Effects of KRN23, an Anti-FGF23 Antibody in Patients With Tumor-Induced Osteomalacia and Epidermal Nevus Syndrome: Results from an Ongoing Phase 2 Study

Thomas Carpenter, MD
Yale University School of Medicine
New Haven, Connecticut, USA

Disclosures

- Dr. Carpenter: grant support and travel fees from Ultragenyx Pharmaceuticals Inc. (Ultragenyx)
- Dr. Miller: Scientific advisory board and research grants from Ultragenyx
- Dr. Weber: PI on 2 clinical trials, travel fees and honoraria from Ultragenyx
- Dr. Peacock: PI on 2 clinical trials sponsored by Ultragenyx
- Dr. Ruppe: PI on 4 clinical trials sponsored by Ultragenyx
- Dr. Insogna: No disclosures
- Dr. Jan de Beur: PI on 2 clinical trials sponsored by Ultragenyx and consultant for Ultragenyx
- Dr. Osei: previous employee of Ultragenyx
- Drs. Luca, Skrinar, and San Martin: employees of Ultragenyx
- This study was sponsored and funded by Ultragenyx in partnership with Kyowa Hakko Kirin Co., Ltd.
- Holly Zoog, PhD (Ultragenyx) and Chu Kong Liew, PhD (ProScribe) provided medical writing support
Background

- Tumor-induced osteomalacia (TIO) and epidermal nevus syndrome (ENS) are rare diseases of excess Fibroblast Growth Factor 23 (FGF23) that are characterized by hypophosphatemia secondary to phosphaturia and impaired active vitamin D synthesis that results in bone pain, osteomalacia, fractures, and muscle weakness.
- TIO is caused by small, slow growing, FGF23- secreting mesenchymal tumors and is cured when the tumor is completely resected.
  - Medical therapy with oral phosphate and calcitriol is indicated when the tumor can not be fully resected or located.
- ENS is characterized by skin lesions often associated with skeletal defects.
Excess of FGF23 Impairs Renal Phosphate Reabsorption

KRN23, a Monoclonal Antibody, Is Designed to Bind and Inhibit FGF23
## Study Design: Phase 2, Open-Label, Single-Arm, Dose-Finding Study

### KRN23 Treatment Period: 48 weeks
- Q4W SC administration (0.3-2.0 mg/kg)
- N=16

### Co-primary endpoints
- Increase in serum phosphorus and improvement in osteomalacia as determined by bone biopsy

### Additional efficacy measures
- Serum 1,25(OH)₂D, TmP/GFR, bone turnover markers
- Whole body bone scans, DXA
- Functional and mobility tests, patient reported outcomes

### Key Inclusion Criteria
- Diagnosis of TIO with unidentified or unresectable tumor; or diagnosis of ENS
- Hypophosphatemia and low TmP/GFR (<2.5 mg/dL)
- FGF23 ≥2x ULN by Kainos assay (later amended to ≥ 100 pg/mL)

### Current Data Summary
- N=8 subjects with Baseline and Week 24 data; N=1 subject with Week 48 bone biopsy
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>KRN23 (N = 8)</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIO</td>
<td>7 (88%)</td>
<td></td>
</tr>
<tr>
<td>ENS</td>
<td>1 (12%)</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>5 (62%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>51.8 (18.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Years since diagnosis</strong></td>
<td>1 - 37</td>
<td></td>
</tr>
<tr>
<td><strong>Received prior treatment with phosphate and/or active vitamin D</strong></td>
<td>8 (100%)</td>
<td></td>
</tr>
<tr>
<td><em><em>Tumor located (TIO only</em>)</em>*</td>
<td>4 (57%)</td>
<td></td>
</tr>
<tr>
<td><strong>Serum phosphorus, mg/dL</strong></td>
<td>1.69 (0.57)</td>
<td>2.5 - 4.5</td>
</tr>
<tr>
<td><strong>TmP/GFR, mg/dL</strong></td>
<td>1.39 (0.67)</td>
<td>2.5 - 4.5</td>
</tr>
<tr>
<td><strong>Serum iPTH, pg/mL</strong></td>
<td>84.6 (47, 198)</td>
<td>10 - 65</td>
</tr>
<tr>
<td><strong>Serum FGF23, mg/dL</strong></td>
<td>288.5 (94, 2569)</td>
<td></td>
</tr>
</tbody>
</table>

Values presented as mean (SD), median (min, max), range, or n (%) as indicated. SD, standard deviation
*N=7
Pharmacodynamics

Serum Phosphorus

TmP/GFR

Serum 1,25(OH)₂D

iPTH
Bone Mineral Density and Bone Turnover Markers

BMD at Week 24 Increased in Most Subjects

BMD% Change from Baseline

Subject

2.3 3.0 2.9 4.1 1.3 6.0 11.0 3.6 1.2

Lumbar Spine Total Hip

Bone Turnover Markers Increased

P1NP

CTX-I
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Patient incidence (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events (AEs)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>AEs of interest</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Restless leg syndrome</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1 (12.5%)</td>
</tr>
</tbody>
</table>

- SAE of neoplasm progression occurred in 1 non-responder subject: 68-year-old female with TIO Metastatic Spindle Sarcoma since 2002 and lower left limb amputation/multiple surgeries to remove metastatic lesions
  - No increase in serum phosphorus after dose escalation to 1.4 mg/kg Q4
  - Chemotherapy is planned
  - Due to lack of response and progression of underlying disease requiring more aggressive treatment, the PI and Sponsor agreed to discontinue the subject from the study
Case 1: 33-year-old male with TIO; 18 years since diagnosis

At Week 24:
- Tc99 bone scan consistent with resolution of 4 rib/tibia fractures
- BMD (lumbar spine and total hip) increased by 2% and 3% respectively

<table>
<thead>
<tr>
<th>Bone biopsy indices</th>
<th>Baseline</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoid thickness (µm)</td>
<td>16.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Osteoid/bone surface (%)</td>
<td>94</td>
<td>75</td>
</tr>
<tr>
<td>Osteoid/bone volume (%)</td>
<td>21</td>
<td>10.3</td>
</tr>
<tr>
<td>Mineralization lag time (days)</td>
<td>Unquantifiable</td>
<td>329.2</td>
</tr>
<tr>
<td>Mineralizing surface (%)</td>
<td>1.9</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Conclusion
- Severe osteomalacia
- Mild osteomalacia
Summary and Conclusions

- In patients with TIO or ENS, KRN23 improved mean serum phosphorus, $1,25(\text{OH})_2\text{D}$, and TmP/GFR over 24 weeks of treatment.
- KRN23 improved bone mineralization as demonstrated by the first bone biopsy results.
- The increases in BMD and bone turnover markers over 24 weeks provide additional clinical evidence of an improvement in skeletal health.
- Treatment-related adverse events were mild in severity.
- These data suggest KRN23 has the potential to reverse hypophosphatemia and provide clinical benefit to patients with TIO and ENS.
Baseline
48 weeks