TransCon CNP, a Sustained-Release C-type Natriuretic Peptide Prodrug, for the Treatment of Achondroplasia

Caroline Elisabeth Rasmussen[1], Kennett Sprogøe[1], Ulrich Hersel[2], Thomas Wegge[2], Frank Faltinger[2], Per H. Mygind,[1] and Vibeke Miller Breinholt[1]
Ascendis Pharma A/S[1]; Ascendis Pharma GmbH[2]

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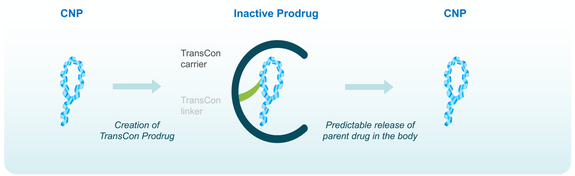
Background

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. CNP counteracts the effects of this mutation and has demonstrated efficacy in stimulating longitudinal growth.[1,2]

Vosoritide, a mutated CNP analogue with $T_{1/2}$ of ~20 minutes, is in Phase 3 development for ACH. Humans and animals dosed with vosoritide have demonstrated hypotension coinciding with maximum blood concentrations (C_{max}), indicating a causal relationship.[1,2]

TransCon CNP, a once-weekly prodrug of C-Type Natriuretic Peptide (CNP), is being developed for the treatment of ACH. 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.



Methods

Efficacy of Intermittent vs. Continuous CNP

To investigate the efficacy of intermittent vs. continuous administration, equimolar doses of vosoritide (50 nmol/kg/day) were administered either as subcutaneous (SC) injections or continuous infusion (via an Alzet pump) and compared to vehicle in FVB mice. After 35 days, the length of the right tibia was measured.

Methods

TransCon CNP PK Profile

In cynomolgus monkeys, the TransCon CNP pharmacokinetic (PK) profile was investigated following a single SC dose of 146 µg/kg.

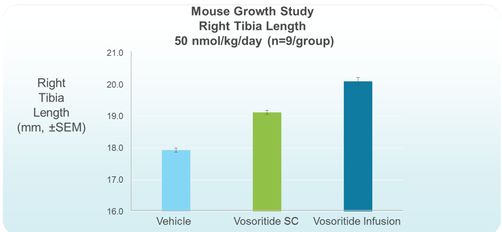
TransCon CNP Hemodynamic Tolerability in Monkeys and Mice

The hemodynamic tolerability of SC TransCon CNP was investigated in telemetrized cynomolgus monkeys and Crl:CD1(ICR) mice. Monkeys were given a single dose of 100 µg/kg and compared to monkeys administered dose-equivalent vosoritide or vehicle. Mice were given a single dose of 800 µg/kg and compared to mice administered dose-equivalent free CNP** or vehicle. Systolic arterial blood pressure (SAP) was assessed for up to 48 hours post-dose.

Results

Efficacy of Intermittent vs. Continuous CNP

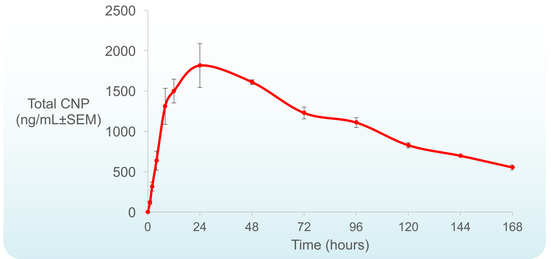
Mice (n=9/group) were administered vehicle versus daily or continuous vosoritide*. In equimolar doses, continuous vosoritide showed better efficacy, with right tibia lengths longer than with intermittent, daily injections.



Results

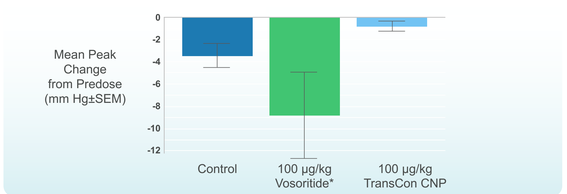
TransCon CNP PK Profile

The pharmacokinetic profile after single dose administration of TransCon CNP in monkeys (n=3) exhibited a half-life of ~80 hours, supporting once weekly dosing.



TransCon CNP Hemodynamic Tolerability in Monkeys

In monkeys (n=4), no decrease in SAP was detected at doses of up to 100 µg/kg TransCon CNP during a 48-hour monitoring period. In contrast, an equivalent dose of vosoritide led to a decrease on SAP at 0-1 hours post-dose.



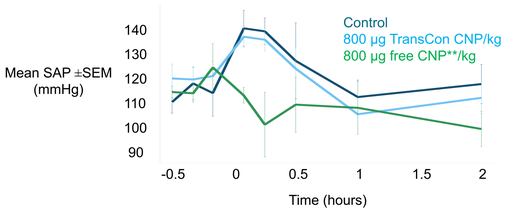
[1] BioMarin R&D Day 2016 Presentation
[2] Wendt et al. J Pharmacol Exp Ther, 2015; 353, 132–149
[3] Ascendis Pharma 2016 R&D Day Presentation

* "Vosoritide" refers to a synthesized molecule with the amino acid sequence prepared by Ascendis Pharma.
** Free CNP of identical amino acid sequence as the peptide included in TransCon CNP.

Results

TransCon CNP Hemodynamic Tolerability in Mice

In mice (n=4), TransCon CNP doses up to 800 µg/kg exhibited similar hemodynamic profile comparable to control animals during a 48-hour monitoring period. The initial SAP increase was considered to be a normal physiological response due to animal handling/dosing. In contrast, an equivalent dose of free CNP** showed a decrease in SAP during the 0-2 hours post-dose.



Conclusion

Continuous exposure to CNP showed better efficacy than intermittent, daily injections.

TransCon CNP exhibits a substantially longer half-life in cynomolgus monkeys compared to daily CNP analogues, supporting once weekly dosing in humans.

TransCon CNP showed no adverse hemodynamic effects in cynomolgus monkeys or mice at doses exceeding the expected therapeutic dose.

TransCon CNP may improve efficacy and safety over daily administered CNP.