 22.

RGI-C, Radiographic Global Impression of Change; RSS, rickets severity score; SC, subcutaneous; TRP, tubular reabsorption of phosphate
# Burosumab-CL205 Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Burosumab Q2W (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>2.94 (1.15)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (69.2)</td>
</tr>
<tr>
<td>White</td>
<td>12 (92.3)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>12.92 (1.82)</td>
</tr>
<tr>
<td>Height Z score</td>
<td>-1.38 (1.19)</td>
</tr>
<tr>
<td>RSS total score</td>
<td>2.92 (1.37)</td>
</tr>
<tr>
<td>Range</td>
<td>(1.0-6.5)</td>
</tr>
<tr>
<td>Received prior oral P / active vitamin D</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Duration of prior oral P / active vitamin D, mos</td>
<td>16.91 (13.90)</td>
</tr>
</tbody>
</table>

Values as mean (SD), median (min-max), or n (%) as indicated.

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Example: Baseline radiographs of 2-year-old male patient from this study

<table>
<thead>
<tr>
<th>RSS</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>1.5</td>
</tr>
<tr>
<td>Wrist</td>
<td>2.0</td>
</tr>
<tr>
<td>Global</td>
<td>3.5</td>
</tr>
</tbody>
</table>

P, phosphate; RSS, Thacher Rickets Severity Score.
Improvement in Serum Phosphorus, 1,25(OH)$_2$D, and ALP

- No hyperphosphatemia in any patient
- For serum phosphorus and 1,25(OH)$_2$D, N = 10-13 based on available samples

*** P<0.0001 based on the Generalized Estimation Equation; Statistical comparisons only conducted for serum phosphorus.
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*Due to missing baseline value, the screening alkaline phosphatase value was used for the baseline value for 1 patient.
## Summary of Safety Measures*

<table>
<thead>
<tr>
<th>Incident (N = 13)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any related treatment-emergent adverse events (AEs)</td>
<td>13 (100)</td>
</tr>
<tr>
<td><strong>AEs of Interest</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Blood parathyroid hormone increased</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Contusion</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Week 24 and including additional safety data through January 6, 2017
Week 40 Rickets Assessment Expected Late 2017

Example **baseline** radiographs in 3-year-old male patient from this study

Example **baseline** radiograph in 3-year-old male patient from this study

Example **week 40** radiographs in same patient

Example **week 40** radiograph in same patient
In children 1-4 years old with XLH, treatment with burosumab for up to 24 weeks improved key pharmacodynamic parameters in XLH consistent with inhibiting FGF23:

- Increased serum phosphorus
- Increased serum 1,25(OH)$_2$D
- Decreased serum alkaline phosphatase

Burosumab had a similar safety profile to previous pediatric trials; adverse events were predominately mild to moderate

- There were no instances of hyperphosphatemia and no clinically meaningful changes observed in serum PTH, serum or urine calcium, hematology, or urine biochemical parameters

Radiographic assessment of rickets will be conducted at week 40 and 64

PTH, Parathyroid hormone.
Improvement in Serum Phosphorus, 1,25(OH)₂D, and ALP

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