TransCon CNP: Preliminary Phase 1 Data

November 28, 2018
Normal Growth Depends on Balanced Pathways

TransCon CNP is designed to provide continuous exposure to CNP to optimize efficacy with a well-tolerated and convenient once-weekly dose.
Achondroplasia Signaling Defect is Well Understood

- FGFR3 negatively regulates chondrocyte proliferation and differentiation and hence bone growth
- Achondroplasia results from a mutation in FGFR3 which leaves the receptor constitutively activated
- CNP inhibits the FGFR3 pathway and thereby promotes proliferation and differentiation of chondrocytes to restore bone growth

1 Adapted from Current Opin Pediatrics 2010; 22:516-523
TransCon Technology Offers Potential Solution

- **TransCon technology provides effective shielding of CNP:**
  - From neutral endopeptidase degradation in subcutaneous tissue and blood compartment
  - Minimize binding of TransCon CNP to the NPR-C clearance receptor
  - Reduce binding of TransCon CNP to the NPR-B receptor in vasculature to avoid hypotension

- **Unmodified CNP liberated from TransCon CNP maintains small enough size to allow penetration into growth plates**
TransCon CNP: Phase 1 Trial

A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Dose Escalation Trial Evaluating Safety, Tolerability and Pharmacokinetics of Subcutaneous Single Doses of TransCon CNP in Healthy Adult Male Subjects
Phase 1 Trial Design

45 healthy adult male subjects enrolled at two study centers in Australia
TransCon CNP vs. placebo (4:1 randomization)

Each dose tested sequentially starting at lowest dose

- 3.0 µg/kg
- 10 µg/kg
- 25 µg/kg
- 75 µg/kg
- 150 µg/kg

Up to 10 subjects randomized in each dose cohort in a blinded manner

Data Safety Monitoring Board (DSMB) reviews blinded data after each dose cohort and approves escalation to next dose

Dosing assignments unblinded after DSMB review

Primary Endpoint
- Frequency of adverse events (AEs) reported after administration of TransCon CNP

Secondary/Exploratory Endpoints
- Safety parameters and local tolerability assessment
- Pharmacokinetic parameters
- Other exploratory endpoints

1 300 µg CNP/kg cohort was deemed not clinically relevant based on emerging pharmacokinetic data from previous cohorts and therefore not dosed.
A single dose of TransCon CNP provided continuous CNP exposure with low inter-subject variability over the entire week.
Dose-related Increase in CNP Exposure

TransCon CNP 10, 25, 75 and 150 µg/kg  
(n=5-8/group)

- Dose-related increase in CNP exposure suggests ability to titrate dosing
- Phase 1 showed effective CNP t_{1/2} of ~ 90 hours (native CNP t_{1/2} of 2-3 minutes)

\[ CNP^1 \text{(pM) (Mean ± SEM)} \]

\[ C_{max} \text{ CNP}^1 \text{(pM)} \]

\[ \text{Dose CNP (µg/kg)} \]

\(^1\) CNP measured as CNP-38.
Mean Resting Blood Pressure Unchanged from Predose

- Placebo (n=9)
- TransCon CNP 25 µg/kg (n=8)
- TransCon CNP 75 µg/kg (n=8)
- TransCon CNP 150 µg/kg (n=8)

1. 3.0 and 10 µg/kg dose levels are not represented. Data from these cohorts are consistent with placebo.
Mean Resting Heart Rate Unchanged from Predose

- Placebo (n=9)
- TransCon 25 μg/kg (n=8)
- TransCon CNP 75 μg/kg (n=8)
- TransCon 150 μg/kg (n=8)

1. 3.0 and 10 μg/kg dose levels are not represented. Data from these cohorts are consistent with placebo.
Well-tolerated Safety Profile

- No serious AEs were reported in the trial
- TransCon CNP was generally well tolerated at doses up to 150 µg/kg
- Mean resting blood pressure and heart rate were unchanged from predose at all time points, in all cohorts
- Mean orthostatic changes in vital signs appear unrelated to TransCon CNP exposure; consistent between placebo and TransCon CNP cohorts
- Injections were well tolerated in all dose cohorts; no reported injection AEs
Achieved Target Product Profile in Phase 1

- TransCon CNP phase 1 data reproduced PK profile and cardiovascular safety from preclinical studies.

- Provided continuous CNP exposure over seven days with a single subcutaneous administration, supporting once-weekly dosing.

- Delivered continuous CNP exposure at target levels which is important for balancing the CNP/FGFR3 pathways and normalizing growth.

- Generally well tolerated across all cohorts:
  - Unchanged mean resting blood pressure and heart rate compared to predose.
  - Well-tolerated injections.

- Potential for a significant impact on patients’ lives, not only affecting height but also addressing many comorbidities associated with achondroplasia.