MO 0695

The Effects of Burosumab (KRN23), a Fully Human Anti-FGF23 Monoclonal Antibody, on Phosphate Metabolism and Rickets in 1 to 4-Year-Old Children with X-linked Hypophosphatemia (XLH)

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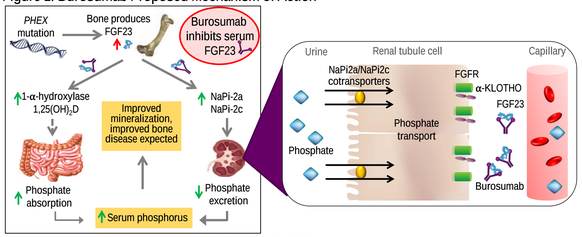
INTRODUCTION

- 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]
- 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[3]
- Burosumab is an investigational fully human immunoglobulin G1 monoclonal antibody that specifically binds to FGF23 and inhibits its activity (**Figure 1**)

Figure 1. Burosumab Proposed Mechanism of Action

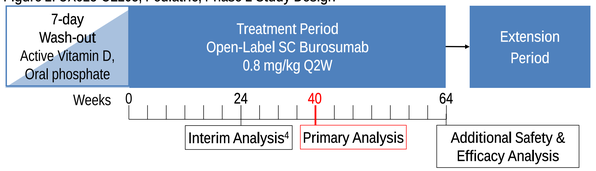


Razzaque MS. *Nat Rev Endocrinol.* 2009;5:611-9. Martin A, et al. *Physiol Rev.* 2012;92:131-55.

METHODS

- In UX023-CL205 (NCT02750618), 13 children with XLH (age 1-4 years) received burosumab subcutaneously (SC) every two weeks (Q2W) for 64 weeks (**Figure 2**). Here, we summarize findings from the week 40 interim analysis
  - Rickets Severity Score (RSS) at the Knee of ≥ 1.5 was required in ≥ 5 subjects
  - Oral phosphate and active vitamin D were discontinued
- Key endpoints summarized here:
  - **Pharmacodynamics**: Serum phosphorus (primary), serum 1,25(OH)$_2$D, serum alkaline phosphatase, urine phosphorus
  - **Rickets and lower extremity skeletal abnormalities:** Radiographic Global Impression of Change (RGI-C) and Thacher Rickets Severity Score (RSS)[5] at week 40 and 64 (**Figure 3**)
  - **Safety**: Adverse events (AEs)

Figure 2. UX023-CL205, Pediatric, Phase 2 Study Design

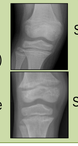


- Dose was increased to 1.2 mg/kg if serum phosphorus increased by < 0.16 mmol/L (0.5 mg/dL) from baseline or 2 consecutive measurements were below normal range
  - The mean dose (mg/kg) ranged from 0.80-0.89 between week 1 and 40

Figure 3. Two Rickets Scoring Systems

RSS[5]
- Range: 0–10 (increasing with severity)
- Total 0–10: wrist (0–4) plus knee (0–6)
- Read centrally by an expert blinded to dose and subject

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 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

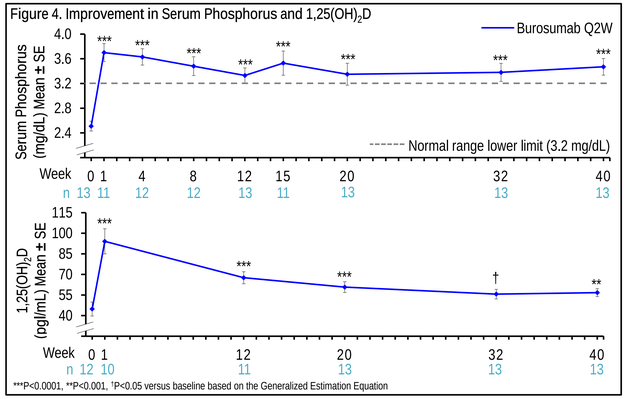
- All (13/13) patients had radiographic rickets at baseline and 92% (12/13) of children had an RSS ≥ 1.5 at baseline despite prior conventional therapy for a median of 13 months (**Table 1**)

Table 1. Baseline Characteristics

Characteristic	Burosumab Q2W (N = 13)
Age, yrs, mean (SD)	2.94 (1.15)
Male, n (%)	9 (69)
White, n (%)	12 (92)
Weight, kg, mean (SD)	12.92 (1.82)
Height Z score, mean (SD)	-1.4 (1.2)
Serum phosphorus, mg/dL, mean (SD)	2.51 (0.284)
Serum 1,25(OH)$_2$D, pg/mL, mean (SD)	44.83 (17.62)
Total RSS, mean (SD) [Range]	2.92 (1.37) [1.0-6.5]
Received prior oral P / active vitamin D, n (%)	12 (92)
Duration of prior oral P / active vitamin D, months, mean (SD)	17 (14)

- During burosumab treatment, mean (SE) serum phosphorus (mg/dL) increased by 1.2 (0.08) at week 1, and was maintained through week 20 (0.8 [0.14]) and 40 (0.96 [0.122]) (**Figure 4**)
- Normal serum phosphorus levels (3.2-6.1 mg/dL) were achieved in 82%, 62%, and 77% of children at Weeks 1, 20, and 40

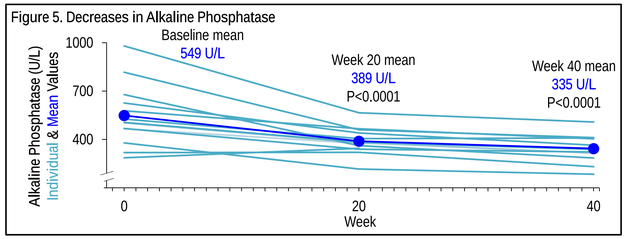
Figure 4. Improvement in Serum Phosphorus and 1,25(OH)$_2$D



***P<0.0001, **P<0.001, †P<0.05 versus baseline based on the Generalized Estimation Equation

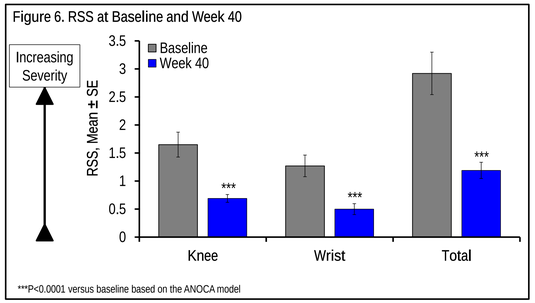
- There was a significant reduction in alkaline phosphatase at week 20 (mean percent change from baseline -25%; P<0.0001) and 40 (-36%; P<0.001) (**Figure 5**)

Figure 5. Decreases in Alkaline Phosphatase



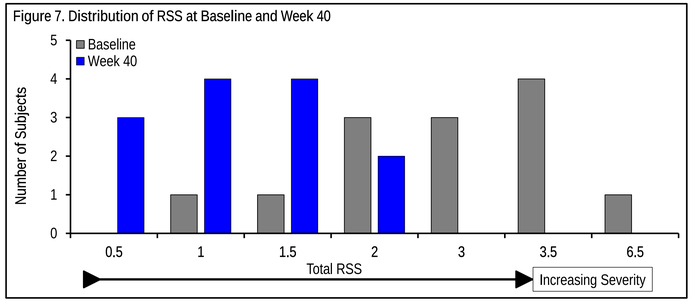
- Mean Total RSS score decreased by 59% from baseline (2.92) to week 40 (1.19). After 40 weeks of burosumab treatment, there was an overall downward shift in RSS (**Figure 6** and **7**).

Figure 6. RSS at Baseline and Week 40



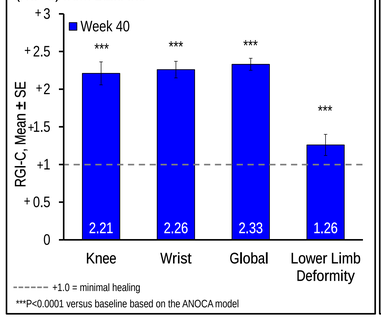
***P<0.0001 versus baseline based on the ANOCA model

Figure 7. Distribution of RSS at Baseline and Week 40



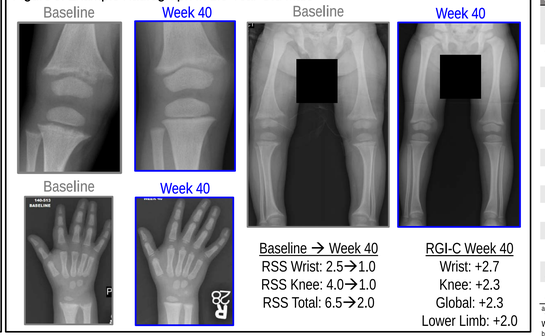
- At week 40, all 13 subjects achieved substantial healing of rickets, defined as an RGI-C Global score of +2.0 (**Figure 8**)
- Example radiographs from a 1.6-year old male show improvement after 40 weeks of burosumab treatment (**Figure 9**)

Figure 8. Radiographic Global Impression of Change (RGI-C) from Baseline



***P<0.0001 versus baseline based on the ANOCA model

Figure 9. Example Radiograph in 1.6-Year Old Male



Baseline → Week 40
RSS Wrist: 2.5→1.0
RSS Knee: 4.0→1.0
RSS Total: 6.5→2.0

RGI-C Week 40
Wrist: +2.7
Knee: +2.3
Global: +2.3
Lower Limb: +2.0

- During 40 weeks of treatment there was 1 serious AE, a dental abscess, while all other AEs were mild or moderate, except for a Grade 3 food allergy considered unrelated to study drug (**Table 2**)
- No clinically meaningful increases in calcium or parathyroid hormone (PTH) were observed during treatment

Table 2. Safety

Incident (N = 13)	n (%)
Subjects with any related treatment-emergent adverse events (TEAEs)	13 (100)
TEAEs occurring in >50% of subjects	
Cough	10 (76.9)
Pyrexia	8 (61.5)
Upper respiratory tract infection	7 (53.8)
Events to Monitor	
Injection site reaction	3 (23.1)
Hypersensitivity[a]	4 (30.8)
Hyperphosphatemia	0 (0)
Ectopic mineralization	0 (0)
Restless leg syndrome	0 (0)
Serious AEs	1 (7.7)[b]
AEs leading to discontinuation	0 (0)
AEs leading to death	0 (0)

[a]All events were mild and unrelated to study drug: facial swelling concurrent with tooth abscess, urticaria after Miralax, environmental allergies, and rash. [b]Dental abscess.

CONCLUSIONS

- In children 1-4 years old with XLH, treatment with burosumab for up to 40 weeks:
  - Increased serum phosphorus
  - Increased serum 1,25(OH)$_2$D
  - Decreased serum alkaline phosphatase
  - Significantly reduced rickets severity as assessed by RSS and RGI-C
  - Significantly improved bowing as assessed by RGI-C lower limb deformity
- Burosumab had a similar safety profile to previous pediatric trials; adverse events were predominantly 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
- These findings are consistent with previous studies investigating burosumab for XLH and suggest that early use of burosumab may result in positive clinical outcomes in children with XLH

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DISCLOSURES

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