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ACMG THERAPEUTICS BULLETIN

Vosoritide approved for treatment of linear growth in pediatric patients with achondroplasia: A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Achondroplasia is an autosomal dominant genetic diagnosis that occurs secondary to heterozygous pathogenic variants in *FGFR3*.[1] Gain of function variants in *FGFR3* inhibit chondrocyte proliferation and differentiation, which negatively regulates bone growth. Features of achondroplasia may include disproportionate short stature, relative macrocephaly with characteristic facial features, narrowed craniocervical junction, spinal stenosis, additional axial and appendicular skeletal features, restrictive pulmonary disease, obstructive sleep apnea, and more. Developmental delay often occurs, but intelligence is normal in the absence of hydrocephalus or other central nervous system complications.

Management and Treatment

Recommendations for health supervision and management of individuals with achondroplasia have been published by

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multiple groups, including the American Academy of Pediatrics Committee on Genetics.[2,3] Highlights of current recommendations include baseline imaging of the brain and craniocervical junction, polysomnography, audiology evaluation, surveillance for and treatment of specific manifestations, avoiding circumstances that increase risk of spinal cord compression or may worsen kyphosis, and optimization of functional status.

There were no U.S. Food and Drug Administration (FDA)–approved therapies that were specifically designed for use in patients with achondroplasia before 2021.

Newly Approved Therapy

Indication and approved treatment population

Vosoritide (trade name: VOXZOGO) is a C-type natriuretic peptide analog designed to increase linear growth that has been FDA-approved for treatment in pediatric patients aged 5 years and older with achondroplasia and open epiphyses.[4] FDA approval was obtained via accelerated approval.

Mechanism of action

Vosoritide is administered via daily subcutaneous injection.[4] The drug binds to natriuretic peptide receptor-B (NPR-B), which inhibits extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the mitogen-activated protein kinase pathway.[4] This antagonizes *FGFR3* downstream signaling, which in turn, promotes chondrocyte proliferation and differentiation.

Outcomes and efficacy

The initial phase 3 study was a 52-week, multicenter, randomized, anonymized, and placebo-controlled trial.[1,4,5] In this study, vosoritide showed an increase in the annualized growth velocity of 1.57 cm/year compared with placebo (95% CI = 1.22-1.93). A 2-year, open-label, phase 3 extension study later demonstrated sustained improvement in growth velocity, including an increase from 5.39 cm/year at 52 weeks to 5.52 cm/year at 104 weeks in the vosoritide-treatment group and an increase from 3.81 cm/year to 5.43 cm/year in children who crossed over from placebo to vosoritide.[6]

Adverse effects and toxicity

The most common adverse reactions noted were injection site reactions and transient hypotension, which could be addressed with a meal and drinking 8 to 12 ounces of fluids.[1] Additional common adverse reactions included arthralgia, dizziness, fatigue, and gastrointestinal concerns (vomiting, diarrhea, gastroenteritis).[4] Two subjects discontinued use of vosoritide because of the pain and anxiety with injections. No new adverse effects were detected in the extension study referenced above.[6]

Vosoritide does not have any boxed warnings.

Additional Considerations

Ongoing evaluations of clinical benefit of vosoritide through additional confirmatory clinical trials are being undertaken.[5,6] Continued FDA approval for vosoritide may be reliant upon further demonstration of clinical benefit.

At the time of this writing, multiple additional interventional clinical trials for achondroplasia were being conducted, each at multiple sites nationally in the United States.[7] One trial was a phase 2, open-label, dose-escalation and dose-expansion study in children aged 3 to 11 years to evaluate infigratinib, an FGFR 1 to 3–selective tyrosine kinase inhibitor. Another was a phase 2, double-blind, randomized, placebo-controlled, dose-escalation study in children aged 2 to 10 years to evaluate TransCon, a subcutaneous continuous form of C-type natriuretic peptide. A third was an open-label extension study in children aged 15 months to 12 years to evaluate the safety and efficacy of Recifercept, a decoy compound designed to sequester FGFR3 ligands and reduce FGFR3 signaling.[8]

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Conflict of Interest

The authors declare no conflicts of interest.

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