Pediatric Endocrinology

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A Prospective Clinical Trial of Vosoritide in Selected Genetic Causes of Short Stature

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Objectives: Vosoritide is a C-type natriuretic peptide analog which binds its receptor on chondrocytes, leading to increased chondrocyte proliferation and differentiation via its inhibition of the ERK1/2-MAPK pathway. It was recently approved for increasing linear growth in children with achondroplasia. Our study aims to assess the safety and efficacy of vosoritide in children with genetic mutations in 6 categories: hypochondroplasia, Rasopathies (including Noonan syndrome), aggrecan deficiency, carriers of heterozygous NPR2 mutations, CNP deficiency, and SHOX deficiency.

Methods: This is a prospective, Phase II study with a goal N of 35 subjects. All subjects must have a documented genetic mutation in one of the 6 categories, be prepubertal between the ages of 3 and 11 for boys and 3 and 10 for girls, and have a height < -2.25 SD. Subjects are followed for a
6-month observation period to establish a baseline annualized growth velocity (AGV) and then receive daily subcutaneous vosoritide (15 mcg/kg/day) for 12 months. The primary outcomes are rate of AEs and change in AGV from baseline. Pharmacokinetic studies and pharmacodynamic studies, using cGMP production as a pharmacodynamic marker, are completed at Day 1 and Months 6 and 12.

**Results:** To date, 27 subjects have enrolled in the trial (20 hypochondroplasia, 3 Noonan, 2 NPR2, 2 Aggrecan). Median baseline height is -3.1 SD (IQR -3.6, -2.6). 14 subjects have initiated on vosoritide, and 10 completed 6 months of therapy. Median increase in AGV was 3.9 cm/yr (IQR 2.2, 4.6). The two subjects with NPR2 mutations had increased AGVs of 4.4 and 9.2 cm/yr. The two subjects with Noonan syndrome had an increase in AGV of 7.5 and 3.3 cm/yr. One subject with Noonan syndrome, a 4-year-old male, had previously been treated with growth hormone (GH) for 2 years. His AGV was 6.7 cm/yr while on GH, 4.1 cm/yr during the 6-month observation period, and 11.6 cm/year during the first 6 months of vosoritide treatment. There were no serious adverse events related to vosoritide treatment. One subject had a brief episode of syncope with her first injection which self-resolved, and she continued on therapy with no further incidents. PK parameters were similar to previously published parameters for vosoritide in children with achondroplasia. In preliminary data, vosoritide Cmax and AUC correlated strongly with peak increase in cGMP (r=0.70, p=0.01; r=0.84, p<0.01, respectively) but not with increase in AGV (r=0.35, p=0.32).

**Conclusions:** This is the first clinical trial of vosoritide for children with genetic short stature who do not have achondroplasia. Vosoritide treatment may work as a precision therapy to improve growth in multiple genetic conditions which interact with the ERK1/2-MAPK pathway.

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