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OR13-2 Burosumab Resulted in Greater Improvement in Rickets Than Conventional Therapy in Children with X-Linked Hypophosphatemia (XLH)

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Abstract

XLH is characterized by excess FGF23, hypophosphatemia, skeletal deformities, and growth impairment. For the last 40 years, XLH has been treated with multiple daily doses of oral phosphate and active vitamin D (Pi/D). Burosumab, a fully human monoclonal antibody to FGF23, has been approved by the FDA for the treatment of XLH in patients ≥ 1 year-old. In this Phase 3 trial ([NCT02915705](#)), 61 children with XLH (1-12 years old) were randomized (1:1) to receive subcutaneous burosumab starting at 0.8 mg/kg every 2 weeks or continue Pi/D titrated and individualized for each subject by investigators. Eligibility criteria included a Total Rickets Severity Score (RSS) ≥ 2.0 despite prior treatment with Pi/D (>7 -day washout before baseline). The primary endpoint was healing of rickets at Week 40 assessed by radiologists blinded to

treatment using the Radiographic Global Impression of Change (RGI-C). The mean \pm SE daily oral phosphate dose from baseline to Week 40 was 37.8 ± 3.2 mg/kg, with $>99\%$ compliance reported based on days of dosing. Compared with Pi/D, 40 weeks of burosumab resulted in a greater LS mean \pm SE increase in serum phosphorus (0.92 ± 0.08 vs 0.20 ± 0.06 mg/dL), TmP/GFR (1.19 ± 0.11 vs -0.16 ± 0.05 mg/dL), and $1,25(\text{OH})_2\text{D}$ (30 ± 4 vs 19 ± 4 pg/mL). At Week 40, rickets improved in both groups; RGI-C global score was significantly higher in burosumab subjects than in Pi/D subjects (LS mean \pm SE: $+1.9 \pm 0.1$ vs $+0.8 \pm 0.1$; $p < 0.0001$). More burosumab subjects had substantial healing (RGI-C $\geq +2.0$), compared with Pi/D subjects (21/29, 72% vs 2/32, 6%; odds ratio of 39.1, $p < 0.0001$). Improvement in the RGI-C lower limb deformity score was greater with burosumab than with Pi/D ($+0.62 \pm 0.12$ vs $+0.21 \pm 0.12$; $p = 0.02$). Alkaline phosphatase decreased more with burosumab compared with Pi/D (-131 ± 13 vs 35 ± 19 ; $p < 0.0001$). Consistent with decreases in rickets severity, burosumab improved growth and mobility. Standing height Z-score increased by a LS mean change (95% CI) of $+0.15$ (0.05, 0.25) for burosumab and $+0.08$ (-0.02, 0.19) for Pi/D. The 6 Minute Walk Test percent predicted distance increased with burosumab (Baseline to Week 40: 62% to 72%) and was unchanged with Pi/D (76% to 75%). Nephrocalcinosis score (range 0-4) shifted 0 in 20 Pi/D and 24 burosumab subjects; +1 in 3 Pi/D and 0 burosumab subjects; and -1 in 3 Pi/D and 2 burosumab subjects. Pre-defined adverse events (AEs) of interest, including hypersensitivity and injection site reactions, were higher in the burosumab group and were mild to moderate in severity overall. There were 4 serious AEs (3 burosumab, 1 Pi/D); none were treatment-related and all resolved. No subject discontinued study drug in either group. Data after 64 weeks of treatment will be available at the time of presentation. In this randomized Phase 3 trial, burosumab resulted in increases in growth and mobility, and significantly greater improvements in rickets than Pi/D in 1-12 year-old children with XLH.

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