SU0325

Effects of Burosumab (KRN23), a Human Monoclonal Antibody to FGF23, in Patients with Tumor-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS)

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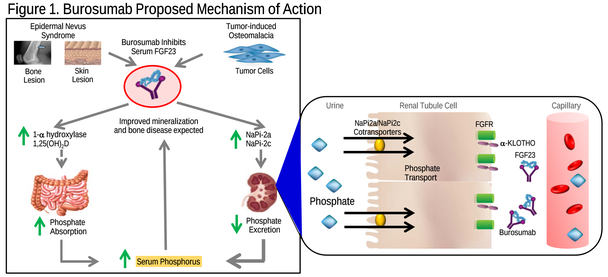
INTRODUCTION

- Tumor-induced osteomalacia (TIO) and epidermal nevus syndrome (ENS)-associated osteomalacia are rare diseases characterized by excess fibroblast growth factor 23 (FGF23), hypophosphatemia secondary to phosphaturia, and impaired active vitamin D synthesis. As a result, patients with TIO and ENS have bone pain, osteomalacia, fractures, and muscle weakness
- TIO is usually 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 cannot be fully resected or located, but this does not impact renal phosphate wasting or development of osteomalacia
- ENS-associated osteomalacia is characterized by skin lesions often associated with skeletal defects
  - The source of the excess FGF23 in ENS-associated osteomalacia is unclear
  - When feasible, the response to resection of skin lesions has been variable, with biochemical/clinical improvement only in some. Oral phosphate and calcitriol is considered standard care for ENS-associated osteomalacia as well
- Burosumab (KRN23) is an investigational fully human monoclonal antibody that binds FGF23 and inhibits its activity (Figure 1)

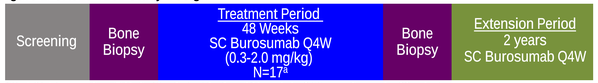
Figure 1. Burosumab Proposed Mechanism of Action



METHODS

- UX023-T201 is an open-label, single-arm, dose-finding, Phase 2 clinical trial investigating the safety and efficacy of burosumab for TIO and ENS (Figure 2)

Figure 2. UX023-T201 Study Design



[a]Week 24 data was only available for 16 patients at the time of this analysis. Q4W, every four weeks; SC, subcutaneous

- Key Inclusion Criteria
  - Diagnosis of ENS or TIO with unidentified or unresectable tumor
  - Hypophosphatemia (serum phosphorus <2.5 mg/dL) and low ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR <2.5 mg/dL)
  - FGF23 ≥2x upper limit of normal (ULN) by Kainos assay (later amended to ≥100 pg/mL)
- Co-primary endpoints are change in serum phosphorus and biopsy parameters of osteomalacia
- Additional efficacy measures
  - Serum $1,25(OH)_2D$, TmP/GFR, bone turnover markers
  - Dual-energy X-ray absorptiometry (DXA), ^{99}Tc-methylene diphosphonate (MDP) bone scan
  - Clinical outcome measurements: Sit-to-Stand, Weighted Arm Lift, Hand-Held Dynamometry, and the 6-Minute Walk Test
  - Patient-reported outcomes: Brief Pain Inventory, Brief Fatigue Inventory, and Short Form Health Survey
- Current Data Summary
  - 16 patients with Baseline and Week 24 data biochemistry data
  - The mean (SD) burosumab dose at week 24 was 0.84 (0.37) mg/kg
  - 4 patients with Week 48 bone biopsy; 1 of these patients was not included in this analysis because they did not consistently receive burosumab treatment

RESULTS

- Patients in UX023-T201 had moderate to severe osteomalacia at baseline, as assessed by histomorphometric indices of osteomalacia (Table 1)

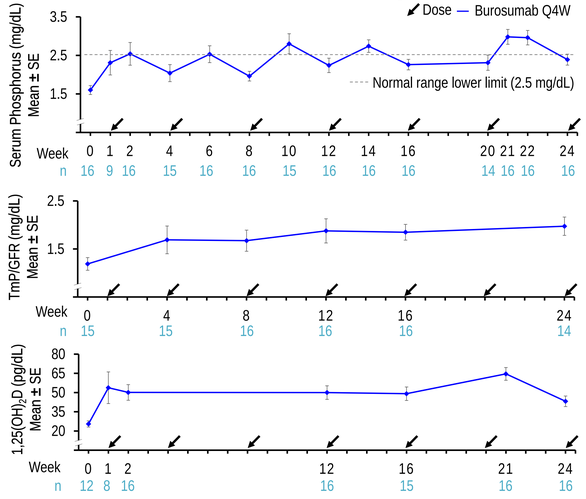
Table 1. Baseline Characteristics

Characteristic	Statistic	Burosumab (N = 16)	Normal Range
TIO	n (%)	15 (94)	
ENS		1 (6)	
Male		8 (50)	
Received Prior Phosphate treatment		14 (87.5)	
Received Prior Active vitamin D		16 (100)	
Tumor located		10 (63)	
Serum FGF23, pg/mL	Median (min, max)	416.0 (94, 2569)	
Serum iPTH pg/mL		95.4 (11, 513)	14 - 72
Age, years	Mean ± SE	52.4 ± 3.52	
Serum phosphorus, mg/dL		1.60 ± 0.12	2.5 - 4.5[a]
TmP/GFR, mg/dL		1.19 ± 0.13	
Osteoid thickness, µm		15.88 ± 3.04	6.9 ± 1.2
Osteoid surface/ bone surface,%		59.8 ± 8.05	17 ± 5
Osteoid volume/ bone volume, %		17.39 ± 4.97	1.6 ± 0.7
Mineralization lag time, days		1978 ± 505.51	17.3 ± 6.5
Mineralizing apposition rate, µm/day		0.378 ± 0.05	0.75 ± 0.09

For osteoid parameters n=13; for mineralization parameters n=12. [a]Target dosing range.
FGF23, fibroblast growth hormone 23; iPTH, intact parathyroid hormone; TmP/GFR, tubular maximum reabsorption of phosphate / glomerular filtration rate

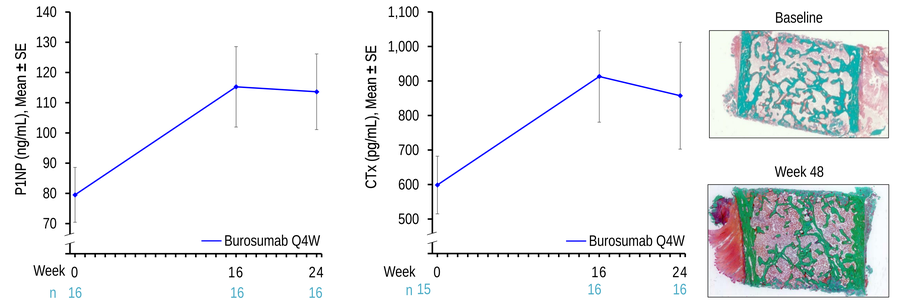
- Mean TmP/GFR, serum phosphorus, and serum $1,25(OH)_2D$ levels increased after the first dose of treatment and remained above baseline through week 24 (Figure 3)

Figure 3. Improvements in Serum Phosphorus, TmP/GFR, and $1,25(OH)_2D$



- At week 24, mean levels procollagen type 1 N (P1NP) and collagen type 1 cross-linked C-telopeptide (CTx) levels increased by 51% and 38%, respectively (P1NP p<0.001; CTx p<0.01) (Figure 4)
- Burosumab treatment was associated with improvements in histomorphometric indices of osteomalacia in 3 patients with baseline and week 48 bone biopsies (Table 2)

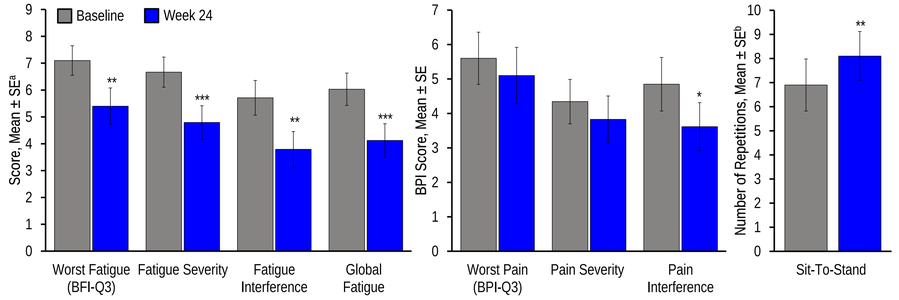
Figure 4. Increase in Markers of Bone Turnover



Example Bone Biopsy Pair

- Burosumab treatment was associated with significant improvements in patient-reported outcomes after 24 weeks of treatment (Figure 5)
  - There were significant reductions in all four fatigue parameters (least squares mean [LSM] change from baseline: Worst Fatigue -1.53, Fatigue Severity -1.76, Fatigue Interference -1.82, Global Fatigue -1.80)
  - Overall, pain scores decreased from baseline to week 24, with significant improvement in pain interference (LSM change -1.23)
  - Sit-to-Stand repetitions increased in the 12 patients with complete baseline and week 24 assessments (LSM change 1.40); of the 8/12 patients that needed to use their arms at baseline, 6 patients did not use their arms to complete the week 24 assessment

Figure 5. Improvement in Fatigue, Pain, and Muscle Strength



[a]Baseline fatigue parameters n=15; [b]Both baseline and Week 24 Sit-To-Stand assessment n=14.
*p<0.05; **p<0.01; ***p<0.001; BFI-Q3, Brief Fatigue Inventory-Questionnaire 3; BPI-Q3, Brief Pain Inventory-Questionnaire 3

Table 2. Histomorphometric Indices for Patients with Baseline and Week 48 Bone Biopsies

Indices		Subject 1	Subject 3	Subject 4
Osteoid Volume/ Bone Volume, %	Baseline	21	5.9	11
	Week 48	10.3	5.9	7.8
	% Change	-51	0	-29.1
Osteoid Surface/ Bone Surface, %	Baseline	94	57	53
	Week 48	75	61	64
	% Change	-20.2	7	20.8
Osteoid Thickness, um	Baseline	16.5	8.2	13.6
	Week 48	9.9	7.6	8.1
	% Change	-40	-7.3	-40.4
Mineralization lag time, days	Baseline	2750	1102	1462.4
	Week 48	329.2	147.7	122.3
	% Change	-88	-86.6	-91.6

[a]A 4th subject completed baseline and week 48 bone biopsies, but was not included in this analysis because the subject was not consistently treated with burosumab

- All patients experienced an adverse event (AE) and 3 patients experienced a serious AE (Table 3)
- Most AEs were grade 1 or 2
- There were 3 Serious AEs (SAEs) in 3 patients: tumor progression, thoracic epidural tumor compression, and mesenchymal tumor progression
  - No SAEs were considered treatment-related
  - 3 patients with SAEs had evidence of the event at baseline or prior history of tumor progression
  - 1 patients discontinued to treat progression

Table 3. Week 24 Safety Summary

Adverse Event	Patient Incidence, n (%)
Any adverse events (AEs)	16 (100)
AEs of interest	
Injection site reaction	2 (13)
Restless leg syndrome	2 (13)
Treatment-related AEs	7 (44)
Vitamin D deficiency	1 (6)
Rash	1 (6)
Dysgeusia	1 (6)
Hyperphosphatemia	1 (6)
Arthralgia	1 (6)
Serious AEs (SAEs)	3 (19)
Treatment-related SAEs	0 (0)

SUMMARY & CONCLUSIONS

- In patients with TIO or ENS, burosumab improved mean serum phosphorus, $1,25(OH)_2D$, and TmP/GFR over 24 weeks of treatment
- Burosumab increased markers of bone turnover after 16 and 24 weeks of treatment
- Treatment with burosumab was associated with an increase in lower limb strength, as seen in the Sit-to-Stand test, and decreases in pain and fatigue
- Adverse events reported to date generally reflect the patients' underlying diseases
- These data suggest burosumab has the potential to reverse hypophosphatemia and provide clinical benefit to patients with TIO and ENS

DISCLOSURES

SjdB, MP, and KI have received research support from Ultragenyx Pharmaceutical Inc. PDM, TJW, MR, and TOC have received honorarium and research support from Ultragenyx Pharmaceutical Inc. DL, CT-O, and JSM are employees of Ultragenyx Pharmaceutical Inc. This study was sponsored and funded by Ultragenyx Pharmaceutical Inc in partnership with Kyowa Kirin International plc. Catherine Woods, PhD, an employee of Ultragenyx Pharmaceutical Inc, provided medical writing support.

Presented at *The Annual American Society for Bone and Mineral Research Meeting*, September 13-16 2017; Denver, CO, USA