Official Title: ACcomplisH: A Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose escalation trial evaluating safety, efficacy, and pharmacokinetics of subcutaneous doses of TransCon CNP administered once weekly for 52 weeks in prepubertal children with achondroplasia followed by an Open-Label Extension Period

NCT Number: NCT04085523

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NCT04085523

STATISTICAL ANALYSIS PLAN

Title	**ACcomplisH: A Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose escalation trial evaluating safety, efficacy, and pharmacokinetics of subcutaneous doses of TransCon CNP administered once weekly for 52 weeks in prepubertal children with achondroplasia followed by an Open-Label Extension Period**
Protocol:	**TransCon CNP TCC-201 Version 4.0**
Investigational Product:	**TransCon CNP**
Phase:	**2**
Sponsor:	Ascendis Pharma Bone Diseases A/S Tuborg Boulevard 12, DK-2900, Hellerup, Denmark
Author:	PPD
Date:	**11 October, 2022**
Version Number:	**Version 2.0**

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ABBREVIATIONS

µg	Microgram
CCI [redacted]	[redacted]
ACH	Achondroplasia
ADA	Anti-drug Antibodies
AE	Adverse event
AHV	Annualized height velocity
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Anthropometric
CCI [redacted]	[redacted]
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CCI [redacted]	[redacted]
cm	Centimeter
CNP	C-type natriuretic peptide
CRF	Case report form
CV	Coefficient of variation
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
HDL	High-density lipoprotein
IWRS	Interactive web response system
Kg	Kilogram
LDL	Low-density lipoprotein
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MCS	Mental component score
mPEG	Methoxypolyethylene glycol
ObsRO	Observer-reported outcome
OLE	Open-Label Extension
PCS	Physical component score

PedsQL 4.0	Pediatric Quality of Life Inventory Version 4.0
PEG	Polyethylene glycol
CCI [redacted]	[redacted]
PINP	Propeptide of type I procollagen, N-terminal
PK	Pharmacokinetics
PR	PR interval of ECG
PRO	Patient-reported outcome
PT	Preferred term
CCI [redacted]	[redacted]
QRS	Duration of ventricular muscle depolarization of ECG
QT	Duration of ventricular depolarization and repolarization of ECG
QTcF	QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓)
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDS	Standard Deviation Score
SE	Standard error
CCI [redacted]	[redacted]
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a more technical and detailed elaboration of the statistical analyses of efficacy and safety data as outlined and/or specified in the study protocol (version dated 12August2021). A population PK analysis plan for pharmacokinetic (PK) data was prepared separately (MODCNP001).

2 STUDY DESIGN

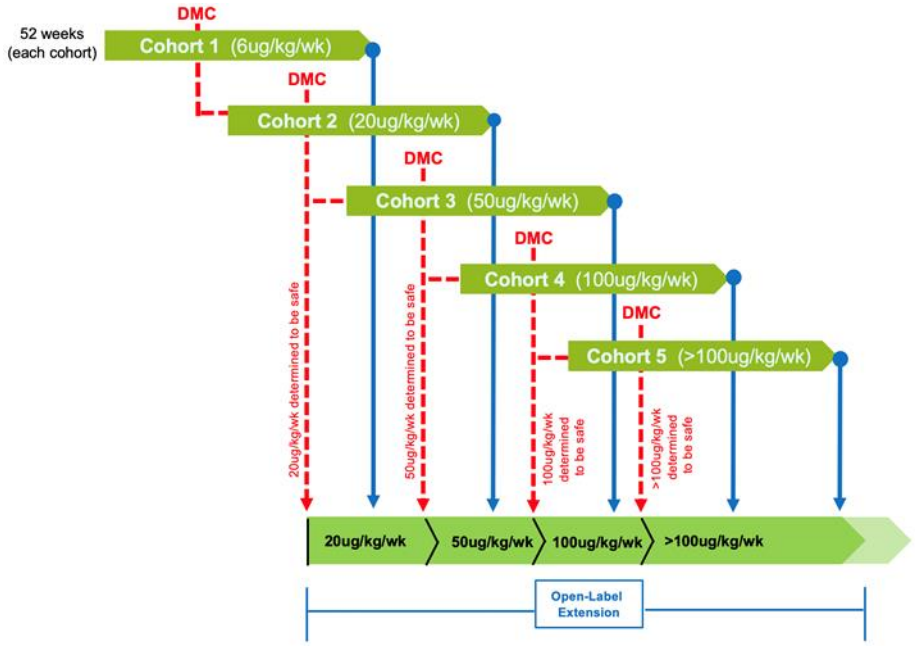
Study TCC-201 is a multicenter trial consisting of two treatment periods: A 52 week double-blind, randomized, placebo controlled, dose escalation trial evaluating up to 5 different dose levels of weekly TransCon CNP administered subcutaneously in prepubertal children 2 to 10 years old, inclusive, with ACH. For this part of the trial participants are randomized into 2 treatment groups for each cohort in a 3:1 TransCon CNP: placebo ratio, with approximately ≥9 participants on TransCon CNP and ≥3 participants on placebo in each cohort. Participants are to remain on the same dose of study drug throughout the entire 52-week Randomized Treatment Period.

After completing 52 weeks of their assigned cohort dose (or placebo), participants who fulfill the rollover criteria can continue into the 104 weeks Open-Label Extension Period. In the extension period, participants may receive the highest dose level of TransCon CNP that has passed safety review and is recommended by the Data Monitoring Committee (DMC) (trial design scheme below).

The study is expected to enroll approximately 60 subjects from approximately 35 sites worldwide.

The total duration of the trial for an individual participant is up to approximately 165 weeks. Duration includes up to approximately 4 weeks of screening, plus 156 weeks of treatment (52 weeks of treatment in the Randomized Period and an additional 104 weeks of treatment in the Open-Label Extension Period) and a 5-week follow-up period.

Trial design scheme



Visit Schedule diagram in the Randomized and Open-Label Extension Periods

Visit Schedule in the **Randomized Period**

Visit	Screening Visit	Visit 1	Phone Visit	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Follow Up
Week	-4 to -1	0	2	4	8	12	26	39	52	57

Visit Schedule in the **Open-Label Period (Year 1)**

Visit	Visit 7	Phone Visit	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Week	52	54	56	65	78	91	104

Visit Schedule in the **Open-Label Period (Year 2)**

Visit	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Follow Up (OLE)
Week	104	117	130	143	156	161

2.1 BLINDING AND RANDOMIZATION METHODS

Eligible subjects will be enrolled in the study and assigned an identification number. A randomization schedule will be developed by an independent party to maintain blinding. Overall, approximately 60 subjects will be randomized TransCon CNP to Placebo in a 3:1 ratio to one of the following via an Interactive Web Randomization System (IWRS):

Cohort	Planned Dose Level	Approximate Number of Participants**
1	6 µg CNP/kg/week	9 on TransCon CNP, 3 on placebo
2	20 µg CNP/kg/week	≥9 on TransCon CNP, ≥3 on placebo
3	50 µg CNP/kg/week	≥9 on TransCon CNP, ≥3 on placebo
4	100 µg CNP/kg/week	≥9 on TransCon CNP, ≥3 on placebo
5	> 100 µg CNP/kg/week*	≥9 on TransCon CNP, ≥3 on placebo

*At a dose to be determined based on emerging data

**Minimum of 12 participants per cohort will be enrolled. Plan to enroll approximately 14 participants per cohort to account for potential drop-outs due to COVID-19.

The Randomized Period will be double-blind so that neither the sponsor, subject, or site personnel involved in study conduct will know the identity of a subject's treatment. The Randomized Period will be followed by a 104-week Open-Label Extension treatment period where all participants will receive TransCon CNP.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

In prepubertal children with achondroplasia (ACH) at 52 weeks:

- To determine the safety of once weekly subcutaneous (SC) doses of TransCon CNP
- To evaluate the effect of once weekly SC doses of TransCon CNP on annualized height velocity (AHV)

3.2 SECONDARY OBJECTIVES

- To evaluate the effect of once weekly SC doses of TransCon CNP on body proportionality (upper to lower body segment ratio) in prepubertal children with ACH at 52 weeks
- To evaluate the pharmacokinetic (PK) properties of once weekly SC doses of TransCon CNP
- To assess the potential immunogenic response to once weekly SC doses of TransCon CNP

3.3 EXPLORATORY OBJECTIVES

CCI

CCI

[redacted]

4 SAMPLE SIZE CALCULATION

A sample size of 9 in active groups (per cohort) and 12 in the placebo group (combined across cohorts) will provide 97% power to detect a treatment difference of 2 cm/year in 12-month AHV at a 2-sided significance level of 5%, assuming the SD is 1.1 cm/yr.

5 PLANNED ANALYSIS

Planned Analysis will include the following:

- DMC analysis: Summary analysis for DMC meetings are planned to monitor safety and determine dose escalation (the analysis scope and frequency will be specified in the DMC charter).
- Interim by-cohort analysis: In each cohort, after all participants have completed or withdrawn from the Randomized Period and the database for the Randomized Period has been locked and unblinded for the same cohort, interim by-cohort analysis will be performed.
- Primary analysis: The primary analysis will be performed after all participants have completed or withdrawn from the Randomized Period and the database for the Randomized Period has been locked and unblinded.
- Final analysis: The final analysis will be performed after all participants have completed or withdrawn from the study and the clinical trial database has been locked.

6 DATA MONITORING COMMITTEE

DMC meetings will be held by the Sponsor upon review of the following data to assess whether the next cohort should be initiated as planned:

- Initiation of Cohort 2: Cohort 1 data with a minimum of 12 weeks of follow up for all participants
- Initiation of Cohort 3: Cohort 2 data with a minimum of 12 weeks of follow up for all participants and available data from all other cohorts

- Initiation of Cohort 4: Cohort 3 data with a minimum of 12 weeks of follow up for all participants and available data from all other cohorts

Following the DMC meeting, the Sponsor will take into consideration the recommendation of the DMC to decide to either proceed to the next dose cohort as planned, modify the dose of the next cohort, or stop dose escalation. If available data are inadequate to decide on the action to be taken, the decision may be deferred until after data through Visit 5 (Week 26) of the highest dosed cohort are available, at which time the DMC meeting will be reconvened.

A DMC meeting will also be held when all participants in Cohort 4 have a minimum of 12 weeks of follow up. If 100 µg CNP/kg/week is deemed safe at this meeting, then participants in the Open-Label Period may have their dose increased to 100 µg CNP/kg/week.

Upon completion of 26 weeks of treatment (Visit 5) for all participants in Cohort 4, a DMC meeting will be held. After review of the data and consultation with the DMC, the Sponsor will decide whether a higher dose level should be investigated (up to 200 µg CNP/kg/week).

The DMC will make the recommendation regarding dose escalation for cohorts in the Open-Label Extension Period, which could be up to the highest dose level of TransCon CNP that has been reviewed by the DMC for safety and has passed DMC safety review. Dose escalation for the individual participant should be implemented at the next scheduled visit (except Visit 8) in the Open-Label Extension Period. After discussion with the Medical Monitor, an Investigator may choose to not increase the dose for an individual participant or may decrease to a prior dose.

In addition, ad hoc DMC meetings may be called by the Sponsor at any time for review of newly identified safety concerns.

The detailed roles and responsibilities of the DMC are specified in the DMC Charter.

7 ANALYSIS ENDPOINTS

7.1 EFFICACY ENDPOINTS

7.1.1 Primary Endpoint

- AHV as measured at 52 weeks of weekly TransCon CNP treatment or placebo.

7.1.2 Secondary Endpoint

- Change in upper to lower body segment ratio as measured at 52 weeks of weekly TransCon CNP treatment or placebo

7.1.3 Exploratory Endpoints

CCI [redacted]

CCI

7.2 SAFETY ENDPOINTS:

The following safety endpoints will be assessed for both Randomized Period and Open-Label Extension Period:

- Incidence of AEs
- All blood chemistry, hematology, lipid panel, and urinalysis parameters
- Vital sign measurements and physical examination assessments
- 12-lead ECG
- Radiographic findings from:
  - Bone age X-ray
  - DXA
  - Anterior-posterior standing lower extremity X-ray
  - Anterior-posterior and lateral spine X-ray
- Incidence of anti-drug antibodies

7.3 PHARMACOKINETIC ENDPOINTS:

- Plasma concentration of Total CNP
- Plasma concentration of Free CNP
- Plasma concentration of methoxypolyethylene glycol (mPEG) and mPEG-linker

8 DEFINITIONS

8.1 BASELINE

The initial baseline is defined as the last non-missing assessment prior to the initiation of the first dose of investigational product (CNP or Placebo).

OLE Baseline is defined as the last non-missing assessment prior to the initiation of the first dose of CNP in OLE Period.

For radiographic assessment of bone, the initial baseline is defined as the last non-missing assessment prior to or on visit 1, and the OLE baseline is defined as the last non-missing assessment prior to or on visit 7.

Historical height measurement will be used to calculate baseline for AHV. Among all available historical height measurements taken between 6 months and 15 months prior to the first dose of investigational product, the measurement that is closest to the time of 12 months will be considered. If there are two measurements with equal distance to one year prior to the first dose of investigational product, the earlier one will be used to calculate baseline AHV and the baseline AHV will be calculated as follows,

[Height (Baseline) - Height (Historical Measurement)] * 365.25/[Date (Baseline) - Date (Historical Measurement)+1]

8.2 DURATION OF EXPOSURE

During the Randomized Period, duration of exposure to investigational product (Placebo or CNP), in days, is defined as last date of investigational product in the Randomized Period – first date of investigational product in the Randomized Period + 7 days.

During the OLE Period, duration of exposure to CNP, in days, is defined as last dose date of CNP in the OLE Period – First OLE Dose Date + 7 days.

Total duration of exposure to CNP, in days, is defined as last dose date of CNP – First dose date of CNP + 7 days.

8.3 TOTAL NUMBER OF PLANNED DOSES AND TOTAL/AVERAGE WEEKLY ACTUAL DOSAGE

For each dose, the last non-missing weight prior to the initiation of current dosing will be used to calculate the actual dosage.

Total number of actual doses will be counted based on exposure recorded on eCRF. Multiple injections administered within 24 hours will be counted as one dose.

During the Randomized Period,

Total number of planned doses is defined as (last dose date in the Randomized Period – first dose date in the Randomized Period + 7)/7 truncated to the nearest integer.

Total actual dosage (µg/kg) is defined as Sum (concentration (mg/mL) x volume (mL)*1000/weight(kg)) over all injections during the Randomized Period.

Average weekly actual dosage (µg/kg/week) is defined as total actual dosage/total number of actual doses.

During the OLE Period,

Total number of planned doses is defined as (last dose date in the OLE Period – first OLE dose date + 7)/7 truncated to the nearest integer.

Total actual dosage (µg/kg) is defined as Sum (concentration (mg/mL) x volume (mL)*1000/weight(kg)) over all injections during the OLE Period.

Average weekly actual dosage (µg/kg/week) is defined as total actual dosage/total number of actual doses.

TransCon CNP Overall

Total number of planned CNP doses is (last dose date of CNP during the study – first dose date of CNP during the study + 7)/7 truncated to the nearest integer.

Total actual CNP dosage is the sum of total actual CNP dosage in the Randomized Period and OLE Period.

Average weekly actual CNP dosage (µg/kg/week) is defined as total actual CNP dosage/total number of actual CNP doses during the study including Randomized and OLE Periods.

8.4 DOSE COMPLIANCE

Dosing compliance (%) during the Randomized Period or OLE Period is defined as the (Total number of actual doses/total number of planned doses during the specific period) * 100.

CNP Dosing compliance (%) is defined as the (Total number of actual CNP doses/total number of planned CNP doses) * 100.

8.5 STUDY DAY

The study day for all assessments is calculated as the difference between the date of the event (visit date, assessment date, etc.) and the start of study treatment plus one day if on or after first dose of investigational product:

Study day = (event date – date of the first dose of investigational product + 1)

If the event date is prior the first dose of investigational product:

Study day = event date – date of the first dose of investigational product

8.6 AGE

Unless specified, the age will be derived based on the first dose date of investigational product: Age = (First Dose Date – Birth Date+1)/365.25. When date of birth is missing, the age recorded on electronic case report forms (eCRF) will be used.

If birth date is missing and age recorded on eCRF is also missing, the birth date will be imputed to calculate (See Section 10.2.1 the algorithm to impute birth date) age.

8.7 ANNUALIZED HEIGHT VELOCITY

During the Randomized Period, the AHV at visit x will be derived based on the height at the initial baseline**:

[Height (Visit x) - Height (Initial Baseline)] * 365.25/[Date (Visit x) - Date (Baseline)+1]

** Refer to Section 8.1 for definition of initial baseline height.

The height velocity will be calculated for Randomization period and OLE period separately.

During the OLE Period, the OLE baseline value will be used for each successive AHV calculation until Week 104. And starting from Week 117 until end of study, the baseline value used for each successive AHV calculation will be the subject's height measured 52 weeks prior, e.g. height at Week 65 served as the baseline value to determine AHV at Week 117. If height at visit 52 weeks prior is missing then the most recent height prior to that visit will be used.

8.8 6-MONTH ANNUALIZED HEIGHT VELOCITY

6- Month AHV will be derived based on height measured 26 weeks prior during the study:

[Height (Visit x) - Height (Visit 26 week prior)] * 365.25/[Date (Visit x) - Date (Visit 26 week prior)+1]

During the Randomized Period, the 6-Month AHV at Week 26 will be calculated using initial baseline height as defined in Section 8.1. Starting from Week 39 until end of Randomized Period, the baseline value used for each successive AHV calculation will be the subject's height measured 26 weeks prior, e.g. height at Week 12 served as the baseline value to determine AHV at Week 39. If height at the visit 26 weeks prior is missing then the most recent height prior to that visit will be used.

The 6-Month AHV will be calculated for Randomization period and OLE period separately.

During the OLE Period, the 6-Month AHV at Week 78 will be calculated using OLE baseline height. And starting from Week 91 until end of study, the baseline value used for each successive 6-Month AHV calculation will be the subject's height measured 26 weeks prior during the OLE Period. If height at the visit 26 weeks prior is missing then the most recent height prior to that visit will be used.

8.9 3-MONTH ANNUALIZED HEIGHT VELOCITY

The 3-Month AHV will be derived based on height measured approximately 12 weeks apart during the study:

[Height (Visit x) - Height (Visit 12 week prior)] * 365.25/[Date (Visit x) - Date (Visit 12 week prior)+1].

Similar to the 6-month annualized height velocity, the 3-Month AHV during Randomized Period and OLE Period will be calculated using the corresponding baseline height. If height at the visit 12 weeks prior is missing (or not available) then the most recent height prior to that visit will be used.

8.10 HEIGHT STANDARD DEVIATION SCORE

Height expressed in Standard Deviation Score (SDS) is derived using CDC 2000 (United States of America)/Kuczmarski method as,

(((Height/M)^L)-1)/(L x S)

Where M=median, S= generalized coefficient of variation, and L= power in the Box-Cox transformation. The M, S, L values are obtained from the CDC website; Percentile Data Files with LMS Values. M, L, and S need to be interpolated based on the next lower age category, and the next upper age category. Age at the corresponding visit with height measurement will be used for the derivation.

In addition, ACH specific height SDS is derived using age and gender specific mean and (upper or lower, depending on whether the height value is larger or smaller than its age and

sex specific mean height) standard deviations from ACH population [1], as follows: (Height – mean)/standard deviation.

9 ANALYSIS POPULATIONS

9.1 SCREENED POPULATION

The Screened Population will consist of all subjects who underwent a Screening Visit and received a subject identification number.

9.2 RANDOMIZED POPULATION

The Randomized Population will include all subjects who were randomized to a treatment group in the trial.

9.3 FULL ANALYSIS SET

The Full Analysis Set will include all randomized subjects who have received at least one dose of investigational product and have a non-missing baseline height as well as at least one post-baseline height measurement. Subjects will be analyzed according to study treatment as randomized.

9.4 SAFETY ANALYSIS SET

The Safety Analysis Set will include all randomized subjects who have received at least one dose of investigational product. Subjects will be analyzed according to study treatment as treated.

9.5 PHARMACOKINETIC POPULATION

The PK Population includes all subjects in the Full Analysis Set who have the primary PK data that are considered sufficient and interpretable.

10 DATA SCREENING AND ACCEPTANCE

10.1 GENERAL PRINCIPLES

Data will be reviewed periodically. Any questionable data will be reported to the clinical data manager promptly for query and resolution.

10.2 HANDLING OF MISSING AND INCOMPLETE DATA

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

10.2.1 Missing Birth Dates

To impute missing birth date, the following rules will be applied:

- If day is missing, impute 15.
- If month is missing, impute June.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is later than any study visit date/observed adverse event start date/ observed concomitant medication start date, then earliest available visit date/adverse event start date/concomitant medication start date will be used without changing observed information.

10.2.2 Missing Date Imputation for Historical Anthropometric measurements

Imputation will be done if only day is missing and month and year are present in historical/rollover measurements. If day is missing impute 15, unless the imputed date is later than screening date then screening date will be the imputed date.

10.2.3 Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

<u>Missing Start Dates</u>

- If the day is unknown, then:
  - If the month and year match the first dose of investigational product start date month and year in this study, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If both day and month are unknown, then:
  - If the year matches the year of the first dose of investigational product date in this trial, then impute the day and month of the first dose date in this trial.
  - Otherwise, assign ‘January 01’.
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed date is earlier than birth date, then birth date will be used. If the imputed start date is later than the end date, then the start date will be set as the same date as the end date.

Missing End Dates for "not ongoing" CM

- If the day is unknown, then assign the last day of the month.
- If both day and month are unknown, then assign 'December 31.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing.

If the resulting end date is after the date of study completion / discontinuation/ data cutoff, set the imputed end date to the date of study completion / discontinuation/ data cutoff, whichever is earlier.

10.2.4 Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to the investigational product is missing for an AE that started on or after the date of the first dose of investigational product, a causality of "related" will be assigned. The imputed values for causal relationship to investigational product will be used for the incidence summary; the values will be shown as missing in the data listings.

10.2.5 Missing Primary Endpoint

Subjects with missing primary endpoint will have height value imputed using a multiple imputation model that contains the following variables: gender, baseline age, baseline height SDS, and height values at post-baseline visits. The multiple imputation will be stratified by treatment ([4-5]), which is detailed in Appendix 3.

10.3 VISIT TIME WINDOWS

Unscheduled visit (occurred after the date of initiation of the first dose) or end of study visit will be mapped to the closet scheduled visit. If the unscheduled visit is in the middle of two scheduled visits, map it to the later one.

After mapping, if there are more than one visits in the same window, the scheduled visit will be used if available; if there is no scheduled visit in the same window, the mapped visit closer to the target assessment day will be used. If more than one visits have the equal distance to the target day then the later one will be used, if more than one visits on the same day, use the time or the sequence number to select the later record. For listings and shift tables, all data points will be included.

Table 10.3–1 presents the visit window assigned for assessments scheduled and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 10.3–1: Analysis Window to Map Unscheduled and Early Termination Visits

Period	Visit	Week	Scheduled Visit Day	Window
Randomized Period	Visit 1	Baseline	Day 1	Days ≤ 1
	Visit 2	Week 4	Day 29	Days [2, 43]
	Visit 3	Week 8	Day 57	Days [44, 71]
	Visit 4	Week 12	Day 85	Days [72, 134]
	Visit 5	Week 26	Day 183	Days [135, 228]
	Visit 6	Week 39	Day 274	Days [229, 319]
	Visit 7	Week 52	Day 365	[320, study day of first OLE dose date*]
OLE Period	Visit 8	Week 56	Day 393	[study day of first OLE dose date + 1, 424]
	Visit 9	Week 65	Day 456	Days [425, 501]
	Visit 10	Week 78	Day 547	Days [502, 592]
	Visit 11	Week 91	Day 638	Days [593, 684]
	Visit 12	Week 104	Day 730	Days [685, 775]
	Visit 13	Week 117	Day 821	Days [776, 866]
	Visit 14	Week 130	Day 912	Days [867, 957]
	Visit 15	Week 143	Day 1003	Days [958,1049]
	Visit 16	Week 156	Day 1095	Days ≥ 1050

*If a subject entered into OLE Period, the date of OLE first dose will be used. Otherwise, the last visit date during the Randomized Period will be used.

10.4 SOFTWARE

SAS® software version 9.4 or higher will be used to perform statistical analyses unless otherwise specified.

11 STATISTICAL METHODS OF ANALYSES

11.1 GENERAL PRINCIPLES

Efficacy analyses will be based on the Full Analysis Set and safety analyses will be based on Safety Analysis Set. PK analysis will be based on the PK population. Continuous variables will be presented using number of subjects, mean, standard deviation (SD), standard error

(SE), median, minimum and maximum. Categorical data will be presented using counts and percentages of subjects.

In general, analyses will be done by dose levels, and placebo subjects will be pooled as placebo group. Results for the Randomization Period and OLE Period will be summarized by treatment group assigned during the Randomized Period. In addition, by-cohort analysis will also be performed after each cohort completes Randomized Period and Database is locked and unblinded for that cohort.

All statistical tests will be two-sided and tested at statistical significance level of 0.05. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

11.2 SUBJECT ACCOUNTABILITY

The number and percentage of subjects in each of the study populations (Screened, Randomized, Full Analysis Set, Safety Analysis Set and PK) will be summarized. Subjects excluded from the analysis set will be listed.

Screen-failure subjects (i.e., subjects screened but not randomized) and the associated reasons for failure to randomize will be listed.

The number and percentage of subjects who complete the treatment period and of subjects who prematurely discontinue will be presented for each treatment group for the Randomized Population. The reasons for premature discontinuation from treatment and/or the study as recorded on eCRFs will be summarized. Disposition data will be listed by subject for the Randomized Population.

11.3 PROTOCOL DEVIATIONS

Important protocol deviations will be summarized by type in each treatment group for the Randomized Population. Both important and non-important deviations will be listed.

Deviations related to COVID-19 pandemic, if applicable, will be listed.

11.4 INVESTIGATIONAL PRODUCT ADMINISTRATION

11.4.1 Extent of Exposure

Exposure to the investigational product for the Safety Analysis Set will be summarized by treatment group.

For the Randomized Period, the following parameters will be presented:

- Duration of exposure
- Total number of planned doses
- Total number of actual doses
- Total actual dosage
- Average actual weekly dosage

For the OLE Period, the following parameters will be presented:

- Duration of exposure
- Total number of planned doses
- Total number of actual doses
- Total actual dosage
- Average actual weekly dose

In additional, overall TransCon CNP exposure will be summarized for the following parameters:

- Duration of exposure to TransCon CNP
- Total number of planned CNP doses
- Total number of actual CNP doses
- Total actual CNP dosage
- Average actual weekly CNP dosage

Duration of exposure to actual dose of investigational product throughout Randomized Period and OLE Period will be summarized for each treatment group assigned during the Randomized Period.

11.4.2 Measurement of Treatment Compliance

Descriptive statistics for investigational product compliance will be presented by treatment group for the Safety Analysis Set. Treatment compliance will be calculated as defined in Section 8.4.

11.4.3 Demographic and Baseline Characteristics

Demographic parameters (age, age group, race/ethnicity, sex, height, height SDS, weight, BMI) and other baseline characteristics (age at ACH diagnosis, type of mutation, and baseline AHV) will be summarized descriptively by treatment group for the Full Analysis Set.

11.4.4 Medical History

Medical history will also be summarized by system organ class (SOC) and preferred term (PT) for the Full Analysis Set by treatment group.

11.4.5 Prior and Concomitant Medication

Prior medication is defined as any medication started before the date of the first dose of investigational product (medication start date prior to the first dose date).

Concomitant medication is defined as any medication taken on or after the date of the first dose of investigational product (medication end date on or after first dose date [or ongoing],

and medication start date prior or on the last dose date). Any concomitant medications started after the date of the last dose of investigational product will not be presented in the summary tables but will be included in the subject data listings.

Both prior and concomitant medications will be coded by drug name and therapeutic class using World Health Organization (WHO) Drug Dictionary. Both prior and concomitant medications will be summarized by treatment group for the Full Analysis Set.

If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class.

11.5 EFFICACY ANALYSIS

The efficacy analysis will be performed using the Full Analysis Set.

For the Randomized Period, Analysis of Covariance (ANCOVA) model will be used as the primary analysis for the primary and secondary efficacy endpoint to compare different dose levels of TransCon CNP groups vs. pooled placebo group (combined across cohort).

During the OLE Period, the efficacy endpoints and applicable change from baseline will be summarized descriptively and in general, OLE baseline will be used.

11.5.1 Analysis of Primary Efficacy Endpoint

11.5.1.1 Primary Analysis

The estimand formulation is as follows,

The following primary hypothesis will be tested (two-tailed):

H_0: Difference in mean AHV at Week 52 between CNP treatment group and the placebo group = 0
H_1: Difference in mean AHV at Week 52 between CNP treatment group and the placebo group ≠ 0

Population:

Full Analysis Set

Variable

AHV as measured at 52 weeks of weekly TransCon CNP treatment or placebo.

Intercurrent events and their handling rules are as follows:

Subjects who discontinue study treatment due to any reason will have their data collected after discontinuation of study treatment (up to Visit 7 if discontinued during the Randomized

Period), and included in the study database and analysis, whenever possible (Treatment Policy).

For subjects with missing primary efficacy endpoint will have the height value imputed using the multiple imputation method as specified in Section 10.2.5 and Appendix 3, will be used.

Analysis:

The primary analysis is ANCOVA model with the AHV at Week 52 as the response variable, treatment (dose groups and placebo) and sex as factors, baseline age and baseline height SDS as covariates.

Population-level Summary:

Difference in estimated means between the CNP treatment group and placebo.

11.5.1.2 Sensitivity Analysis

To assess the robustness of the primary analysis, following sensitivity analyses of the primary endpoint will be performed on Full Analysis Set.

Sensitivity Analysis 1

ANCOVA model with the AHV at Week 52 as the response variable, covariates including treatment, sex, baseline age group (<5 vs. ≥ 5 years), and baseline height SDS.

Sensitivity Analysis 2

Piecewise ANCOVA model with the AHV at Week 52 as the response variable, covariates including treatment, sex, baseline age for age <5 years and age ≥ 5 years, and baseline height SDS.

Sensitivity Analysis 3

The change from baseline to Week 52 in AHV will be analyzed using ANCOVA model with treatment and sex as factors, baseline age, baseline height SDS, and baseline AHV as covariates.

Sensitivity Analysis 4

The 6-month AHV at Week 52 will be analyzed using ANCOVA model with 6-month AHV at Week 52 as the response variable, treatment (dose groups and placebo) and sex as factors, baseline age and baseline height SDS as covariates.

11.5.2 Analysis of Secondary Efficacy Endpoint

To analyze change from baseline to Week 52 in upper to lower body segment ratio, ANCOVA model will be performed with treatment and sex as factors, baseline age, and baseline upper to lower body segment ratio as covariates.

11.5.3 Sequential Testing Procedure for Primary and Secondary Efficacy Endpoint

Once the highest tolerated dose is established, the following multiplicity adjustment schema will be used for the comparison between the highest tolerated dose group and pooled placebo group.

The primary analysis for AHV at Week 52 will be performed first. If the p-value for comparing the highest tolerated dose group and pooled placebo is <0.05, then the formal hypothesis test for upper to lower body segment ratio will be performed.

11.5.4 Analysis of Exploratory Efficacy Endpoints

An ANCOVA model with treatment and sex as factors, baseline age and corresponding baseline endpoint measurements as covariates, will be used to analyze the following exploratory endpoints,

CCI

[redacted]

11.5.4.1 PRO/ObsRO Measures

PRO/ObsRO measures for the trial consist of the following scales:

CCI

[redacted]

To analyze change from baseline to Week 52 in above PRO/ObsRO measures, ANCOVA model will be performed with treatment and sex as factors, baseline age and corresponding baseline PRO/ObsRO measures as covariates. The observed values and change from baseline at each timepoint of the above PRO/ObsRO scales, will be summarized descriptively by treatment group, for both Randomized Period and OLE Period.

11.6 SAFETY ANALYSIS

The safety analysis will be performed using the Safety Analysis Set for Randomization Period and OLE Period. The safety parameters include AEs, clinical laboratory, vital sign, physical examinations, ECG parameters, radiographic findings and antibody parameters.

For safety endpoints, all analyses will be based on the observed data (i.e., with no imputation of missing data), unless otherwise stated.

11.6.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The investigator will grade an AE as mild, moderate or severe.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) in the Randomized Period, if the AE start date occurs or worsens in severity on or after the first dose of study drug in the Randomized Period, or before the first dose of study drug in the OLE Period, if subjects continue to OLE Period.

An AE (classified by preferred term) will be considered a TEAE in the OLE Period, if the AE start date occurs or worsens in severity on or after the first dose of study drug in the OLE Period.

An AE that occurs within 30 days after the last dose of study drug in the last treatment period (Randomized Period or OLE Period) will be assigned to the last treatment period as TEAE.

Subject incidence of TEAEs will be tabulated by treatment group as the following Summary of TEAEs

- TEAEs by SOC and PT (preferred term)
- Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- Grade 3 or Higher TEAEs by SOC and PT
- Comorbidity of ACH TEAE by SOC and PT
- Related to Study Procedures TEAE by SOC and PT
- TEAEs leading to Deaths by SOC and PT
- TEAEs leading to discontinuation of study by SOC and PT
- TEAEs leading to discontinuation of treatment by SOC and PT
- TEAEs by PT
- Related TEAEs by PT
- Serious TEAEs by PT

- TEAEs leading to Deaths by PT

Detailed listings for all AEs, serious TEAEs, AEs leading to the discontinuation of study, AEs leading to the discontinuation of treatment, and death will also be generated.

In addition, subject incidence of TEAEs by actual dose of investigational product throughout Randomized Period and OLE Period will be summarized for the following:

- TEAEs by SOC and PT by Grade
- Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- TEAEs by PT

11.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in conventional and SI units) and changes from the baseline values at each assessment time point will be presented by treatment group and treatment period for the following laboratory parameters:

- **Chemistry**
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Magnesium
  - Phosphate
  - Calcium
  - Glucose
  - Alkaline Phosphatase
  - Aspartate Aminotransferase (AST)
  - Alanine Aminotransferase (ALT)
  - Creatinine
  - Creatine Phosphokinase
  - Albumin
  - Direct Bilirubin
  - Total Bilirubin
  - Blood urea nitrogen (BUN)
  - Gamma Glutamyl Transferase

- Lactate Dehydrogenase
- Total Protein
- Uric Acid

- **Hematology**
- Hemoglobin
- Hematocrit
- Red blood cell (RBC) Count
- White blood cell (WBC) Count
- Differential Cell Count
- Platelet Count

- **Lipid panel**
- Total cholesterol
- Low-density lipoprotein (LDL)
- High-density lipoprotein (HDL)
- Triglycerides

- **Urine Chemistry**
- Urine Calcium
- Urine Creatinine
- Urine Phosphate

Data listings for laboratory will be provided. Listings of clinically significant laboratory findings will be provided separately.

11.6.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, heart rate, and temperature) and changes from baseline values at each assessment time point will be presented by treatment group and treatment period.

Descriptive statistics for orthostatic changes for vital signs (systolic and diastolic blood pressures and heart rate) and changes from baseline values at each assessment time point will be presented by treatment group, as appropriate.

Data listings for vital signs will be provided.

11.6.4 Physical Examination

For sleep and snoring patterns, the number and percentage of subjects with abnormal findings at Screening will be summarized by treatment group. Changes from Screening and from last visits at each assessment time point will be summarized by treatment group and treatment period.

Descriptive statistics for pubertal status will be provided by sex and treatment group.

Data listings for physical examination will be provided.

11.6.5 Electrocardiogram

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and QTcF) and changes from baseline values at each assessment time point will be presented by treatment group and treatment period.

Data listings for ECG parameters will be provided.

11.6.6 Radiographic findings

Results from the following radiographic assessments will be summarized.

- Bone age X-ray
- dual-energy X-ray absorptiometry (DXA)
- Anterior-posterior standing lower extremity X-ray
- Anterior-posterior and lateral spine X-ray

The change in bone age, the ratio of bone age over chronical age, and delay in bone age will be calculated and summarized by treatment group and treatment period.

Data listings for radiographic findings will be provided.

11.6.7 Antibody Parameters

The appropriateness of the approach taken to analyze and report anti-drug antibody data should be evaluated on a case-by-case basis [2], following recent regulatory guidance and white papers [3]. Statistical analysis of antibodies against drug (ADA) will include (but not be limited to) the following tabulated summaries of antibody frequencies and population percentages:

1. Incidence of pre-existing anti-CNP-38 binding antibodies (positive baseline)
2. Incidence of treatment induced anti- CNP-38 binding antibodies by positive types (treatment emergent positive and treatment boosted positive) and overall
3. Incidence of persistent anti-CNP-38 binding antibodies by positive types and overall
4. Incidence of transient anti-CNP-38 binding antibodies by positive types and overall
5. Incidence of pre-existing anti-CNP-22 binding antibodies (positive baseline)
6. Incidence of treatment induced anti- CNP-22 binding antibodies by positive types and overall
7. Incidence of persistent anti-CNP-22 binding antibodies by positive types and overall
8. Incidence of transient anti-CNP-22 binding antibodies by positive types and overall
9. Incidence of treatment induced anti-CNP neutralizing antibodies[1] by positive types and overall

10. Incidence of persistent anti-CNP neutralizing antibodies by positive types and overall
11. Incidence of transient anti-CNP neutralizing antibodies by positive types and overall
12. Incidence of pre-existing anti-prodrug antibodies (positive baseline)
13. Incidence of treatment induced anti-prodrug binding antibodies by positive types and overall
14. Incidence of persistent anti-prodrug antibodies by positive types and overall
15. Incidence of transient anti-prodrug antibodies by positive types and overall

Neutralizing antibodies are defined as confirmed binding anti-CNP antibodies that are confirmed positive in a cell-based neutralizing antibody assay.

Treatment induced ADA will include two positive types:

- Treatment emergent positive: if baseline (pre-treatment sample) is negative for ADA and at least 1 post-treatment sample is positive for ADA
- Treatment boosted positive: if baseline (pre-treatment sample) is positive and at least 1 post-treatment sample has a titer which is at least 4-fold higher than the pre-treatment sample.

Transient ADA is defined as treatment-induced ADA detected only at one sampling time point during study, or when there is less than 16 weeks between the first and the last ADA positive post-treatment samples.

Persistent ADA is defined as when there is more than (or equal to) 16 weeks between the first and the last ADA positive post-treatment samples.

For Randomized Period, antibody data will be summarized by treatment group. In addition, antibody data for overall CNP treatment period (both Randomized and OLE Period for CNP treatment group; OLE Period for placebo treatment group) will also be summarized separately, and the initial baseline will be used for antibody analysis.

11.7 PHARMACOKINETIC ANALYSIS

Summary statistics will be provided for plasma concentration of Total CNP, Free CNP and mPEG and mPEG-linker at scheduled visits/time points. Plasma concentration values below the limit of quantitation will be treated as zero in the descriptive statistics calculations. Missing values will be treated as if the sample was not taken. The summary tables will include the number of subjects, number of samples with values below the limit of quantitation, mean, standard deviation, standard error, percent coefficient of variation (%CV), 95% CI, median, minimum, maximum geometric mean, and geometric %CV. Plasma concentration data versus visit/time points will be presented in figures.

12 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

NA

13 CHANGES TO PREVIOUS SAP

Section Number	Section	Changes
8.9	3-Month Annualized Height Velocity	Added details for 3-Month AHV calculation.
8.10	Height Standard Deviation Score	Added details on the calculation of ACH specific height SDS.
11.3	Protocol Deviations	Changed major and minor protocol deviations to important and non-important protocol deviations.
11.4.1	Extent of Exposure	Added summaries for duration of exposure to actual dose of investigational product.
11.5.1.2	Sensitivity Analysis	Added additional sensitivity analyses.
11.5.4	Analysis of Exploratory Efficacy Endpoints	CCI [redacted]
11.6.1	Adverse Events	Added summaries of TEAEs by actual dose of investigational product.

14 REFERENCES

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15 APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS IN THE RANDOMIZED PERIOD

Visit	**Screen**	**1**	**Phone[a]**	**2[b]**	**3**	**4**	**5[b]**	**6**	**7/ET[b]**	**Follow-Up[c]**
Week		**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**57**
Window	**-4 to -1 weeks**		**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
Consent	X									
Demographics	X									
Verification of eligibility, including genetic test for ACH[d]	X									
Medical history[e]	X	X								
Prior/Concomitant medication	X	X	X	X	X	X	X	X	X	
Adverse events review[f]		X	X	X	X	X	X	X	X	X
Limited, symptom-directed physical examination[g]		X		X	X	X		X		
Full physical examination[h]	X						X		X	
Thorough skeletal physical exam[i]	X	X		X	X	X	X	X	X	
Assessment of pubertal status[j]	X						X		X	
Vital signs[k]	X	X		X	X	X	X	X	X	
Weight	X	X		X	X	X	X	X	X	
Standing height and sitting height	X			X	X	X		X		
All anthropometric measurements		X					X		X	
12-lead ECG	X	X[l]		X	X		X		X	
Bone age X-ray		X[m]							X[m]	
DXA[n]		X[m]							X[m]	
AP standing lower extremity X-ray		X[m]				X[o]			X[m]	
AP and lateral Spine X-ray		X[m]				X[o]			X[m]	

Qualitative assessment of sleep and snoring pattern	X	X		X	X	X	X	X	X	
Pharmacokinetics		X[p]		X	X	X	X	X	X	
Blood chemistry	X	X		X	X	X	X	X	X	
Hematology	X	X		X	X	X	X	X	X	
Lipid panel	X				X			X	X	
25(OH) Vitamin D	X						X		X	
Biomarkers	X	X		X		X	X	X	X	
Anti-drug antibodies	X	X		X		X	X	X	X	X
Urine collection	X					X	X	X	X	
PRO/ObsRO Validation Battery[q]	X								X	
Subset of PRO/ObsRO Validation Battery[q]		X			X	X	X	X		
CCI [r]	X	X			X	X	X	X	X	
Dispensing of study drug and diary		X		X	X	X	X	X		
Study drug administration on site		X								

Error! Reference source not found. All participants will be contacted by phone during Week 2 for follow up. During the call, the study staff will ask the caregiver about the general well-being of the child, inquire regarding correct administration of study drug procedures, record any AEs, record any concomitant medication changes and answer any questions.

[b] Visit 2 (Week 4), Visit 5 (Week 26), and Visit 7 (Week 52) labs are drawn at trough. Therefore, study drug cannot be administered within 6 days prior to these visits. The last dose of study drug will be administered at least 6 days prior to Visit 7

[c] Only for participants not proceeding to the Open-Label Extension Period.

[d] Previous genetic testing will be accepted. The documented lab result should be reviewed by the investigator to confirm the result along with the specific FGFR3 mutation. If not available in medical record, Screening will include testing for G380R mutation, but further testing may be pursued on an individual basis as indicated.

[e] Medical history should elicit all major illnesses, diagnoses, and surgeries that the participant has ever had, and any prior or existing medical conditions that might interfere with study participation or safety. Medical history includes historical anthropometric measurements, as available.

[f] Includes review of ACH comorbidities based on age, including risk of sleep apnea and CMC.

[g] Limited, symptom-directed physical examination should be performed as needed at the discretion of the investigator to provide appropriate medical care to the participants and to verify no clinically relevant changes have occurred since the Screening Visit. On Visit 1, injection site must be visually inspected prior to dosing and at 1 hour and 2 hours after injection of study drug. For participants that undergo blood collection for pharmacokinetic analyses at 8, 24, and 48 hours following first dose, injection site will be inspected at the time of each blood collection. All subsequent visits should also include a visual inspection of injection sites.

[h] Includes assessments of all major body systems including general appearance, HEENT, Neck (including thyroid), Lung/pulmonary, Chest, CV, Abdomen, Back, GU, Neurological, Extremities, and Skin. All visits, except at the Screening Visit, should also include a visual inspection of injection sites.

[i] Thorough skeletal physical exam will be performed by palpating the bone structure and joints for tenderness and mobility and other abnormal changes not normally found in children with ACH. Special attention will be paid to the hip exam, which will include a supine assessment of abduction and adduction of hips to assess for pain and any limitation of range of motion. If changes are noted further evaluation will be required as clinically indicated, including imaging and/or orthopedic consultation. DMC will be apprised of any safety findings.

[j] Boys will be assessed for testis volumes, and girls for breast development according to Tanner stages ([6]). Pubic hair rating will also be recorded according to Tanner stages but will not be used to assess eligibility. All participants must be Tanner Stage 1 for breast development (girls) - no glandular development/breast buds, and Tanner Stage 1 for gonadal development (boys) - testicular volume < 4 mL ([7]). Tanner stage progression during the course of the trial will not impact study treatment. See Protocol Appendix 3 for details.

[k] Participants should rest for at least 5 minutes before vital sign measurement and vital signs are to be taken before blood samples are drawn. Temperature measured in degrees Celsius (°C) or Fahrenheit (°F), blood pressure, and heart rate must be measured at Screening Visit and Visit 1. Orthostatic HR and systolic/diastolic BP will also be measured at Visit 1 prior to administration of study drug following first dose when the participant is at rest for 5 minutes (preferably supine) and again after standing at 3 minutes for assessment of orthostatic hypotension. Additionally, at Visit 1, all vital signs must be monitored at 1 hour and 2 hours post injection of the study drug. For participants that undergo blood collection for pharmacokinetic analyses at 8, 24, and 48 hours following first dose, orthostatic vital signs (HR, and BP) will also be measured prior to each PK blood collection. At all other visits, resting heart rate and blood pressure must be measured.

[l] At approximately 48 hours after the first dose for participants that undergo PK blood collection for PK analysis at that time.

[m] Radiographic assessments may not be required, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to the visit. If radiographic assessments cannot be completed prior to study drug administration at Visit 1 due to scheduling conflicts, the assessments may be completed at up to 24 hours after study drug administration.

[n] DXA scan are at Visit 1 and Visit 7 for children aged 5 years and older only.

[o] Scheduled radiographic assessments may be performed within 1 week prior to or after the visit if all scheduled assessments cannot be completed within the same day.

[p] PK blood collection will be performed for all participants prior to injection of study drug. For participants who weigh ≥11 kg, blood collection will be performed at approximately 8, 24, and 48 hours after injection at Visit 1 for pharmacokinetic analyses. Allowances will be made for accommodation. Exceptions to the extended PK blood collection will be considered on an individual basis (e.g. if travel creates an undue hardship for a family).

[q] PRO/ObsRO validation batteries must be completed by the caregiver without assistance and should be completed prior to conducting any clinical assessments. The same caregiver should complete all PRO/ObsRO validation batteries throughout participation in the trial. If the same caregiver is unable to attend a particular visit, an alternate caregiver may complete the PRO/ObsRO validation batteries at the visit.

[r] The CCI must be completed by the investigator who medically assessed the participant at the visit after all clinical assessments are completed. The same assessor should assess the participant at every visit.

APPENDIX 2. SCHEDULE OF EVENTS IN THE OPEN-LABEL PERIOD

Visit	**7**	**Phone[a]**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ET**	**Follow-Up OLE**
Week	**52**	**54**	**56**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**	**161**
Window		**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
Consent	X											
Prior/Concomitant medication		X	X	X	X	X	X	X	X	X	X	
Adverse events review[b]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[d]		X	X	X	X	X	X	X	X	X	
Limited physical examination[e]			X	X		X		X		X		
Full physical examination[f]					X		X		X		X	
Thorough skeletal physical exam[g]			X	X	X	X	X	X	X	X	X	
Assessment of pubertal status and childbearing potential[h]	X		X	X	X	X	X	X	X	X	X	
Weight			X	X	X	X	X	X	X	X	X	
Standing height and sitting height			X	X		X		X		X		
All anthropometric measurements					X		X		X		X	
12-lead ECG	X[i]		X	X[p]	X	X[p]	X		X		X	
Bone X-ray[j]							X				X	
DXA[j, k]							X				X	
AP standing lower extremity X-ray[j]				X			X	X			X	
AP and lateral Spine X-ray[j]				X			X	X			X	
Qualitative assessment of sleep and snoring pattern			X	X	X	X	X	X	X	X	X	
Pharmacokinetics	X[l]		X	X[p]	X	X[p]	X		X		X	
Blood chemistry			X	X	X	X	X	X	X	X	X	
Hematology			X	X	X	X	X	X	X	X	X	
Lipid panel					X		X		X		X	
25(OH) Vitamin D					X		X		X		X	
Anti-drug antibodies			X	X	X	X	X	X	X	X	X	X
Biomarkers			X	X	X	X	X	X	X	X	X	

Visit	7	Phone[a]	8	9	10	11	12	13	14	15	16/ET	Follow-Up OLE
Week	**52**	**54**	**56**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**	**161**
Window		**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
Urine collection	X		X	X	X	X	X	X	X	X	X	
Urine collection for hCG testing for females of childbearing potential[m]	X		X	X	X	X	X	X	X	X	X	
PRO and ObsRO Validation Battery[n]							X				X	
Subset of PRO/ObsRO Validation Battery[n]					X				X			
CCI				X	X	X	X	X	X	X	X	
Dispensing of study drug and diary	X		X	X	X	X	X	X	X	X		
Study drug administration on site	X											

[a] All participants will be contacted by phone during Week 54 for follow up. During the call, the study staff will ask the caregiver about the general well-being of the child, inquire regarding correct administration of study drug procedures, record any AEs, record any concomitant medication changes and answer any questions.

[b] Includes review of ACH comorbidities based on age, including risk of sleep apnea and CMC.

[c] Participants should rest for at least 5 minutes before vital sign measurement and vital signs are to be taken before blood samples are drawn. Temperature measured in degrees Celsius (°C) or Fahrenheit (°F).

[d] Orthostatic HR and systolic/diastolic BP will be measured at Visit 7 following first dose when the participant is at rest for 5 minutes (preferably supine) and again after standing at 3 minutes for assessment of orthostatic hypotension. Additionally, at Visit 7, all vital signs must be monitored at 1 hour and 2 hours post injection of the study drug. For participants that undergo blood collection for pharmacokinetic analyses at 8, 24, and 48 hours following first dose, orthostatic vital signs (HR, and BP) will also be measured prior to each PK blood collection.

[e] Limited, symptom-directed physical examination should be performed as needed at the discretion of the investigator to provide appropriate medical care to the participants and to verify no clinically relevant changes have occurred since the last visit. On Visit 7, injection site must be visually inspected prior to dosing and at 1 hour and 2 hours after injection of study drug. For participants that undergo blood collection for pharmacokinetic analyses at 8, 24, and 48 hours following first dose, injection site will be inspected at the time of each blood collection. All subsequent visits should also include a visual inspection of injection sites.

[f] Includes assessments of all major body systems including general appearance, HEENT, Neck (including thyroid), Lung/pulmonary, Chest, CV, Abdomen, Back, GU, Neurological, Extremities, and Skin. All visits should also include a visual inspection of injection sites.

[g] Thorough skeletal physical exam will be performed by palpating the bone structure and joints for tenderness and mobility and other abnormal changes not normally found in children with ACH. Special attention will be paid to the hip exam, which will include a supine assessment of abduction and adduction of hips to assess for pain and any limitation of range of motion. If changes are noted further evaluation will be required as clinically indicated, including imaging and/or orthopedic consultation. DMC will be apprised of any safety findings.

[h] Boys will be assessed for testis volumes, and girls for breast development according to Tanner stages ([6]). Pubic hair rating will also be recorded according to Tanner stages but will not be used to assess eligibility. Tanner stage progression during the course of the trial will not impact study treatment. See Protocol Appendix 3. During the open-label period, the Investigator should ascertain an individual's risk for becoming pregnant or fathering a child and take appropriate

steps. Pregnancy prevention counseling and pregnancy testing should be provided as appropriate and can be tailored per the Investigator's judgement based on maturity and cultural norms. See Protocol Appendix 6 for details on childbearing potential in females, wherever applicable.

[i] At approximately 48 hours after the first dose for participants that undergo PK blood collection for PK analysis at that time.

[j] Scheduled radiographic assessments may be performed within 1 week prior to or after the visit if all scheduled assessments cannot be completed within the same day. Radiographic assessments may not be required, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to the visit for Visit 16/ET.

[k] For children aged 5 years and older only.

[l] For participants who weigh ≥11 kg, blood collection will be performed at approximately 8, 24, and 48 hours after injection at Visit 7 for pharmacokinetic analyses. Allowances will be made for accommodation. Exceptions to the extended PK blood collection will be considered on an individual basis (e.g. if travel creates an undue hardship for a family).

[m] Urinary hCG test for females of childbearing potential according to Protocol Appendix 6 will be performed for all visits.

[n] PRO/ObsRO measures must be completed by the caregiver without assistance and should be completed prior to conducting any clinical assessments. The same caregiver should complete all PRO/ObsRO measures throughout participation in the trial. The PRO/ObsRO measures must be completed at the visit. If the same caregiver is unable to attend a particular visit, an alternate caregiver may complete the PRO/ObsRO measures at the visit.

[o] The CCI must be completed by the study staff who medically assessed the participant at the visit after all clinical assessments are completed. The same assessor should assess the participant at every visit.

[p] ECG and blood collection for pharmacokinetics should be performed prior to study drug administration and only at visits where the dose is escalated

APPENDIX 3. MULTIPLE IMPUTATION FOR MISSING DATA IN PRIMARY ENDPOINT

Imputation of missing data will be conducted under a working assumption of missing at random (MAR). Missing at random means that the missing data mechanism is assumed not to depend on unobserved missing values but may depend on any other available information collected in the trial.

The imputations will be performed for post-baseline visits. The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing height values by treatment group. The variable list for imputations will include gender, baseline age, baseline height SDS, as well as all available post-baseline height values. The SAS procedure PROC MI will be used in the multiple simulation. The MCMC method will impute 100 datasets. Multiple imputation replaces each missing value with a set of m = 100 plausible possibilities. The set of these possibilities represent the uncertainty about the unobserved 'true' value that was imputed.

Step I: Imputation of Missing Data

Default EM algorithm will be used to derive a set of initial parameter estimates for MCMC method. A non-informative prior (default Jeffreys' prior) will be used to derive the posterior distribution of the parameters. Trace plots and autocorrelation plots of the variables will be examined. The number of burn-in iterations may be modified (the default is 200 burn-in iterations) to ensure the iterations converge to the stationary distribution before the imputation.

Step II: Inference

For each of the 100 imputed datasets, height velocity will be recalculated based on the multiply imputed height values. The primary efficacy analysis will then be performed using an ANCOVA model with the AHV at Week 52 as the response variable, treatment (dose groups and placebo) and sex as factors, baseline age and baseline height SDS as covariates.

The estimates from the 100 fitted models for each of the 100 imputed datasets will be combined to provide an overall estimate of the least square mean with a corresponding confidence interval for each treatment group and an overall estimate of the difference in least square means between the CNP treatment *vs.* the placebo group and a p-value ([8]).

Approval Signatures

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