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OR13-1 Burosumab Improves the Biochemical, Skeletal, and Clinical Symptoms of Tumor-Induced Osteomalacia Syndrome

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Abstract

Tumor-induced Osteomalacia (TIO) and Epidermal Nevus Syndrome with osteomalacia (ENS) are rare conditions in which ectopic production of FGF23 by tumor (TIO) and bone (ENS) lead to renal phosphate wasting, impaired $1,25(OH)_2D$ synthesis, osteomalacia, fractures, weakness, fatigue and decreased mobility. In an ongoing open-label Phase 2 study (NCT02304367), 17 adults were enrolled and treated with burosumab, a fully human monoclonal antibody against FGF23. Key endpoints were change in serum phosphorus and osteomalacia as assessed from trans-iliac crest bone biopsies. The per protocol (PP) analysis included 14/17 subjects who received 0.3-2.0 mg/kg burosumab every 4 weeks (W). Three subjects were excluded: 1 received subthreshold dosing (0.3 mg/kg at Day 0 and 0.15 mg/kg at W8, W32, and W72); 2 were diagnosed with X-linked hypophosphatemia post-enrollment. Ten subjects in the PP group had paired bone biopsies at baseline and W48. Mean ± SE histomorphometric values for the 8/10 subjects with osteomalacia at baseline were 20.4 ± 4.2 μm for osteoid thickness (OT), 23.0 ± 7.2% for osteoid volume/bone volume (OV/BV), and 66.1 ± 10.6% for osteoid surface/bone surface (OS/BS); baseline median (Q1, Q3) for mineralization lag time (MLT) was 1672 (1102, 2929) days. At W48, histomorphometric indices improved as shown by mean percentage changes in OT (37%), OV/BV (40%),

OS/BS (-5%), and MLT (median percentage change -78%). Serum phosphorus, fatigue, and physical functioning are reported for the PP group. Mean (SD) serum phosphorus was 1.5 (0.3) mg/dL at baseline and 2.6 (0.8) mg/dL when averaged across the mid-point of the dose interval through W24. After W24, serum phosphorus, assessed only at the end of the dose interval, maintained this increase through W72. Mean (SD) Global Fatigue Score decreased from 5.3 (2.8) at baseline to 3.6 (2.9) at W48 (p=0.020) and to 3.3 (2.7) at W72 (p=0.004). The SF-36 mean (SD) physical component summary score increased from 34 (11) at baseline to 39 (10) at W48 (p=0.059) and to 42 (10) at W72 (p=0.003). Mean (SD) vitality score increased from 41 (14) to 47 (12) at W48 (p=0.075) and to 49 (12) at W72 (p=0.012). The mean (SD) number of sit-to-stand repetitions increased from 6.9 (4.0) at baseline to 8.6 (4.2) at W48 (n=10; p=0.004). By W72, all 17 subjects had ≥1 adverse event (AE). There were 13 serious AEs in 6 subjects, none were considered drug-related. Tumor progression occurred only in subjects with a history of tumor progression prior to enrollment. One subject discontinued treatment prior to W48 to treat tumor progression with chemotherapy. There was 1 death, considered unrelated to treatment. In adults with TIO Syndrome, burosumab was associated with improvements in serum phosphorus, osteomalacia, mobility, quality of life, and reductions in fatigue.