TransCon CNP: A Once Weekly Novel C-type Natriuretic Peptide Therapy in Children with Achondroplasia

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ISDS CONFERENCE
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TransCon CNP is an investigational medicinal product currently in development for treatment of skeletal dysplasias. TransCon CNP has not been approved by any Competent Authority for any medical use.
Achondroplasia results from a mutation in FGFR3 which leaves the receptor constitutively activated.

CNP inhibits the FGFR3 signaling pathway and thereby restores bone growth.

1 Adapted from Current Opin Pediatrics 2010; 22:516-523
TransCon CNP Design

• TransCon technology is designed to provide effective shielding of CNP:
  – From neutral endopeptidase degradation in subcutaneous tissue and blood compartment and from clearance by the NPR-C receptor
  – Minimize binding of TransCon CNP to the NPR-B and NPR-C receptors in vasculature to avoid hypotension

• CNP liberated from TransCon CNP maintains small enough size to allow penetration into growth plates\(^1\)

\(^1\) Breinholt V et al. TransCon CNP, a sustained-release C-Type Natriuretic Peptide prodrug, a potentially safe and efficacious new therapeutic modality for the treatment of comorbidities associated with FGFR3-related skeletal dysplasias. *JPET*, 2019
• Demonstrated dose-proportional tibial linear growth; ulnar growth consistent
• TransCon CNP induced a more robust growth response compared to daily administration of CNP, despite being administered at a 40% lower dose

*Refers to a synthesized molecule with a half-life of ~20 mins prepared by Ascendis Pharma

Breinholt V et al. TransCon CNP, a sustained-release C-Type Natriuretic Peptide prodrug, a potentially safe and efficacious new therapeutic modality for the treatment of comorbidities associated with FGFR3-related skeletal dysplasias. *JPET, 2019*
Phase 1 Trial Design

45 healthy adult male subjects
TransCon CNP vs. placebo (4:1 randomization)

Each dose tested sequentially starting at lowest dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subjects</th>
</tr>
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<tbody>
<tr>
<td>3 µg/kg</td>
<td>Up to 10</td>
</tr>
<tr>
<td>10 µg/kg</td>
<td>Up to 10</td>
</tr>
<tr>
<td>25 µg/kg</td>
<td>Up to 10</td>
</tr>
<tr>
<td>75 µg/kg</td>
<td>Up to 10</td>
</tr>
<tr>
<td>150 µg/kg</td>
<td>Up to 10</td>
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</tbody>
</table>

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.
Sustained CNP Exposure Over One Week

A single dose of TransCon CNP provided continuous CNP exposure over one week.

Continuous CNP exposure results in better efficacy\(^2,3\)

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1. CNP measured as CNP-38
Dose Proportional CNP Exposure For 1 Week

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

- Dose proportional increase in CNP exposure suggests ability to titrate dosing
- Phase 1 showed effective CNP $t_{1/2}$ of approximately 120 hours (native CNP $t_{1/2}$ of 2-3 minutes)
Mean Resting Blood Pressure Unchanged from Predose

Placebo  n=9

75 µg CNP/kg  n=8

150 µg CNP/kg  n=8

Change in blood pressure (mmHg)

Hours

Change in systolic blood pressure  Change in diastolic blood pressure

3.0, 10, and 25 µg/kg dose levels are not represented. Data from these cohorts are consistent with placebo.
## Adverse Event Summary

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 µg CNP/kg (N=6)</td>
</tr>
<tr>
<td>Any AE</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Related AE</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>Moderate AE</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to discontinuation from study</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>0</td>
</tr>
</tbody>
</table>
TransCon CNP: Well-tolerated Safety Profile

- No serious AEs were reported
- TransCon CNP dosed as high as 150 µg CNP/kg
- No anti-CNP antibodies detected
- 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
ACHieve Natural History Study Enrolling

- A global natural history study of ~200 children <8 years with achondroplasia (ACH)
- Evaluates height velocity, body proportionality and comorbidities
- Sites selected in Australia, Austria, Canada, Germany, Ireland, Italy, New Zealand, Portugal, Spain, Switzerland, UK, and US
- Study open and enrolling
ACcomplisH Phase 2 Trial Design

Primary Endpoint
- Annualized height velocity, as measured after 12 months of weekly TransCon CNP treatment

Key Secondary Endpoints
- After 12 months of weekly TransCon CNP treatment:
  - Change in body proportionality (upper to lower body segment ratio)
  - Change in body mass index (BMI)
- Patient-reported outcome (PRO) measures

60 children (ages 2 – 10 years) with achondroplasia

12 subjects randomized in each dose cohort in a blinded manner

TransCon CNP vs. placebo 3:1 randomization

Data Monitoring Committee reviews blinded data after each dose cohort

Extension trial to evaluate safety and efficacy

TransCon CNP treatment:
- 6 µg/kg
- 20 µg/kg
- 50 µg/kg
- 100 µg/kg
- >100 µg/kg

1 Dose to be determined. If needed, based on emerging data.
TransCon CNP: Highlights

- TransCon CNP provided continuous CNP exposure over seven days with a single subcutaneous administration
  - No changes in NTproCNP levels were observed
  - Plasma cGMP levels suggest continuous receptor engagement
  - Continuous CNP exposure may be important for balancing the CNP/FGFR3 pathways and normalizing growth

- Generally well-tolerated across all cohorts

- ACHieve (natural history study) ongoing; initiation of phase 2 ACcomplish trial underway

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

ACHieve STUDY

Ongoing Natural History Study

ACcomplish TRIAL

Phase 2 Study in 2-10 year old children with Achondroplasia starting in Q3 2019

Bay Area, California

Copenhagen, Denmark

Heidelberg, Germany