FR0331 / SA0331

Effects of Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody, on Functional Outcomes in Children with X-linked Hypophosphatemia (XLH): Final Results from a Randomized, 64-week, Open-label Phase 2 Study

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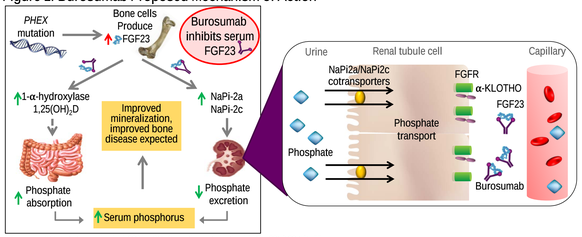
INTRODUCTION

- X-linked hypophosphatemia (XLH) is a rare, lifelong, debilitating, and deformative bone disease mediated by high levels of circulating fibroblast growth factor-23 (FGF23)[1,2]
- XLH-associated skeletal abnormalities, including rickets and bowing of the legs, can significantly impair gross motor function and quality of life in childhood or adulthood
- Burosumab is an investigational fully human immunoglobulin G1 monoclonal antibody that binds FGF23 and inhibits its activity (Figure 1)

Figure 1. Burosumab Proposed Mechanism of Action



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METHODS

- In UX023-CL201 (NCT02163577), 52 children with XLH (age 5–12 years, Tanner ≤2) were randomized to receive burosumab subcutaneously (SC) every two weeks (Q2W) or every four weeks (Q4W) (Figure 2)
- Fasting serum phosphorus was measured every two weeks during the treatment period
- Burosumab dose was titrated (maximum 2 mg/kg) targeting age-appropriate serum phosphorus concentrations
- Key endpoints:
  - Rickets: Total Thacher Rickets Severity Score (RSS)[3] and Radiographic Global Impression of Change (RGI-C) (Figure 3)
  - Pharmacodynamics
  - Safety

Figure 2. UX023-CL201, Pediatric, Phase 2 Study Design

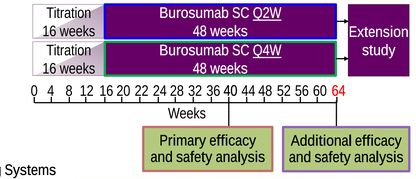
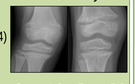


Figure 3. Two Rickets Scoring Systems

RSS
- Range: 0–10 (increasing with severity)
- Total 0–10: wrist (0–4) plus knee (0–6)
- Read centrally by an expert blinded to treatment

Knee X-ray



Score 1.0 Score 2.0

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

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

- Functional endpoints:
  - 6-Minute Walk Test (6MWT): Meters walked in 6 minutes; percent predicted distance is adjusted for age, height, and sex[4]
  - Pediatric Orthopedic Society of North America-Pediatric Outcome Data Collection Instrument (POSNA-PODCI): Assesses functional health outcomes in children with musculoskeletal conditions
    - Mean ± SD score for healthy reference population is 50 ± 10
- Data was analysed by prespecified subgroups:
  - High RSS: baseline Total RSS ≥1.5
  - Low RSS: baseline Total RSS <1.5
  - Substantial functional impairment: baseline Global Functioning score <40
  - Walking impairment: baseline 6MWT <80% predicted norm for age, sex, and height[4]

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RESULTS

Table 1. Baseline Characteristics

Characteristic	Q2W n = 26	Q4W n = 26	Overall N = 52
Mean (SD) age, y	8.7 (1.7)	8.3 (2.0)	8.5 (1.9)
Male, n (%)	12 (46)	12 (46)	24 (46)
White, n (%)	23 (89)	23 (89)	46 (89)
Weight, kg, median (min, max)	33.1 (17.6, 48.4)	26.2 (14.7, 55.2)	30.5 (14.7, 55.2)
Mean (SD) standing height z score	-1.7 (1.0)	-2.1 (1.0)	-1.9 (1.0)
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)	26 (100)	50 (96)
Duration of prior oral P/active vitamin D, y	7.0	6.7	6.9

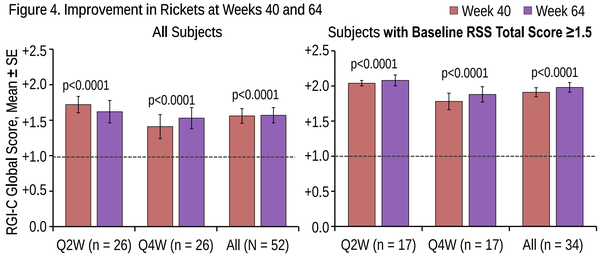
Max, maximum; Min, minimum; P, phosphorus; RSS, Rickets Severity Score; SD, standard deviation; Y, years.

- Burosumab significantly improved serum phosphorus with either dose regimen (data not shown; presented in ASBMR Oral 1154 Whyte et al. Sept 11, 2017, 9:45am)

Rickets

- Burosumab significantly improved rickets at Weeks 40 and 64 (Figure 4)
- At baseline, 34 subjects had high RSS and 18 subjects had low RSS
- Subjects in the Q2W group with high RSS at baseline 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 subjects (46%) had walking impairment
  - 20 of the 24 subjects had high RSS at baseline
- At Week 64 (Figures 5 and 6 and Table 2):
  - There was significant improvement from baseline at weeks 16, 24, 40, and 64 in subjects 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 subjects (<0.0001) and 10.4% in subjects with walking impairment at baseline (<0.0001)
  - Similar improvements occurred between the Q2W and Q4W groups

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

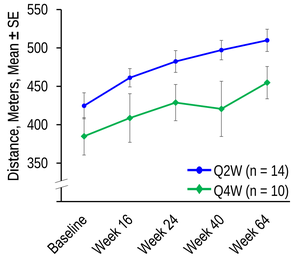
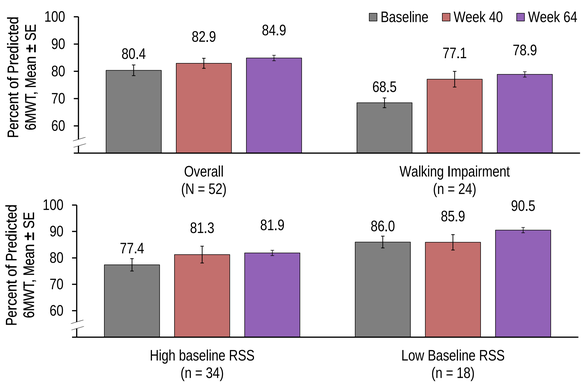


Figure 6. Improvement in 6MWT at Weeks 40 and 64



Precent predicted norm distance accounts for age, sex, and height[4]

Table 2. Improvement in 6MWT at Week 64

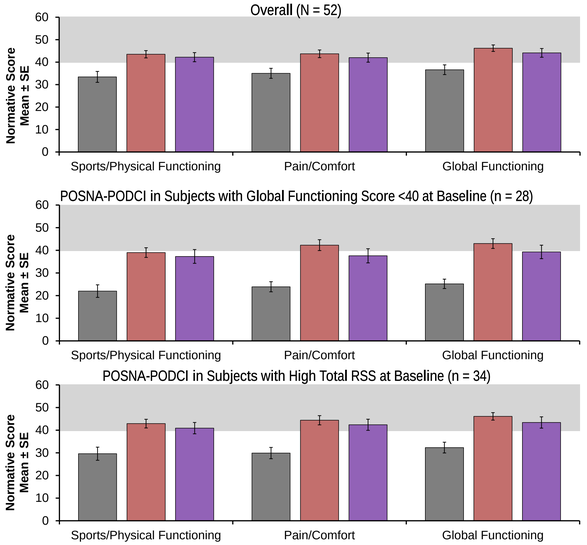
Statistic	Overall	Subjects with Walking Impairment at baseline	Subjects with High Total RSS at baseline	Subjects with Low Total RSS at baseline
Week 64 LSM increase (95% CI) in percent of predicted distance	4.5 (2.2, 6.8)	10.2 (6.3, 14.1)	4.42 (1.77, 7.06)	4.69 (0.84,8.54)
p value	<0.0001	<0.0001	0.0011	0.0169

LSM, least squares mean using the Generalized Estimating Equation

POSNA-PODCI

- Improvements in POSNA-PODCI were evident by Week 40 and persisted to Week 64 in all patients, patients with functional impairment at baseline, and patients with low Total RSS at baseline (Figure 7)
  - Upper extremity and transfer/basic mobility were normal at baseline and did not change with burosumab treatment (data not shown)
- At baseline, 28 of the 51 (55%) evaluable subjects had substantial functional impairment (POSNA-PODCI Global Functioning score <40)
  - 23 of the 28 subjects had high RSS at baseline
  - 5 of the 28 subjects had low RSS 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)
- At Week 64:
  - In all subjects, the LSM score increased 7.4 (p<0.0001), 8.8 (p<0.0001), and 6.7 (p<0.001) for Global Functioning, the Sports/Physical Functioning domain, and the Pain/Comfort domain, respectively
  - Subjects 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 at Weeks 40 and 64



Gray box indicates normal range

Safety

- Overall, burosumab demonstrated an acceptable safety profile (presented in ASBMR Oral 1154 Whyte et al. Sept 11, 2017, 9:45am)
  - 58% of subjects experienced treatment-emergent injection site reaction (ISR) adverse events, including injection site reaction (37%), injection site erythema (23%), injection site swelling (12%), and injection site rash (8%). All treatment-emergent ISR were considered mild and resolved within a few days
  - There were no deaths or discontinuations

CONCLUSIONS

- At baseline, children with XLH presented with significant residual rickets, pain, and impaired function and walking ability despite prior conventional therapy 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 ASBMR Oral 1154 Whyte et al. Sept 11, 2017, 9:45am)
  - 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

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