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 Breinholt[1], Nabil Kaci[3], Caroline Rasmussen[1], Oliver Keil[2], Susanne Adermann[2], Ulrich Hersel[2], Maxence Cornille[3], Martin Guillot[4], Nancy Doyle[4], Aurore Valera[4], Per Mygind[1], Kennett Sprogøe[1], Laurence Legeai-Mallet[3]

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

This study was sponsored by Ascendis Pharma A/S.

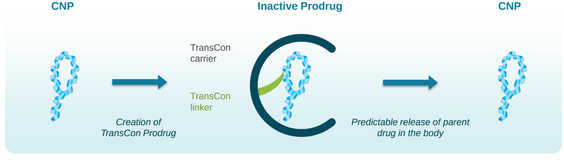
Background

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.[1] Vosoritide, a mutated CNP analogue in phase 3 development, is being assessed for its effects on bone growth in patients with ACH.[2,3]

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.

For results on cardiovascular safety and positive effect on premature synchondrosis closure, please see posters:

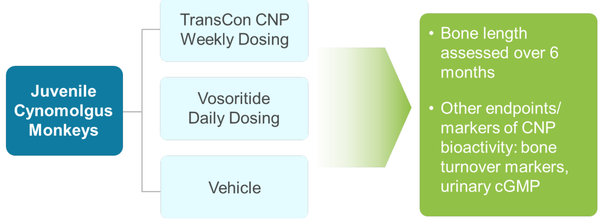
MO0707: TransCon CNP, a sustained-release prodrug of C-type natriuretic peptide, prevents premature synchondrosis closure in an achondroplasia mouse model

SU0337: Pharmacokinetics and Cardiovascular Assessment of TransCon CNP, a Sustained-Release C-type natriuretic Peptide Prodrug, for the Treatment of ACH

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.



Bone Growth in ACH Mice

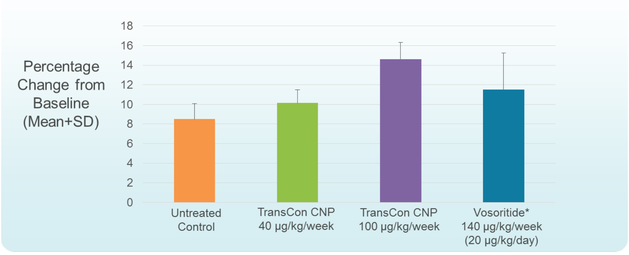
To determine if TransCon CNP would reverse the phenotype in an ACH disease model, newborn ACH mice harboring the *Fgfr3*$^{Y367C/+}$ mutation (n=9) were administered 5.6 mg CNP/kg/day TransCon CNP for 15 days compared to vehicle and the following endpoints were assessed:

- 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.

Results

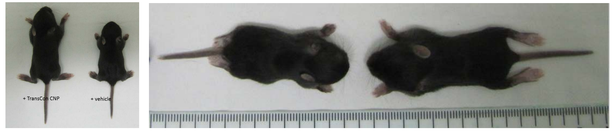
Bone Growth in Healthy Juvenile Monkeys

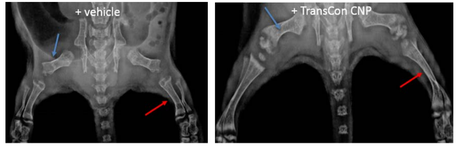
In cynomolgus monkeys, once weekly TransCon CNP afforded dose-proportional increases in tibial bone length (Week 26).



Bone Growth in ACH Mice

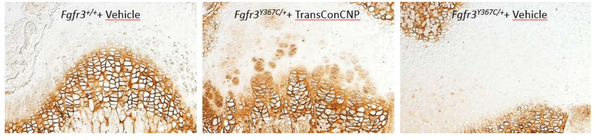
TransCon CNP administration to *Fgfr3*$^{Y367C/+}$ mice from birth to day 15 increased naso-anal length and bone length (femur; blue arrows, tibia; red arrows).



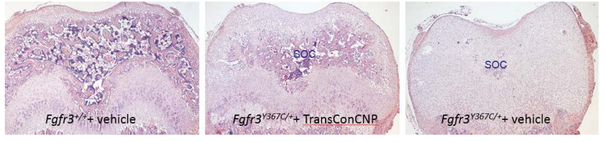


Results

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.



Conclusion

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.

[1]Olney, R.C., et al., J Clin Endocrinol Metab, 2015. **100**(2): p. E355-9.
[2]Wendt, D.J., et al., J Pharmacol Exp Ther, 2015. **353**(1): p. 132-49.
[3]Biomarin 2016, R&D Day

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