P063

Effects of Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody, on Functional Outcomes in Children With X-Linked Hypophosphatemia (XLH): Results From a Randomized, Open-label Phase 2 Study

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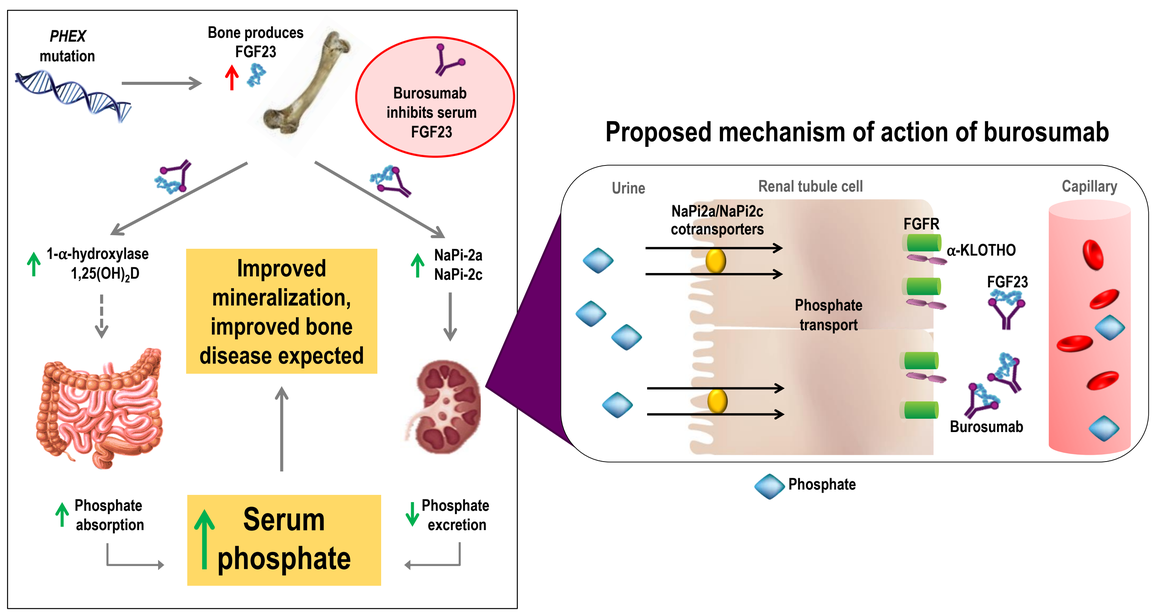
INTRODUCTION

- X-linked hypophosphatemia (XLH) is a rare, lifelong, debilitating, and deformative bone disease mediated by high circulating fibroblast growth factor-23 (FGF23)[1,2]
- The resulting skeletal abnormalities, including rickets and bowing of the legs, can significantly impair gross motor function and quality of life in childhood or adulthood
- One of the objectives of this study was to assess the effect of burosumab on functional outcomes in children with XLH
  - Burosumab is an investigational fully human immunoglobulin G1 monoclonal antibody designed to specifically bind to and inhibit FGF23 (**Figure 1**)

Figure 1. Burosumab Is Designed to Inhibit FGF23

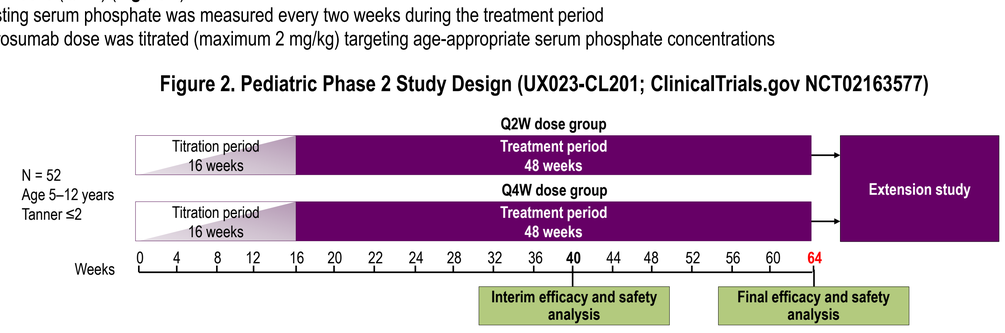


Razzaque MS. *Nat Rev Endocrinol.* 2009;5:611-9. Martin A, et al. *Physiol Rev.* 2012;92:131-55.

METHODS

- In this Phase 2 study, 52 XLH children (age 5–12 years, Tanner ≤2) were randomized to receive burosumab subcutaneously every two weeks (Q2W) or every four weeks (Q4W) (**Figure 2**)
- Fasting serum phosphate was measured every two weeks during the treatment period
- Burosumab dose was titrated (maximum 2 mg/kg) targeting age-appropriate serum phosphate concentrations

Figure 2. Pediatric Phase 2 Study Design (UX023-CL201; ClinicalTrials.gov NCT02163577)

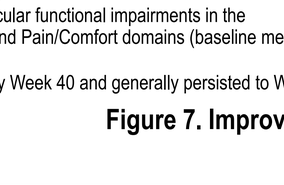


- Key endpoints:
  - Rickets: Total Thacher Rickets Severity Score (RSS)[3] and Radiographic Global Impression of Change (RGI-C) (**Figure 3**)
  - Pharmacodynamics
  - Safety
- Endpoints evaluated in this presentation:
  - 6-Minute Walk Test (6MWT): Distance walked in 6 minutes, corrected for age, height, sex, and weight
  - Pediatric Orthopedic Society of North America-Pediatric Outcome Data Collection Instrument (POSNA-PODCI): Assesses functional health outcomes in children with musculoskeletal conditions
    - Scores are normalized to a mean of 50 and a SD of 10
- Data was analysed by prespecified subgroups based on baseline:
  - RSS
    - High RSS was defined as total RSS ≥1.5
    - Low RSS was defined as total RSS <1.5
  - POSNA-PODCI
    - Substantial functional impairment was defined as Global Functioning score <40
  - 6MWT
    - Walking impairment was defined as distance <80% predicted for age

Figure 3. Two Rickets Scoring Systems Utilized

A **RSS**

- Total 0–10: wrist (0–4) plus knee (0–6)
- Read centrally by an expert blinded to dose and patient



B **RGI-C**

- 7-point scale describing *changes* at wrist, knee, and leg during treatment
- X-rays read by 3 independent experts blinded to dose

-3	-2	-1	0	+1	+2	+3
Severe worsening	Moderate worsening	Minimal worsening	No change	Minimal healing	Substantial healing	Complete or near complete healing

RESULTS

Table 1. Baseline Characteristics

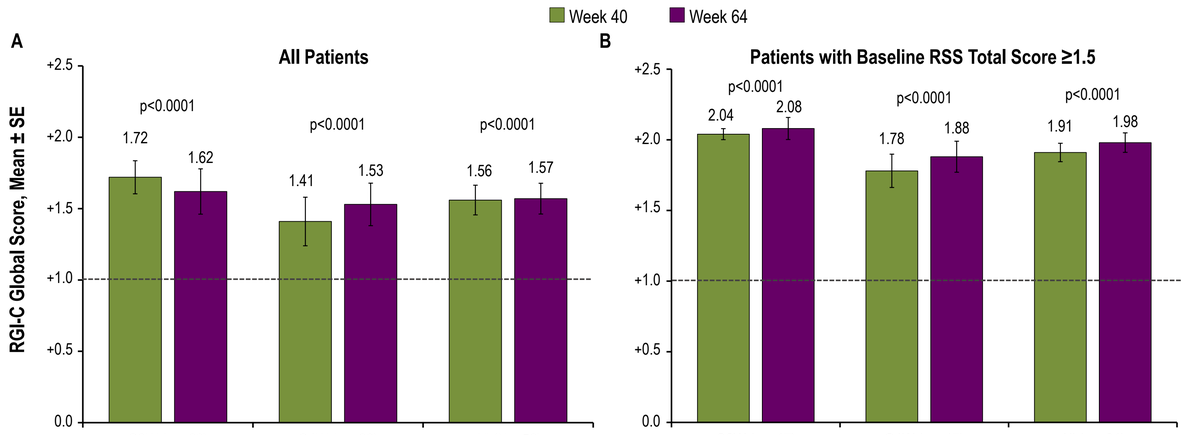
	Burosumab Q2W n = 26	Burosumab Q4W n = 26	Burosumab Overall N = 52
Mean (SD) age, y	8.7 (1.72)	8.3 (2.04)	8.5 (1.87)
Male, n (%)	12 (46.2)	12 (46.2)	24 (46.2)
White, n (%)	23 (88.5)	23 (88.5)	46 (88.5)
Median (min, max) weight, kg	33.05 (17.6, 48.4)	26.15 (14.7, 55.2)	30.50 (14.7, 55.2)
Mean (SD) standing height *z* score	-1.72 (1.03)	-2.05 (0.96)	-1.89 (1.00)
Mean (SD) RSS total score Range	1.92 (1.17) 0.0–4.5	1.67 (1.00) 0.0–3.0	1.80 (1.09) 0.0–4.5
Received prior oral P/active vitamin D, n (%)	24 (92.3)	26 (100)	50 (96.2)
Duration of prior oral P/active vitamin D, y	7.02	6.7	6.86

max, maximum; min, minimum; P, phosphate; RSS, Rickets Severity Score; SD, standard deviation.

Rickets

- Burosumab significantly improved serum phosphorus with either dose regimen (data not shown; presented in OC26 Padidela R et al. ICCBH 2017)
- Burosumab significantly improved rickets at Week 40 and 64 (**Figure 4**)
- At baseline, 34 patients had high RSS (total RSS ≥1.5) and 18 patients had low RSS (total RSS <1.5)
- Patients in the Q2W group with baseline high RSS (total RSS ≥1.5) had substantial healing of rickets (RGI-C score of +2.0) after 40 weeks of burosumab

Figure 4. Improvement in Rickets at Weeks 40 and 64



p value is based on 1-sample *t* test.

RGI-C scores: +1.0 = minimal healing (grey dotted line); +2.0 = substantial healing; +3.0 = complete or near complete healing of rickets.

Six Minute Walk Test (6MWT)

- At baseline, 24 of the 52 patients (46%) had walking impairment (6MWT distance <80% predicted for age)
  - 20 of the 24 patients had high RSS (total RSS ≥1.5) at baseline
- At Week 64 (**Figures 5** and **6**):
  - There was significant improvement from baseline at weeks 16, 24, 40, and 64 in patients with impaired walking ability at baseline treated with burosumab Q2W (p<0.0001 for all weeks)
  - At week 64, the percent predicted 6MWT improved by:
    - 4.5% in all burosumab treated patients (<0.0001)
    - 10.4% in patients with walking impairment at baseline (<0.0001)
  - Similar improvements occurred between the Q2W and Q4W groups

Figure 5. 6MWT in Patients with Impaired Walking Ability at Baseline (<80% Predicted)

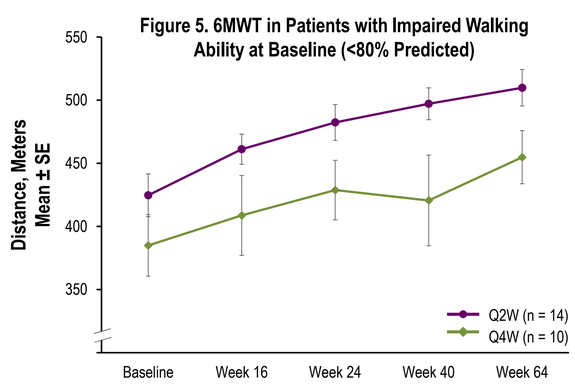
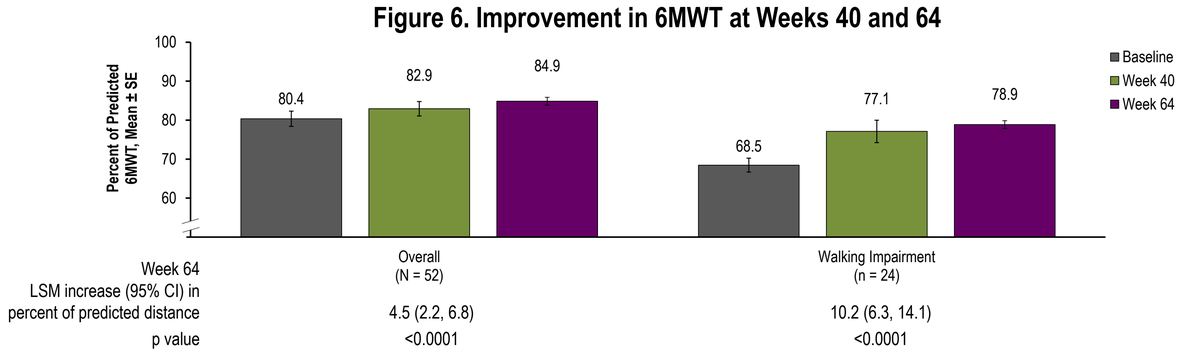


Figure 6. Improvement in 6MWT at Weeks 40 and 64

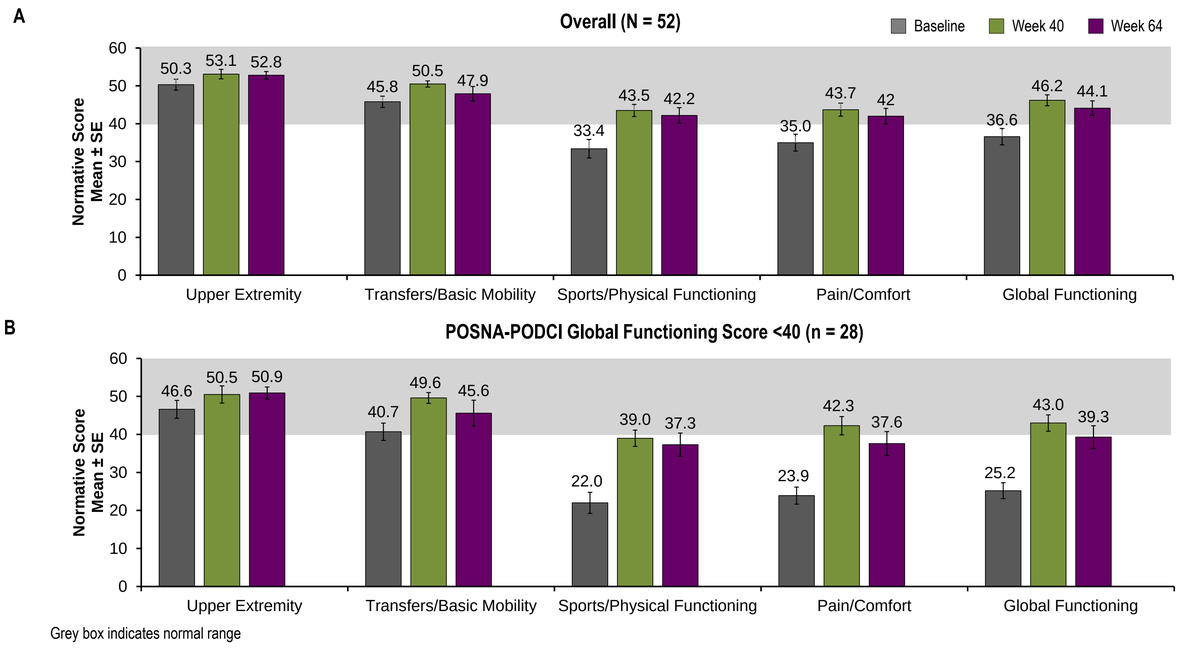


LSM, least squares mean using the Generalized Estimating Equation

POSNA-PODCI

- At baseline, 28 of the 51 (55%) evaluable patients had substantial functional impairment (POSNA-PODCI Global Functioning score <40) (**Figure 7**)
  - 23 of the 28 patients had high RSS (total RSS ≥1.5) at baseline
  - 5 of the 28 patients had low RSS (total RSS <1.5) at baseline
- The mean baseline POSNA-PODCI Global Functioning score among those with functional impairment at baseline was 25.2, or >2 SDs below the normal mean of 50 (1 SD = 10 points)
- Patients' scores showed particular functional impairments in the Sports/Physical Functioning and Pain/Comfort domains (baseline means of 22.0 and 23.9, respectively)
- Improvements were evident by Week 40 and generally persisted to Week 64
- At Week 64:
  - In all patients, the LSM score increased 7.37 (p<0.0001), 8.79 (p<0.0001), and 6.67 (p<0.001) for Global Functioning, the Sports/Physical Functioning domain, and the Pain/Comfort domain, respectively
  - Patients with functional impairment (Global Functioning Score <40) had LSM score increases of 14.1, 15.6, and 13.4 for Global Functioning, the Sports/Physical Functioning domain, and the Pain/Comfort domain, respectively (p<0.0001 for all 3 domains)

Figure 7. Improvement in POSNA-PODCI



Grey box indicates normal range

Safety

- Overall, burosumab demonstrated an acceptable safety profile (presented in OC26 Padidela R et al. ICCBH 2017)
  - Overall, 58% of subjects experienced treatment-emergent injection site reaction adverse events, including injection site reaction (37%), injection site erythema (23%), injection site swelling (12%), and injection site rash (8%)
  - There were no deaths or discontinuations

CONCLUSIONS

- At baseline, children with XLH presented with significant residual rickets, pain, and impairments in walking ability and function despite prior standard of care treatment with oral phosphate and active vitamin D for a mean of 6.9 years
- In children with XLH, burosumab demonstrated an acceptable safety profile and:
  - Increased serum phosphorus and decreased serum alkaline phosphatase (data not shown; presented in OC26 Padidela R et al. ICCBH 2017)
  - Improved rickets
  - Improved walking ability, especially in those with significant walking impairment at baseline
  - Improved health-related quality of life in pediatric XLH, shifting the overall mean POSNA-PODCI score into the normal range

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DISCLOSURES

- EI, AL, AB, WH, AvH, and AP: travel and/or consulting fees from Ultragenyx Pharmaceutical, Inc.
- TC: grant support, travel fees, and consulting fees from Ultragenyx Pharmaceutical, Inc.
- RP: consulting fees from Ultragenyx and/ Alexion Pharmaceuticals, Inc.
- MW: research grant support, honoraria, and travel from Ultragenyx and/or Alexion Pharmaceuticals, Inc
- MM, AS, JSM: employees of Ultragenyx Pharmaceutical, Inc.
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