TransCon CNP (Navepegritide): A Semi-mechanistic Model to Describe the Prolonged Half-life of C-type Natriuretic Peptide Through TransCon Technology

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Introduction

Achondroplasia (ACH) is a rare genetic condition arising from a fibroblast growth factor receptor 3 (FGFR3) variant, which causes serious muscular, neurological, and cardiorespiratory complications in addition to the well-characterized skeletal dysplasia.

C-type natriuretic peptide (CNP) stimulates bone growth via inhibition of the mitogen-activated protein kinase (MAPK) signaling pathway downstream of FGFR3 in growth plate chondrocytes, mediated through activation of the natriuretic peptide receptor-B (NPR-B) counteracting the over-activated FGFR3 induced stunted growth in ACH.[1] NPR-B-induced cyclic guanosine 3',5'-cyclic monophosphate (cGMP) in skeletal muscles may directly improve functionality.

Navepegritide is a prodrug consisting of an inactive CNP moiety transiently conjugated with an inert carrier via a proprietary TransCon® linker, providing sustained release of active CNP following first-order kinetics upon exposure to physiologic pH and temperature **(Figure 1)**, supporting once-weekly dosing. The amino acid sequence of the CNP moiety is identical to the 38 amino acid sequence of residues 89-126 of human CNP.

There are ongoing efforts to develop semi-mechanistic population pharmacokinetic (PK) models for other compounds using TransCon Technology[2] that have shown good in vitro-in vivo correlation between the linker release half-life measured in vitro and the model-fitted in vivo linker release half-life.

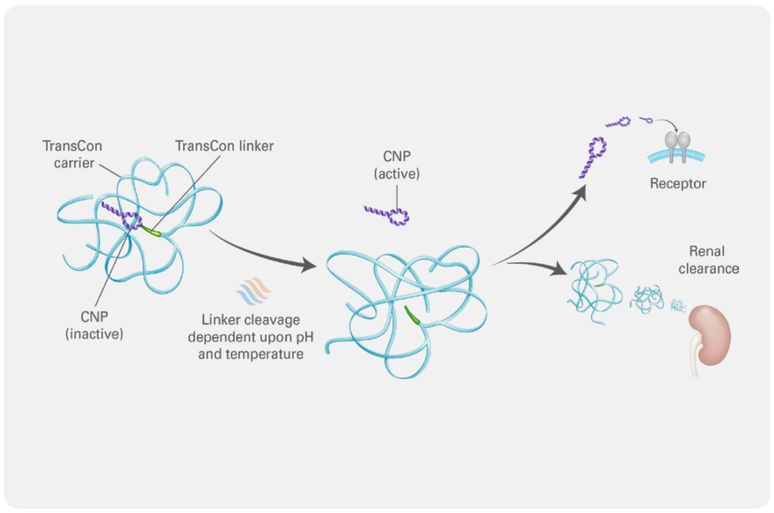
In the current study, a population PK model was developed for navepegritide in prepubertal children with ACH. The starting point model was based on an existing in-house model developed to describe the PK characteristics of Total CNP, Free CNP(89-126) and the associated carrier in healthy adults. Here, we focus on the biologically relevant peptides, Total CNP and Free CNP(89-126).

Objectives

This study aimed to develop a population PK model to:

- Characterize the concentration-time course of Total CNP and Free CNP(89-126) and thereby enhance the understanding of navepegritide drug disposition
- Use the developed model to extrapolate exposure to Free CNP(89-126) to support dose selection in a trial in infants with ACH

Figure 1: **TransCon CNP (Navepegritide)**



Conclusions

The PK and complex interplay between Total CNP and Free CNP(89-126) were successfully characterized by a semi-mechanistic PK model, supporting its use to derive individual predictions of exposure and for simulations.

The model is being used to support further development in younger and older paediatric populations with ACH and can be used to inform future studies in adults. In an ongoing trial in infants with ACH, PK is evaluated in addition to safety. Observed PK measurements are compared to the expected concentration range in sentinel trial participants and used to evaluate dose selection.

The good alignment between the in vitro and in vivo linker release half-lives supports future translational efforts to predict the concentration-time course of prodrug and active drug when clinical PK data is not yet available.

The model developed for navepegritide may further support clinical trial design, dose optimization, and life-cycle management, as well as the prediction of human PK for new TransCon drug candidates.

Methods

Data

- The model was based on data from a Phase I trial in healthy, male volunteers (n = 35)[3] and the double blinded part of a Phase 2 trial in pre-pubertal pediatric patients with ACH (n=42, age 2 to 10 years at screening).[4] The data set for the Phase 2 trial included the complete dosing history obtained from a patient diary, for every weekly dose for 52 weeks of treatment. The data set also included available data from the open label extension part of the Phase 2 trial
- Total CNP and Free CNP(89-126) were measured postdose at 0.5, 2, 4, 8, 12, 15, 18, 24, 30, 36, 48, 54, 60, 72, 96, 120, 144, 168, 336, 504 and 648 hours after the injection in Phase 1, and 0, 4, 8, 12, 26, 39 and 52 weeks after the initiation of the trial in Phase 2. In addition, at the first visit, subjects weighing more or equal to 11 kg had PK samples collected at 8, 24 and 48 hours after injection. The sparse sampling was continued in the open label extension part of the Phase 2 trial

Model Development

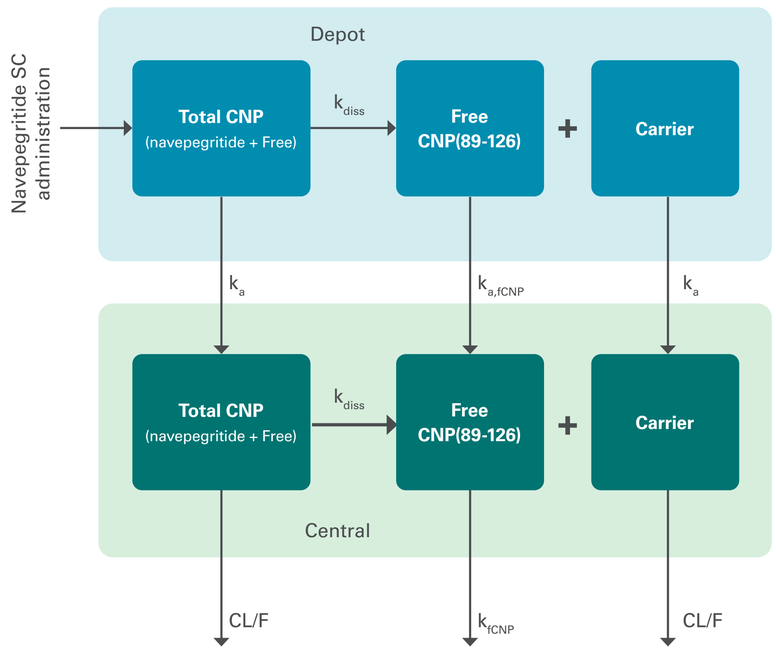
- A semi-mechanistic population PK model was developed to simultaneously characterize the plasma concentrations of Total CNP and Free CNP(89-126) following subcutaneous administration of navepegritide. Irreversible dissociation of navepegritide to Free CNP(89-126) and carrier was assumed to occur both in the central and depot compartment
- All analytes were modeled with differential equations in NONMEM v.7.5.0, using the SAEM estimation method with the ADVAN13 subroutine
- A covariate analysis was conducted to explore intrinsic factors. The final model was updated and used to extrapolate exposure in infants, including a function for renal maturation.[5] A relationship for change in body weight over time in infants with achondroplasia was used in the extrapolation[6]

Results

Navepegritide Population PK Model

- The PK of all entities was 1-compartmental with first-order absorption rates from a depot compartment, and linear elimination from a central compartment **(Figure 2**). Even with sparse sampling over 52 weeks, the average number of observations per participant was 32 in the pediatric trial. The model complexity and dataset structure led to long run times. Final run took 42 minutes
- Model diagnostics for the final model indicated a satisfactory predictive performance for Total CNP and Free CNP(89-126) in the target population **(Figure 3)**
- Furthermore, this study confirms a good alignment between the linker release half-life fitted in vivo and the linker release half-life measured in vitro

Figure 2: **Navepegritide Model Structure**



Abbreviations: CL/F = apparent clearance; **CNP** = C-type natriuretic peptide; k_a = absorption rate; k_{diss} = linker release rate; $k_{a,fCNP}$ = absorption rate of Free CNP; k_{fCNP} = elimination rate of Free CNP; **SC** = subcutaneous

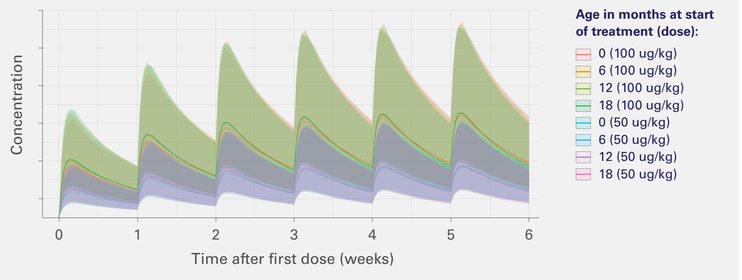
Figure 3: **Model Can Describe Free CNP(89-126) and Total CNP**

Prediction-corrected visual predictive check for the navepegritide population PK model. Semi-logarithmic plot showing the concentration of Free CNP(89-126) **(A)** and Total CNP **(B)** versus time after the first dose in a 52-week double-blind Phase 2 paediatric trial with weekly navepegritide dosing. The data set included available data from the open label extension part of the trial.

Model Application

- By including a renal maturation function, as well as accounting for the development in body weight over time in infants with ACH, an extrapolation could be performed, to support dose setting in an ongoing trial in infants with ACH
- The trial in infants with ACH has been initiated with the inclusion of open-label sentinels, to evaluate safety and PK. The concentrations observed from sparse sampling in the sentinels are compared against the expected concentration ranges from the extrapolation **(Figure 4)**

Figure 4: **Infants Sentinels Extrapolation**



Extrapolation from the navepegritide population PK model: Prediction of the concentration of Free CNP(89-126) versus time after first dose in a paediatric population of infants 0 to 18 months. Weekly doses of navepegritide 50 or 100 µg/kg were used in the simulation. The solid lines represent the geometric mean of the simulation in each group, and the shaded areas represent the 90% predictio n intervals.

Abbreviations

ACH = achondroplasia; **ADVAN13** = general nonlinear model with stiff or nonstiff differential equations using Livermore solver (LSODA); **cGMP** = cyclic monophosphate; **CI** = confidence interval; **CNP** = C-type natriuretic peptide; **FGFR3** = fibroblast growth factor receptor 3; **NONMEM** = nonlinear mixed effects modeling; **PK** = pharmacokinetic; **SAEM** = stochastic approximation expectation maximisation

References:

1. Miyazawa T, et al. Cyclic GMP-dependent protein kinase II plays a critical role in C-type natriuretic peptide-mediated endochondral ossification. *Endocrinology.* 2002;143(9):3604-3610. **2.** Data on file in collaboration with Vollmer J., Ascendis Pharma 2022. **3.** Breinholt VM, et al. Phase 1 safety, tolerability, pharmacokinetics and pharmacodynamics results of a long-acting C-type natriuretic peptide prodrug, TransCon CNP. Br *J Clin Pharmacol.* 2022;88(11):4763-4772. **4.** Savarirayan R. et al. Once-weekly TransCon CNP (navepegritide) in children with achondroplasia (ACcomplisH): a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-escalation trial. *EClinicalMedicine.* 2023;2;65:102258. **5.** Rhodin MM, et al. Human Renal Function Maturation: A Quantitative Description Using Weight and Postmenstrual Age. *Pediatr Nephrol.* 2009;Jan;24(1):67-76. **6.** Hoover-Fong JE, et al. Weight for age charts for children with achondroplasia. *Am J Med Genet A.* 2007;143A(19):2227-35.

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KCCP and **I-EA:** employment with Ascendis Pharma A/S. **FG:** consulting role for Pharmetheus (CRO).
AB: consulting role for Pharmetheus (CRO).

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