TransCon CNP, a Sustained-Release Prodrug of C-Type Natriuretic Peptide, exerts Positive Effects on Bone in Juvenile Cynomolgus Monkeys and in a Mouse Model of Achondroplasia

Vibeke Miller Breinholt1, Nabil Kaci2, Caroline Rasmussen1, Oliver Kédi2, Susanne Adermann2, Ulrich Hersel2, Maxence Cornille3, Martin Guillot4, Nancy Doyle4, Aurore Valera4, Per Mygind1, Kennett Sprogøe1, Laurence Legueal-Mallet2

1Ascendis Pharma A/S, 2Ascendis Pharma GmbH, and 3Imagine Institute, 4Charles River Laboratories

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Background

Achondroplasia (ACH), the most common cause of human dwarfism, is caused by a gain-of-function mutation in FGFR3, a key negative regulator of endochondral ossification. No FDA-approved treatment options exist for ACH.

CNP levels appear to correlate with height velocity in ACH. Vosoritide, a mutated CNP analogue in phase 3 development, is being assessed for its effects on bone growth in patients with ACH.

TransCon CNP is a prodrug designed specifically to release free CNP at a slow rate, resulting in hemodynamically safe and efficacious drug levels employing a weekly dosing regimen. In its prodrug form, CNP is transiently bound to the TransCon carrier via the TransCon linker. Through auto-hydrolysis, fully active, unmodified CNP is released, providing sustained exposure.

The aim of these nonclinical studies was to compare the efficacy of long-acting TransCon CNP to a daily administered CNP analogue in intact monkeys and in an ACH animal model.

Methods

Bone Growth in Healthy Juvenile Monkeys

To determine if once weekly TransCon CNP was efficacious in promoting linear growth, 4 groups of healthy juvenile male cynomolgus monkeys (n=4/group) were administered subcutaneous (SC) TransCon CNP 40 or 100 µg/kg/week once weekly, vosoritide* 20 µg/kg/day daily, or vehicle for 26 weeks. At Weeks 4, 8, 12, 22, and 26, tibial bone length was measured radiographically.

• Body and selected long bones were measured by radiography/µCT and/or with a caliper.
• Collagen X and H&E staining were performed on growth plates to assess bone architecture.

Bone Growth in ACH Mice

To determine if TransCon CNP would reverse the phenotype in an ACH disease model, newborn ACH mice harboring the Fgfr3Y367C/+ mutation (n=9) were administered 5.6 mg CNP/kg/day TransCon CNP for 15 days compared to vehicle and the following endpoints were assessed:

- Body and selected long bones were measured by radiography/µCT and/or with a caliper.
- Collagen X and H&E staining were performed on growth plates to assess bone architecture.
- An increase in the epiphyses and secondary ossification centers (SOC) was demonstrated by H&E staining.
- Positive effects on chondrocyte differentiation and organization as well as an increase in the hypertrophic zone were demonstrated by Collagen X staining.

Results

In cynomolgus monkeys, once weekly TransCon CNP afforded dose-proportional increases in tibial bone length (Week 26).

In young healthy cynomolgus monkeys, once weekly TransCon CNP increased long bone growth in a dose-dependent fashion.

In a murine model of ACH, TransCon CNP improved growth plate architecture and improved phenotypical features.

These data support further development of TransCon CNP as a potential therapy for ACH, providing efficacious CNP levels with weekly administration.

Conclusions

- Positive effects on chondrocyte differentiation and organization as well as an increase in the hypertrophic zone were demonstrated by Collagen X staining.
- An increase in the epiphyses and secondary ossification centers (SOC) was demonstrated by H&E staining.

Bone Growth in Healthy Juvenile Monkeys

Bone Growth in ACH Mice

* “Vosoritide” refers to a synthesized molecule with the same amino acid sequence prepared by Ascendis Pharma.

References

3Biomarin 2016, R&D Day

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