# 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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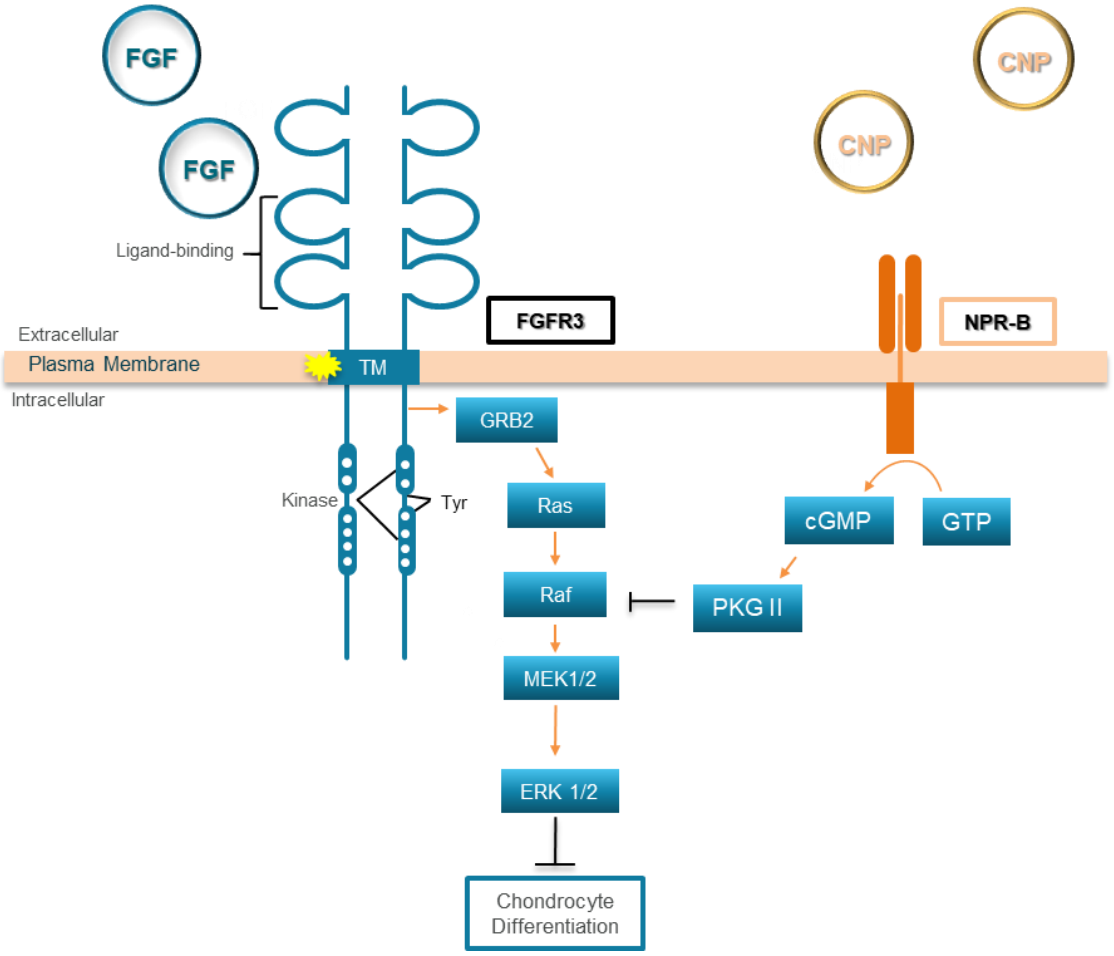
# Disclaimer

- 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.

# CNPs Action in Growth Plate is Well Understood

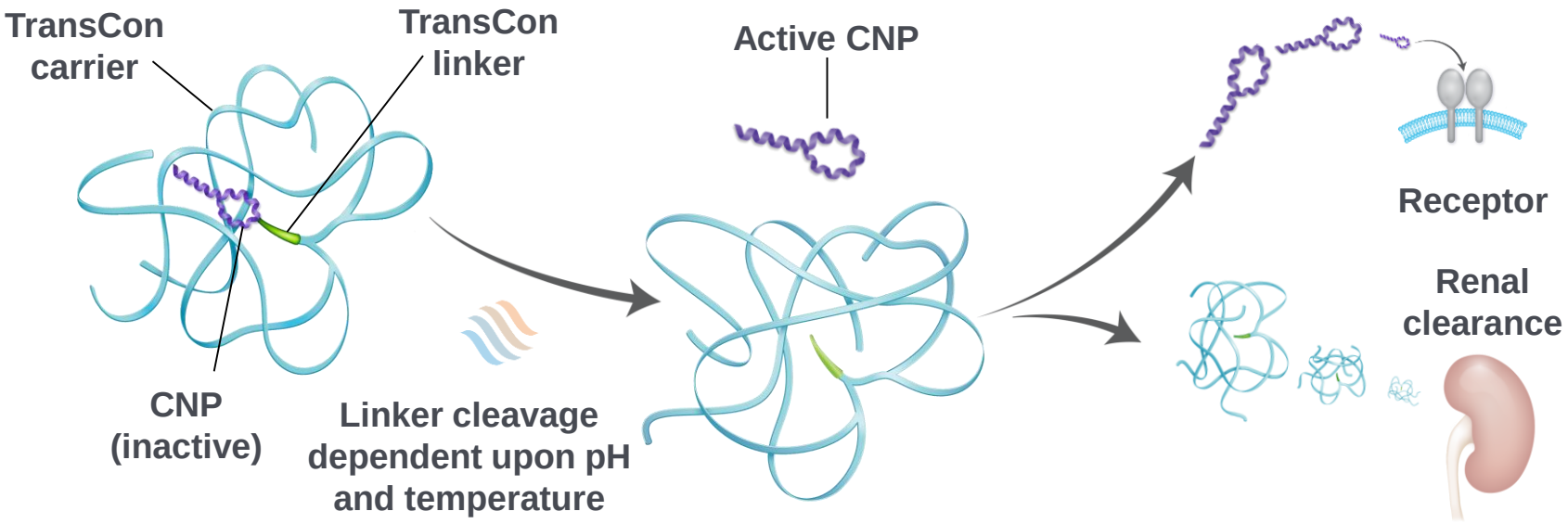
- Achondroplasia results from a mutation in FGFR3 which leaves the receptor constitutively activated
- CNP inhibits the FGFR3 signaling pathway and thereby restores bone growth






[1]Adapted from *Current Opin Pediatrics* 2010; 22:516-523

# TransCon CNP Design

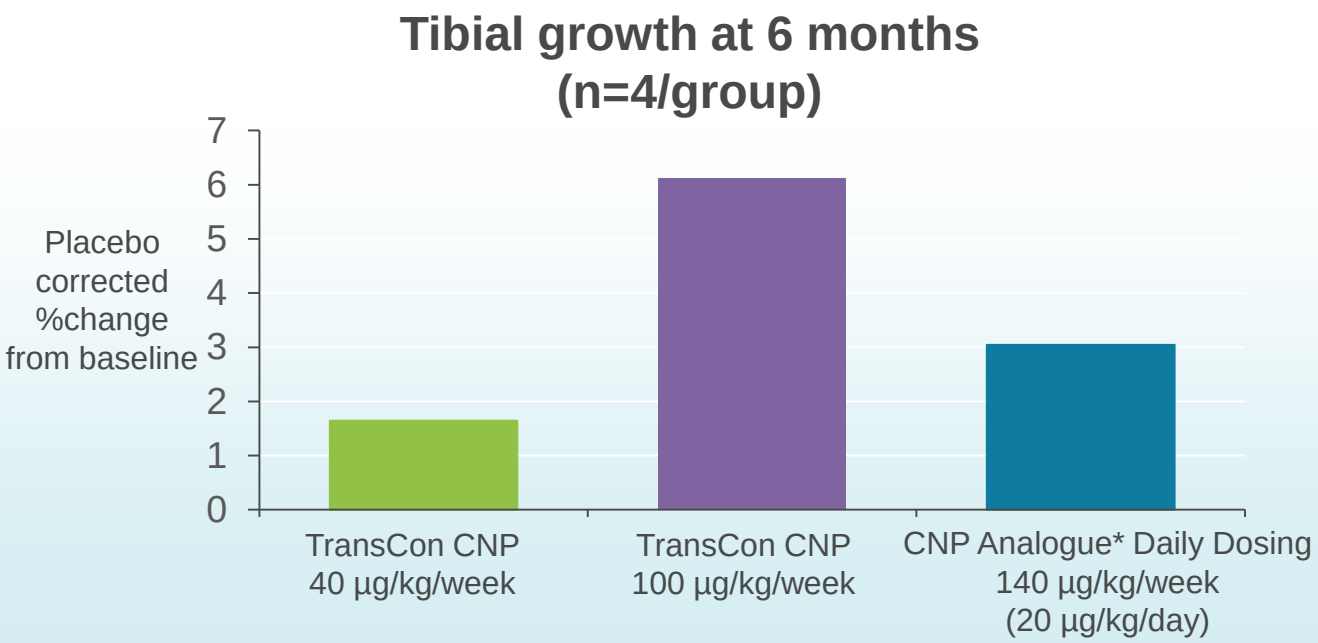



- TransCon technology is designed to provide effective shielding of CNP:
  - From neutral endopeptidase degradation in subcutaneous tissue and blood compartment and from clearance by the NPR-C receptor
  - Minimize binding of TransCon CNP to the NPR-B and NPR-C receptors in vasculature to avoid hypotension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

# Juvenile Healthy Monkey Growth Study




- 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

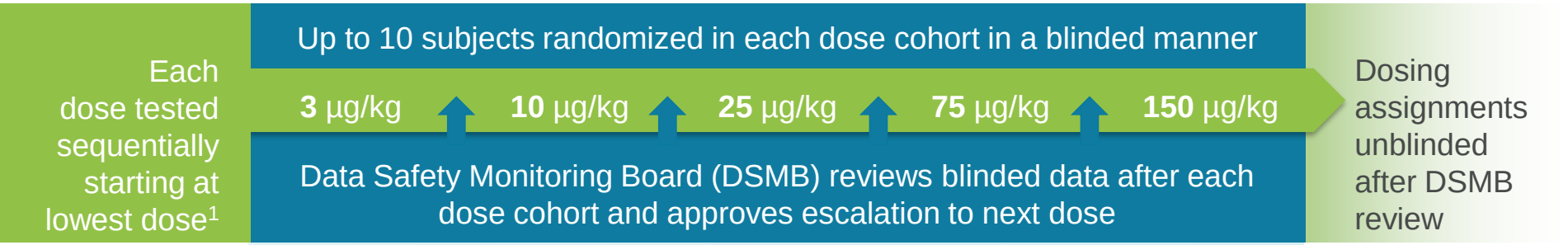
*Refers to a synthesized molecule with a half-life of ~20 mins prepared by Ascendis Pharma



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)**




## Primary Endpoint

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

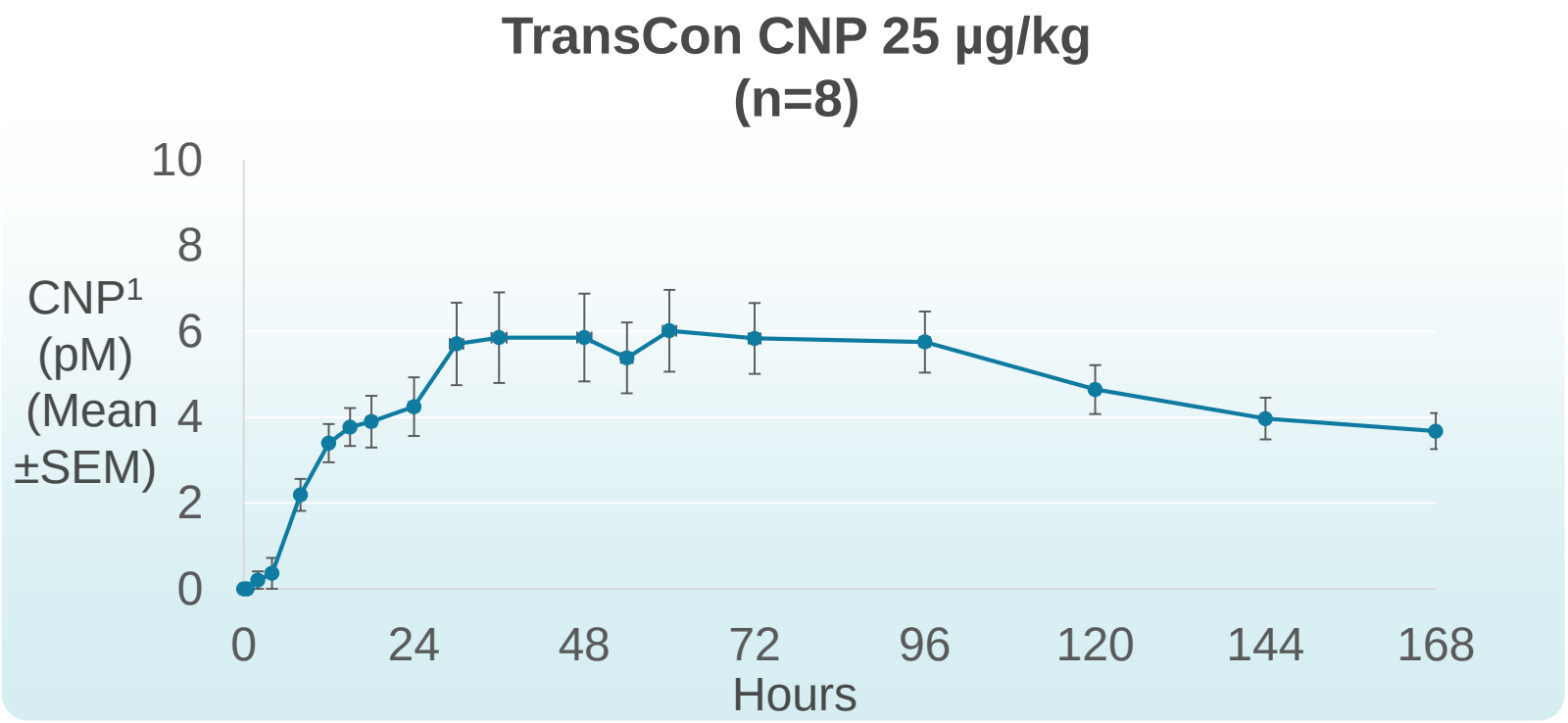
## Secondary/Exploratory Endpoints

- 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]

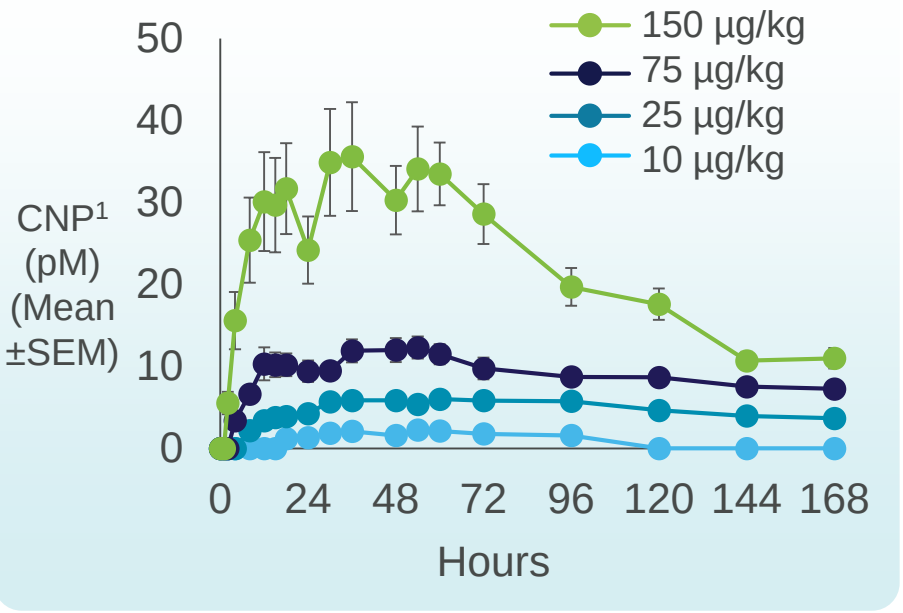
[1] CNP measured as CNP-38

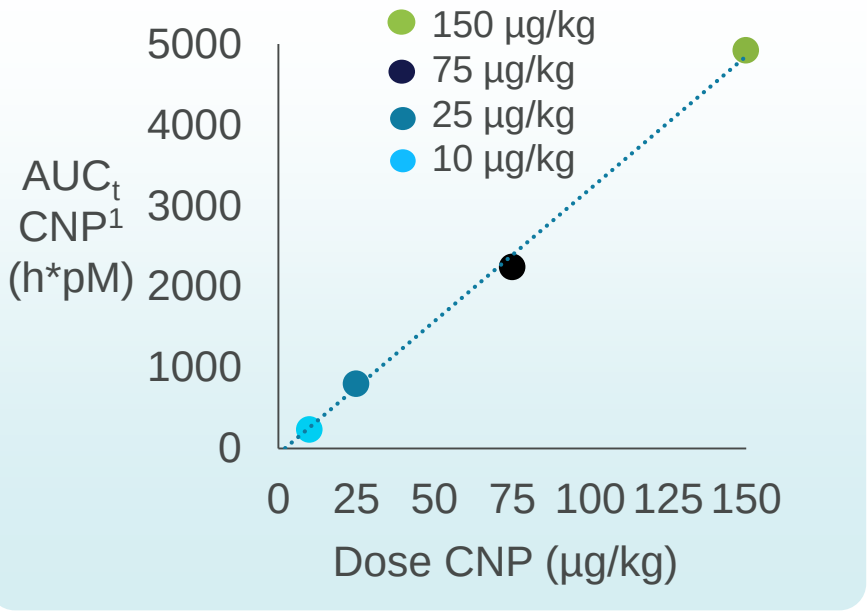
[2] N Morozoumi et al. ASB:201123: A novel C-type natriuretic peptide derivative for treatment of growth failure and dwarfism. *PLoS One*.2019

[3] 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

# Dose Proportional CNP Exposure For 1 Week

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



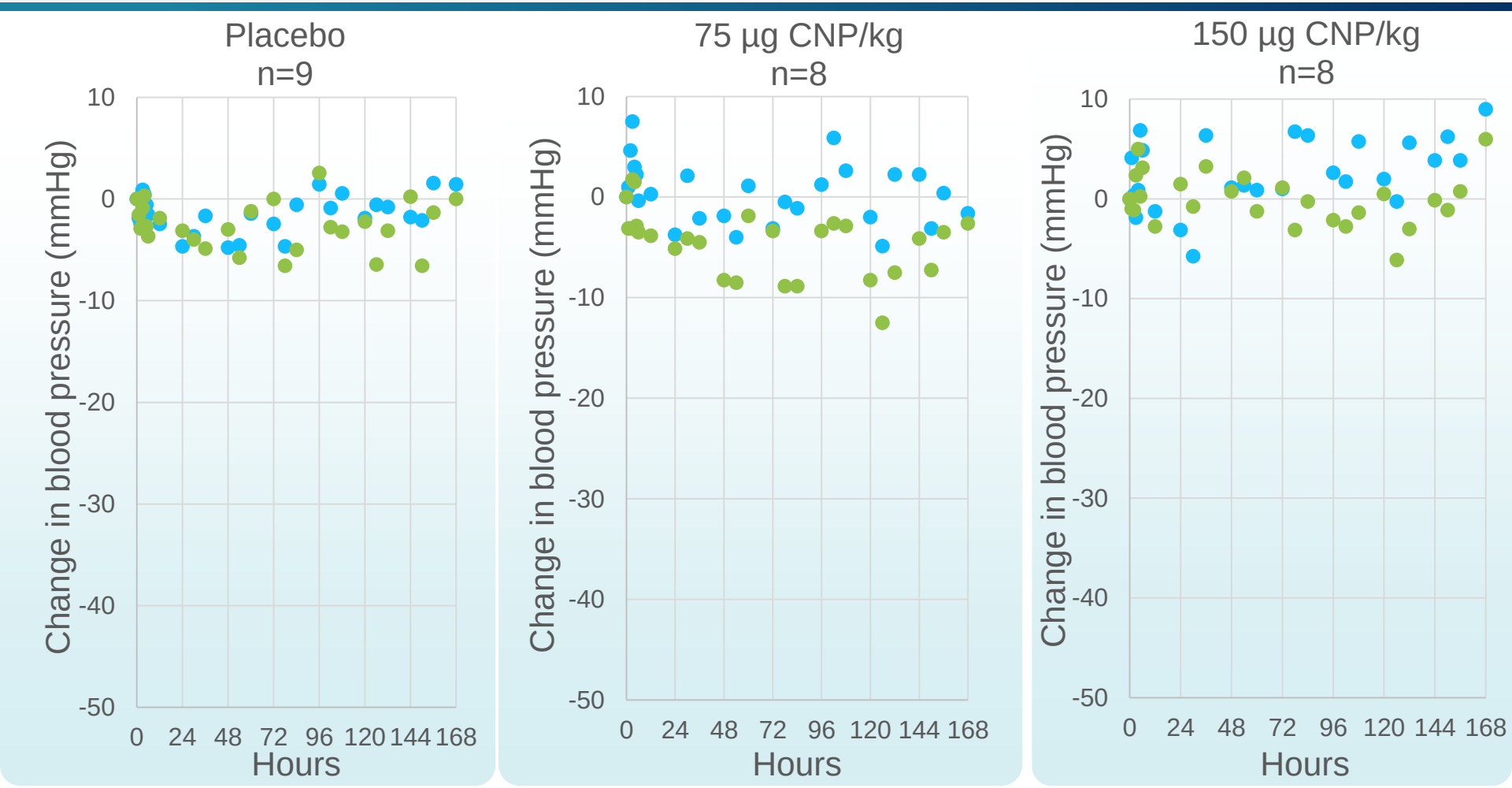




- Dose proportional increase in CNP exposure suggests ability to titrate dosing
- Phase 1 showed effective CNP $t_{1/2}$ of approximately 120 hours (native CNP $t_{1/2}$ of 2-3 minutes)



[1] CNP measured as CNP-38

# Mean Resting Blood Pressure Unchanged from Predose[1]






[1] 3.0, 10, and 25 µg/kg dose levels are not represented. Data from these cohorts are consistent with placebo

# Adverse Event Summary

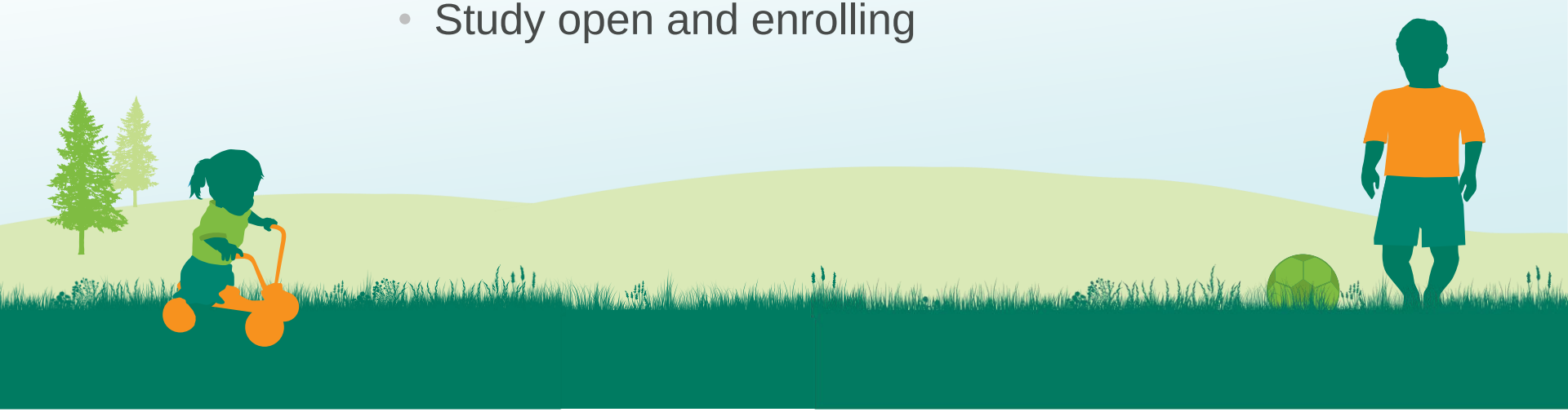
| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| Type of AE | 3 µg CNP/kg (N=6) | 10 µg CNP/kg (N=6) | 25 µg CNP/kg (N=8) | 75 µg CNP/kg (N=8) | 150 µg CNP/kg (N=8) | Placebo (N=9) |
| Any AE | 5 (83%) | 4 (67%) | 5 (63%) | 8 (100%) | 6 (75%) | 7 (78%) |
| Related AE | 3 (50.0%) | 3 (50.0%) | 2 (25%) | 6 (75%) | 6 (75%) | 2 (22%) |
| Moderate AE | 2 (33.3%) | 1 (16.7%) | 0 (0.0%) | 5 (62.5%) | 3 (37.5%) | 2 (22.2%) |
| Severe AE | 0 | 0 | 0 | 1 (12.5%) | 0 | 0 |
| AE leading to discontinuation from study | 0 | 0 | 0 | 0 | 0 | 0 |
| Serious AE | 0 | 0 | 0 | 0 | 0 | 0 |

# 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 pre-dose 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

ACcomplisH TRIAL

**60 children (ages 2 – 10 years) with achondroplasia**

TransCon CNP vs. placebo 3:1 randomization

12 subjects randomized in each dose cohort in a blinded manner

**6** µg/kg → **20** µg/kg → **50** µg/kg → **100** µg/kg → **>100** µg/kg[1]

Data Monitoring Committee reviews blinded data after each dose cohort

Extension trial to evaluate safety and efficacy

## 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



[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 STUDY (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