SHORT COMMUNICATION

HYPOPHOSPHATASIA: ENZYME REPLACEMENT THERAPY (ASFOTASE ALFA) DECREASES TNSALP SUBSTRATE ACCUMULATION AND IMPROVES FUNCTIONAL OUTCOMES IN AFFECTED ADOLESCENTS AND ADULTS

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Introduction
Hypophosphatasia (HPP), an inherited metabolic disease, results from a generalized deficiency of the activity of tissue non-specific alkaline phosphatase (TNSALP). Substrates of TNSALP, including inorganic pyrophosphate (PPi) and pyridoxal 5'-phosphate (PLP), accumulate in HPP and contribute to the pathophysiology which includes impaired skeletal mineralization and other multi-systemic problems including vitamin B6-dependent seizures, nephrocalcinosis, myopathy and pain. There is no approved therapy; asfotase alfa (ENB-0040), a bone-targeted, recombinant, human TNSALP is currently being studied in patients with HPP and improved skeletal mineralization and function has been demonstrated in infants and children.

Objective
Evaluate the TNSALP substrate levels (PPi and PLP) and six-minute walk test (6MWT) following 24 weeks of asfotase alfa treatment in adolescents and adults with HPP.

Methods
6 adolescents and 13 adults with HPP [mean age 42 yrs (14-68 yrs)] were randomized in an open-label, multicenter, no treatment concurrent control study of the safety and efficacy of asfotase alfa. Patients received 2.1 or 3.5 mg/kg/wk by once daily subcutaneous injection or no treatment (controls).

Results
Statistically significant decreases in PPi and PLP levels (p=0.002 and p=0.009, respectively) occurred in the treated groups (2.1 mg/kg/wk and 3.5 mg/kg/wk) versus control group. Serum PPi levels decreased to normal physiologic levels: baseline levels of 5.5 µM to 3.5 µM at week 24 (2.1 mg/kg/wk) and 5 µM at baseline to 2.8 µM at week 24 (3.5 mg/kg/wk). Serum PLP levels decreased to near normal physiologic levels: 324 ng/mL at baseline to 69 ng/mL at week 24 (2.1 mg/kg/wk) and 603 ng/mL to 38 ng/mL at week 24 (3.5 mg/kg/wk). At baseline, the 19 patients averaged 349m (6 - 620m) during the 6MWT, with 10/19 requiring assistive devices during testing. At week 24, treated patients improved +26m vs no improvement (-14m change) for controls. Of 12 patients with functional impairment (baseline 6MWT was 25%- 75% of normal), 9 improved. The mean improvements for the 2.1 and 3.5 mg/kg/wk groups were +35.4m (n=5) and +43.5m (n=4), respectively. Injection site reactions occurred in 7 patients, but did not cause discontinuation of treatment. Six serious adverse events (SAEs) were reported among 3 patients, two observational patients had 4 of the SAEs. No SAEs were associated with asfotase alfa.

Conclusion
Asfotase alfa significantly decreases TNSALP substrates and improves function in adolescents and adults with HPP.