Burosumab (KRN23) for X-Linked Hypophosphatemia* (XLH)

Phase 3 fully human monoclonal antibody against FGF23 (SC injection)

*Also known as X-linked hypophosphatemic rickets or vitamin D-resistant rickets
**XLH:** Excess FGF23\(^1\) causes excess renal phosphate loss

**Key symptoms:** Rickets, deformity, short stature, fractures, pain, osteomalacia, stiffness

**Standard of care:** Oral phosphate + Vitamin D (nephrocalcinosis risk)

**US prevalence:** ~12,000

**Key Programs:**
- Phase 2 study in 5-12 yr olds
- Phase 2 study in 1-4 yr olds
- Pediatric Phase 3 study
- Placebo-controlled adult Phase 3 study
- Adult open label bone quality study

\(^1\)Fibroblast growth factor 23
Key Clinical Programs
### STUDY DESIGN

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
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<th>52</th>
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<td>Final Efficacy and Safety Analysis</td>
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* N = 52 patients, ages 5-12 years

### KEY EFFICACY ENDPOINTS

- **Rickets** comparing baseline to Week 40 using two scoring systems*
- **Functional PROs** using POSNA/PODCI** comparing baseline to Weeks 24, 40, and 64
- **6MWT** comparing baseline to Weeks 24, 40, and 64
- **Growth velocity** comparing 2 yrs prior to study entry to Week 64

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*Thacher Rickets Severity Scoring System (RSS) and Radiographic Global Impression of Change (RGI-C)
**POSNA/PODCI: Pediatric Orthopedic Society North America/Pediatric Outcome Data Collection Instrument
Rickets Significantly Improved by Two Measures
Substantial healing in patients with RSS ≥1.5 and dosed biweekly

**RSS ALL PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>Q2W (N=26)</th>
<th>All (N=52)</th>
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<tbody>
<tr>
<td>Mean RSS Total Score</td>
<td>1.92</td>
<td>1.80</td>
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<tr>
<td>Baseline</td>
<td>1.92</td>
<td>1.80</td>
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<tr>
<td>Week 40</td>
<td>0.75</td>
<td>0.90</td>
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<td>Week 64</td>
<td>0.81</td>
<td>0.88</td>
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**Mean values ± SE; p ≤ 0.0001**

**RSS BASELINE RSS ≥1.5**

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<tr>
<td>Mean RSS Total Score</td>
<td>2.62</td>
<td>2.46</td>
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<tr>
<td>Baseline</td>
<td>2.62</td>
<td>2.46</td>
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<tr>
<td>Week 40</td>
<td>0.76</td>
<td>0.97</td>
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<td>Week 64</td>
<td>1.00</td>
<td>1.01</td>
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**RGI-C ALL PATIENTS**

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<th>Q2W (N=26)</th>
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<tbody>
<tr>
<td>Mean Change in RGI-C Score</td>
<td>1.72</td>
<td>1.56</td>
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<tr>
<td>Baseline</td>
<td>1.72</td>
<td>1.56</td>
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<tr>
<td>Week 40</td>
<td>1.62</td>
<td>1.57</td>
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**RGI-C BASELINE RSS ≥1.5**

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<th>Q2W (N=17)</th>
<th>All (N=34)</th>
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<td>Mean Change in RGI-C Score</td>
<td>2.04</td>
<td>1.91</td>
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<tr>
<td>Baseline</td>
<td>2.04</td>
<td>1.91</td>
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<tr>
<td>Week 40</td>
<td>2.08</td>
<td>1.98</td>
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</table>

**Mean values ± SE; p ≤ 0.0001**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 40</th>
<th>Week 64</th>
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<tbody>
<tr>
<td>Purple</td>
<td>Purple</td>
<td>Purple</td>
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<tr>
<td>Green</td>
<td>Green</td>
<td>Green</td>
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<tr>
<td>White</td>
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Statistically Significant Improvements in Growth

### Standing Height Z-score

**ALL PATIENTS**

- **Week 0:** Baseline
- **Week 64:** Change from Baseline

**BASELINE RSS ≥1.5**

- **Week 0:** Baseline
- **Week 64:** Change from Baseline

### Growth velocity

- **All patients (n=52):** +0.55 cm/year (p=0.0376)
- **Biweekly dosed patients (n=26):** +0.73 cm/year (p=0.0160)
- **Baseline RSS ≥1.5:** +0.86 cm/year (p=0.0175)
- **Baseline RSS ≥1.5 and dosed bi-weekly (n=17):** +1.11 cm/year (p=0.0076)
Safety Profile

- Most common treatment-related adverse event was injection-site reaction (65% of patients); all considered mild
- One patient with serious adverse event considered possibly treatment-related
  - Resolved without sequelae and the patient continues in the study
- No deaths or treatment discontinuations
- No patients at any time point with a serum phosphorus above upper limit of normal
- No safety concerns associated with intact parathyroid hormone levels, serum or urinary calcium levels, or renal ultrasound
Phase 3 Adult XLH Study Design

**STUDY DESIGN**

- Adults 18-65 years with XLH; Serum P < 2.5 mg/dL; Measurable bone/joint pain (BPI)
- Randomized, double-blind, placebo-controlled study
  - N = 134
  - Monthly dosing

**EFFICACY ENDPOINTS**

**Primary Endpoint**
- Serum phosphorus levels (Proportion above lower limit of normal; 2.5mg/dL)

**Key Secondary Endpoints**
- Pain (BPI Q3)
- Stiffness (WOMAC)
- Physical functioning (WOMAC)
Significant Improvement in Serum Phosphorus Levels

Normal levels achieved in 94% burosumab patients vs. 8% placebo (p<0.001)

PEAK SERUM PHOSPHORUS FROM BASELINE

![Graph showing serum phosphorus levels over weeks for placebo and burosumab groups.]
Clinical Improvement in Patients
Key Secondary Endpoint Data

- Statistically significant improvement in stiffness

STIFFNESS SCORE (WOMAC)
CHANGE FROM BASELINE

- Nominally significant improvement in physical function; strong trend in pain
Substantial Increase in Bone Formation/Turnover Biomarkers

**BONE FORMATION**
SERUM PROCOLLAGEN TYPE 1 N-TERMINAL PROPEPTIDE (P1NP)

**BONE RESORPTION/TURNOVER**
SERUM COLLAGEN TYPE 1 CROSS-LINKED TEOPEPTIDE (CTx)
Increased Healing of Fractures with Burosumab
Odds ratio of complete healing 7.76 (p=0.0004)

Fractures identified at baseline – followed at week 12 and week 24
Subset of patients with fractures at baseline have even greater improvement in stiffness and physical functioning on burosumab

PERCENTAGE OF TOTAL FRACTURES COMPLETELY HEALED
(ACTIVE FRACTURES AND PSEUDO-FRACTURES)

Post-hoc analysis
Odds ratio for Burosumab vs Placebo of Active Fracture/Pseudofracture healed at week 24: 7.76 (p=0.0004)
Safety Consistent with Other Burosumab Studies
Much lower rate of Injection Site Reactions at 12%

- No difference in overall frequency of treatment emergent adverse events, treatment related adverse events and serious adverse events between treatment groups
- 2 SAEs in each treatment groups, none treatment-related
- The same rate of Injection site reactions (12%) in BOTH burosumab and placebo treated arms
  - No hypersensitivity reactions to injections
- No differences between groups in serum intact parathyroid levels or ectopic mineralization
- 1 treatment discontinuation in burosumab arm due to consent withdrawal; no deaths
Bone Biopsy Study: Burosumab Improves Osteomalacia in Adults

- Open-label study in adults to evaluate the effects of monthly brosumab (1 mg/kg) on bone quality and osteomalacia associated with XLH

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Baseline</th>
<th>Week 48</th>
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<tbody>
<tr>
<td>% Osteoid volume/bone volume</td>
<td>Osteomalacia Rating</td>
<td>% Osteoid volume/bone volume</td>
</tr>
<tr>
<td>24%</td>
<td>Severe</td>
<td>9%</td>
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<table>
<thead>
<tr>
<th>Patient #2</th>
<th>Baseline</th>
<th>Week 48</th>
</tr>
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<tbody>
<tr>
<td>% Osteoid volume/bone volume</td>
<td>Osteomalacia Rating</td>
<td>% Osteoid volume/bone volume</td>
</tr>
<tr>
<td>29%</td>
<td>Severe</td>
<td>7%</td>
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</table>

- Severe osteomalacia confirmed at baseline in a majority of the 11 patients
  - Mean osteoid volume/bone volume of 26% at baseline vs. normal range of 0.3%-3.1%
Phase 2 Study in One to Four Year Olds

- Open label Phase 2 study (n=13)
- 12/13 patients had previously been on oral phosphate/active Vitamin D therapy
- Patients received 0.8 mg/kg starting dose and have completed 40 weeks of treatment
Early Treatment Key in Treating Bone Disease
Bowing Improvement and Substantial Healing of Rickets

- Mean serum phosphorus levels increased and maintained in low normal range; 77% patients achieved normal levels at week 40

- Significant improvements in rickets, bowing
  - 59% reduction in mean total RSS score (p<0.0001)
  - RGI-C score > 2 (substantial healing) in all patients (p<0.0001)
  - Significant improvement in bowing (p<0.0001)

- Safety consistent with other burosumab studies
  - 1 SAE that was not treatment-related; 1 unrelated Grade 3 food allergy; other events mild or moderate
  - 3 patients w/ injection site reactions; 4 w/ unrelated mild hypersensitivity events
Pre-Launch Activities in U.S.
US XLH Prevalence Assumptions Overview

New claims data analysis support ~12,000 patient estimate

Company estimate of living XLH in US

• 1:25,000 (~12,000)*

Published prevalence of XLH

• 1:20,000 (~16,000)
  • Sources: Danish¹ & Japanese² publications

Additional verification of estimate

• Estimates of diagnosed patients via claims data
  (ICD10, ICD9 codes):
    • Hypophosphatemia, plus Phosphate/Vit D Rx
    • 10-15% adjustment first Dx in family patients

Estimate ~11,500-15,000 prevalent patients

* Source: Ultragenyx.com estimate from 1:20,000 in prevalent population (16,000) minus some assumption for earlier death (12,000 net).
Commercial Philosophy Tailored to Rare Diseases

- Singular **focus on rare diseases**
- Bridges gap between **scientific excellence** and **patient access**
- **Integrated**, compliant, medical and commercial **operations**
  - Deep experience in rare disease commercialization & **customer focus**
  - Highly **qualified medical field teams**

- Holistic response to patients:
  - **Identify & diagnose** patients in need
  - Enable physicians to **better support patients**
  - Ensure eligible patients get the treatments they need – **tailored reimbursement and support**
Patient Identification and Disease Education Underway

Patient Care Continuum

1. **Find**
   - Identify patients with disease—starting before launch and across programs
   - **Patient Diagnostic Liaisons**

2. **Expand**
   - Expand the diagnosis and treating universe beyond the specialized centers
   - **MSLs**

3. **Start**
   - Ensure access to all eligible patients
   - **Commercial Field Force**

4. **Stay**
   - Keep patients on treatment to maximize likelihood of success
   - **Commercial Field Force**

More critical in rare diseases than in established markets
Complete In-House Support Service
For Customized Ongoing Care to Patients

Ultragenyx Patient Services Touch Points with Patients

- Referral Receipt
- Welcome Call
- Benefit Investigation
- Prior Authorization/Appeal
- Site of care coordination
- Financial Assistance
- Product Procurement
- Administration Confirmation
- Persistency & Follow Up
Prepared for Launch

- Compelling data across pediatric and adult patient populations
- BLA accepted and priority review designation granted
  - PDUFA date: April 17, 2018
- Pre-launch activities underway and ready for commercialization
  - U.S.- commercial structure established and patient identification/disease education efforts underway
  - Latin America- key functions in place and ready to leverage FDA/EMA reference approvals