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

Document Date: Protocol Version 5: 28 December 2022

CLINICAL TRIAL PROTOCOL

PRODUCT NAME:	TransCon CNP
PROTOCOL NUMBER:	TCC-201
IND NUMBER:	142685
EUDRACT NUMBER:	2019-002754-22
PHASE:	2
PROTOCOL 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 DATE:	Version 1, 5 July 2019 Version 2, 1 September 2020 Version 3, 8 January 2021 Version 4, 12 August 2021 Version 5, 28 December 2022
PROTOCOL VERSION:	**5**
SPONSORED BY:	Ascendis Pharma Growth Disorders A/S Tuborg Boulevard 12, DK-2900, Hellerup, Denmark
GLOBAL MEDICAL MONITOR:	PPD **, MD** PPD Ascendis Pharma, Inc. 1000 Page Mill Rd, Palo Alto, California 94304, USA
BACK-UP MEDICAL MONITOR, EUROPE:	PPD **, MD PhD** PPD Ascendis Pharma A/S Tuborg Boulevard 12, DK-2900, Hellerup, Denmark
BACK-UP MEDICAL MONITOR:	PPD **, MD** PPD Ascendis Pharma, Inc. 1000 Page Mill Rd, Palo Alto, California 94304, USA

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Conference on Harmonization (ICH) E6 (R2) and regional regulations
- Regional participant data protection laws and regulations
- Other applicable regional and local regulations
- US Federal Regulations, as applicable

1. APPROVAL SIGNATURES

1.1. SPONSOR

I agree to conduct this trial in accordance with the requirements of this Clinical Trial Protocol and also in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Conference on Harmonization (ICH) E6 (R2) and regional regulations
- Regional participant data protection laws and regulations
- Other applicable regional and local regulations
- Clinical trial contractual obligations
- US Federal Regulations, as applicable

CLINICAL TRIAL 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.

See Appended Electronic Signature

PPD, MD

Date

PPD

Ascendis Pharma, Inc

SUMMARY OF CHANGES – VERSION 5, 28 December 2022

Rationale

The following substantial changes are made from protocol v 4.0 to protocol v 5.0:

Section (s)	Change	Rationale
Front page	Updated contact information for medical monitors	Change in Sponsor staff
10.1.3.20; Synopsis	Adding information of a new separate long-term open-label extension study for participants completing treatment in the TCC-201 protocol.	Introducing the potential option to continue treatment in a separate long-term open-label extension study (ASND0039) for the participants who are eligible and if no safety concerns for continued treatment with TransCon CNP have been identified.
10.1.3.21; Synopsis; Appendix 1 (Schedule of Events – OLE)	Follow-Up Visit not required for participants who will continue in the separate long-term open-label study (ASND0039).	The assessments scheduled to be performed at the Follow-Up Visit will be performed in the long-term open-label extension study for the participants who continue in that study.
11.8.1	Change of "Bone Age X-ray" to "Hand and Wrist X-ray".	Clarification of the scope of assessments made from the x-ray of the hand and wrist, as the images will not only be assessed for bone age but also for bone growth.
11.8.2	Adding "bone growth" to the assessments made from the anterior-posterior standing lower extremity x-rays.	Clarification of the scope of assessments made from the x-ray of the lower extremity, as the images will also be assessed for bone growth.
12.4.2	Updated SAE reporting	Reporting of Serious Adverse Events and pregnancies may contain personal identifiable information covered by data privacy regulation. As emails/fax are not considered to be adequately secure for sharing this type of information the current reporting method may therefore impose a risk of data breach. In order to mitigate this risk, Ascendis Pharma is changing the reporting method to secure online reporting through the Ascendis Safety Reporting Portal (safety.ascendispharma.com). This change has previously been implemented in a non-substantial protocol addendum version 1.0 and is now incorporated in the full protocol.

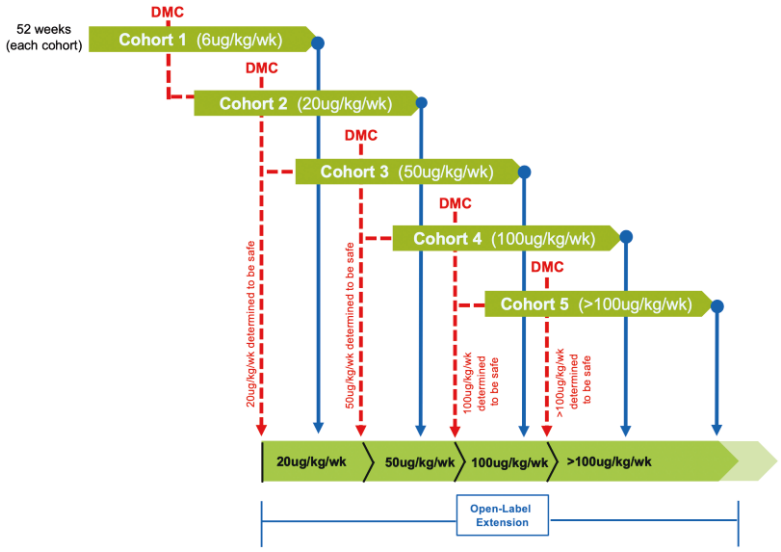
2. SYNOPSIS

PRODUCT NUMBER/NAME	TransCon CNP
PROTOCOL NUMBER	TCC-201
IND NUMBER	142685
EUDRACT NUMBER	2019-002754-22
DEVELOPMENT PHASE	2
PROTOCOL 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
INDICATION	Achondroplasia
OBJECTIVES	**Primary:** 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) **Secondary:** • 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 **Exploratory:** CCI [redacted]

	CCI [redacted]
PLANNED TRIAL SITES	Approximately 35
PLANNED NUMBER OF PARTICIPANTS	Minimum of 60
TRIAL POPULATION	Minimum of 60 male and female prepubertal children with ACH aged 2 to 10 years old
ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Clinical diagnosis of ACH with genetic confirmation (See Section 11.11) 2. Age between 2 to 10 years old (inclusive) at Screening Visit 3. Prepubertal (Stage 1 breasts for girls or testicular volume < 4ml for boys) at Screening Visit (See Section 11.3) 4. Able to stand without assistance 5. Caregiver willing and able to administer subcutaneous injections of study drug 6. Written, signed informed consent of the parent(s) or legal guardian(s) of the participant and written assent of the participant as required by the institutional review board/human research ethics committee/independent ethics committee (IRB/HREC/IEC) **Exclusion Criteria** 1. Clinically significant findings at Screening that: • are expected to require surgical intervention during participation in the trial or • are musculoskeletal in nature, such as Salter-Harris fractures and severe hip pain or • otherwise are considered by investigator or Medical Monitor to make a participant unfit to receive study drug or undergo trial related procedures 2. Have received treatment (>3 months) of human growth hormone (hGH) or other medications known to affect stature or body proportionality at any time 3. Have received any dose of medications intended to affect stature or body proportionality within the previous 6 months of Screening Visit

	4. Have received any study drug or device intended to affect stature or body proportionality at any time 5. History or presence of injury or disease of the growth plate(s), other than ACH, that affects growth potential of long bones 6. History of any bone-related surgery that affects growth potential of long bones, such as orthopedic reconstructive surgery and osteotomy (Limb-lengthening with full recovery is allowed with a minimum of 12 months of bone healing. Foramen magnum decompression and laminectomy with full recovery are allowed with minimum of 6 months of bone healing. History of 8 plate epiphysiodesis is allowed, but the plates must have been removed prior to Screening with minimum 4 weeks of healing.) 7. Have a form of skeletal dysplasia other than ACH or known medical conditions that result in short stature or abnormal growth [such as severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), hypochondroplasia, growth hormone deficiency, Turner syndrome, pseudoachondroplasia, inflammatory bowel disease, chronic renal insufficiency, active celiac disease[1], Vitamin D deficiency[2], untreated hypothyroidism[3], poorly controlled diabetes mellitus (HbA1c ≥8.0%) or diabetic complications[4]] [1]Celiac disease responsive to a gluten-free diet is allowed [2]Vitamin D deficiency or insufficiency treated with supplementation is allowed. Vitamin D deficiency is defined as 25(OH)D level <20ng/mL (<49.9 nmol/L), insufficiency is defined as 25(OH)D level 20-30ng/mL (49.92 - 74.86 nmol/L). Participants with Vitamin D deficiency or insufficiency must be on Vitamin D regimen before randomization. [3]Participants with hypothyroidism must be clinically euthyroid for 3 months prior to Screening Visit and, in the opinion of the investigator, have achieved any catch-up growth expected from thyroxine replacement [4]Participants with diabetes mellitus must have been on stable medication regimen for 3 months prior to randomization (dose adjustments are allowed but addition or discontinuation of medications in this time period is disallowed) 8. History or presence of malignant disease, other than basal cell epithelioma/carcinoma or completely resected squamous skin cancer with no recurrence for 12 months per medical records 9. History or presence of the following: • Chronic anemia (resolved iron deficiency anemia is allowed) • Significant cardiovascular disease per the judgement of the investigator, such as congenital heart disease (uncomplicated patent ductus arteriosus and atrial or ventricular septal defect

	with repair are allowed), aortic insufficiency, clinically significant arrhythmias, congestive heart failure with NYHA class II and above, or other conditions that impair regulation of blood pressure or heart rate • Condition that impacts hemodynamic stability (such as autonomic dysfunction, orthostatic intolerance) • History of chronic renal insufficiency • Chronic or recurrent illness that can affect hydration or volume status. This may include conditions associated with decreased nutritional intake or increased volume loss • Bone fracture within 6 months prior to Screening Visit (within 2 months for fracture of digits) • Any disease or condition that, in the opinion of the investigator, may make the participant unlikely to fully complete the trial, may confound interpretation of trial results, or presents undue risk from receiving study drug 10. Child has significant electrocardiogram abnormalities, including evidence of a previous myocardial infarction, left ventricular hypertrophy, flat T waves (particularly in the inferior leads) or more than minor non-specific ST-T wave changes or: • QRS >90 milliseconds (msec) • QT interval corrected using Fridericia's formula (QTcF) >440 msec • PR interval >170 msec • Complete right or left bundle branch block 11. Requires, or anticipated to require, chronic (> 4 weeks) or repeated (more than twice per year) treatment with oral corticosteroids during participation in the trial (low and mid-dose inhaled corticosteroids are allowed. High-dose inhaled corticosteroids are not allowed.). See Appendix 5 for definition of high doses of inhaled corticosteroids. 12. Use of medication known to prolong the QT/QTc interval within 7 days or 5 half-lives (whichever is longer) prior to the Screening Visit (see https://crediblemeds.org/ for the list of medications that are known to prolong the QT/QTc interval. Note: Only medications on the Known Risk list are excluded, not those on the Possible or Conditional Risk lists) 13. Ongoing treatment with any medication that affects blood pressure or heart rate 14. Known hypersensitivity to the components of the study drug [trehalose, tris(hydroxymethyl)aminomethane, succinate and PEG]

	15. Any other reason that in the opinion of the investigator would prevent the child from complying with the trial requirements or completing the trial
ROLLOVER CRITERIA	Participants are eligible for the Open-Label Extension Period if they fulfill the following rollover criteria: 1. Have completed the 52 weeks randomized treatment period 2. Written, signed informed consent of the parent(s) or legal guardian(s) of the participant and written assent of the participant as required by the institutional review board/human research ethics committee/independent ethics committee (IRB/HREC/IEC) to continue into the Open-Label Extension (OLE) Period 3. Do not fulfill any of the Holding/stopping study drug conditions or symptoms (see Section 9.6)
TRIAL DESIGN	This trial 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. After completing 52 weeks of their assigned cohort dose, participants who fulfill the rollover criteria can continue into the 104 weeks Open-Label Extension Period. In this extension period, participants may receive the highest dose level of TransCon CNP that has been reviewed and recommended by the Data Monitoring Committee (DMC) for safety. CCI **Trial Design Scheme:**  Trial design scheme in the Randomized and Open-Label Extension period. In the Randomized Treatment Period, participants in each cohort will receive their randomized treatment for 52 weeks, after which they are rolled over into the Open-Label Extension. The

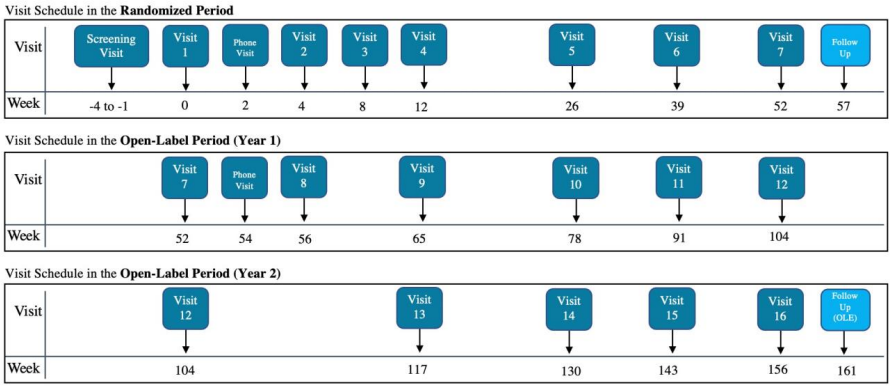
initiation of a new, subsequent cohort in the Randomized Period is gated by a DMC that reviews 3 months of safety data of the current cohort to determine if the dose is safe, after which the DMC can recommend to proceed with the next cohort. In the Open-Label Extension Period, participants may receive the highest dose level of TransCon CNP that has been reviewed and recommended by the Data Monitoring Committee (DMC) for safety and has passed DMC safety review.

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, if needed, 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 dropouts due to COVID-19.

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



Screening Visit (up to approximately 1 to 4 weeks prior to randomization):

Following informed consent, participants will complete the Screening Visit to determine eligibility.

Screening evaluations will include:

1. PRO/ObsRO validation battery
2. Verification of eligibility

	3. Demographics (date of birth, age at screening, biological sex, ethnicity, race) 4. Medical history including family history of ACH, age of diagnosis, date of diagnosis (if available), type of mutation, and historical anthropometric measurements, as available 5. Prior and concomitant medications 6. Vital sign measurements (Temperature, HR, BP) 7. Full physical examination (general appearance, HEENT, Neck (including thyroid), Lung/pulmonary, Chest, CV, Abdomen, Back, GU, Neurological, Extremities, and Skin), including assessment of pubertal status and thorough skeletal exam 8. Baseline qualitative assessment of sleep and snoring pattern (clinical assessment for monitoring) 9. Weight 10. Standing height 11. Sitting height 12. 12-lead ECG 13. Genetic confirmation of ACH (if not done previously). See Section 11.11 14. Blood collection for the following laboratory assessments: a. Chemistry b. TSH c. Hemoglobin A1c d. Hematology e. Lipid panel f. 25(OH) Vitamin D g. Anti-drug antibodies h. Biomarkers 15. Urine collection 16. CCI [redacted] Screening Visit may be conducted remotely (e.g. at the participant's home), at the discretion of the investigator, to minimize the risk of exposure to an infection during a pandemic or due to other restrictions that prevent the participant from being able to travel to the site. In such an event, consent may be obtained remotely as allowed by the applicable IRB/EC requirements, and the Investigator will conduct the scheduled assessments remotely with assistance from the home health nurse (HHN) who will be with the participant. If the PRO/ObsRO validation battery cannot be completed during the Screening Visit due to the visit being conducted remotely, the battery should be completed separately at approximately 14 days prior to Visit 1, up to 7 days prior to Visit 1.

	All anthropometric measurements per medical records for up to one year prior to Screening Visit should be collected. If measurement(s) are not available within one year, the last available measurement(s) prior to Screening Visit should be collected. 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. Qualitative assessment of sleep and snoring pattern should include questions about neck hyperextension during sleep, loud and irregular snoring, glottal stops, observed sleep apnea, deep compensatory sighs, self-arousals, secondary enuresis, night-time emesis, morning headaches, daytime somnolence, or changes in school performance or behavior (Pauli 2019). For the assessment of pubertal status, boys will be assessed for testis volumes, and girls for breast development according to Tanner stages (Tanner 1976). 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 (Emmanuel 2019). Tanner stage progression during the course of the trial will not impact study treatment. See Appendix 3 for details. In case the Screening Visit is conducted remotely, full physical exam including pubertal assessment and thorough skeletal exam, may be conducted at Visit 1 before administration of study drug, with the understanding that an exam consistent with Tanner stage ≥ 2 is exclusionary. If the full physical exam and thorough skeletal exam are done pre-dose at Visit 1, an additional thorough skeletal exam and limited symptom directed physical exam at Visit 1 are not required. **Visit 1 (Randomization/Week 0):** Participants meeting all entry criteria will return to the clinic for Visit 1. The following will be performed prior to randomization and study drug administration: 1. Subset of PRO/ObsRO validation battery 2. Review of changes in medical history 3. Review of concomitant medications

	4. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and cervical medullary compression (CMC)) 5. Vital sign measurements (Temperature, HR, BP), including orthostatic HR and BP 6. Limited symptom-directed physical examination (at investigator's discretion), injection site inspection, and thorough skeletal physical exam 7. Qualitative assessment of changes of sleep and snoring pattern 8. Weight 9. All anthropometric measurements 10. Radiographic assessment of bone a. Left hand and wrist bone age X-ray b. Dual-energy X-ray absorptiometry (DXA) c. Anterior-posterior (AP) standing lower extremity X-ray d. AP and lateral spine X-ray 11. Blood collection for the following laboratory assessments: a. Chemistry b. Hematology c. Pharmacokinetics d. Biomarkers e. Anti-drug antibodies 12. CCI [redacted] 13. After completion of these assessment, participants can proceed to randomization and study drug administration: 14. Randomization 15. Study drug administration at site and diary dispensing If for any reason the PRO/ObsRO validation battery for the Screening Visit was not completed prior to Visit 1, the same battery should be completed during Visit 1 prior to study drug administration in lieu of the subset scheduled for Visit 1. Orthostatic vital signs (HR, BP) will be taken at rest (preferably supine) and upon standing. Orthostatic hypotension is defined as decrease in SBP of ≥ 20 mmHg (Stewart 2018). Accompanying tachycardia is defined as change of heart rate increment of ≥40 bpm and absolute orthostatic HR ≥130 bpm (for ages 13 years and younger) (Singer 2012). Thorough skeletal physical exam will be performed and additional imaging assessments may be conducted as clinically indicated based on the physical exam findings.

	Limited symptom-directed physical examination of other systems should be performed at the discretion of the investigator to verify no clinically relevant changes have occurred since the Screening Visit. Injection site must be visually inspected prior to dosing. If the Screening Visit was conducted remotely, full physical examination must be performed at Visit 1 before administration of study drug. Additional thorough skeletal exam and limited symptom directed physical exam are not required. Anthropometric measurements should be taken following the Anthropometric Parameter Manual. For any anthropometric parameters that could not be measured during the visit, the reason must be documented. Radiographic assessments may not be required at Visit 1, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to Visit 1. If radiographic assessments cannot be completed prior to study drug administration due to scheduling conflicts, the assessments may be completed at up to 24 hours after study drug administration. Bone age using X-ray imaging will be assessed in the left hand and wrist for all participants unless a medical reason prohibits. DXA will be performed only for participants aged 5 years and older. The first dose of study drug will be administered on-site to provide training to the caregiver on study drug administration. Participant will be monitored for at least 2 hours in the clinic after injection for any acute reactions. Visual inspection of the injection site and vital signs measurements (Temperature, HR, and BP) will be performed at 1 hour and 2 hours after injection. Participants should be monitored longer as clinically indicated based on any clinically significant changes that emerge during the 2 hours. For participants who weigh ≥11 kg, the following will also be performed after injection of study drug: • Blood collection for pharmacokinetic analyses at approximately 8, 24, and 48 hours after injection • Orthostatic vital signs (HR, BP) at rest (preferably supine) and upon standing prior to blood collection at approximately 8, 24, and 48 hours after injection • Inspection of injection site at approximately 8, 24, and 48 hours after injection • ECG collection at approximately 48 hours after injection prior to PK blood collection 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). Assessments at 24 hours and 48 hours after injection, including

	orthostatic vital signs, ECG collection, blood collection, and injection site assessment may be conducted remotely by HHN. **Phone Visit (Week 2 ±3 days):** All participants will be contacted by phone during Week 2 (±3 days) 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, record any AEs, record any concomitant medication changes and answer any questions. **Visit 2 (Week 4 ±3 days), Visit 3, 4, 5, 6, (Week 8, 12, 26, 39 ±7 days) Visit:** The following will be performed: 1. Subset of PRO/ObsRO validation battery (Visit 3, 4, 5, 6 only) 2. Review changes in concomitant medications 3. Review of adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC) 4. Vital sign measurements (Temperature, BP, HR) 5. Limited, symptom-directed physical examination, injection site inspection, and thorough skeletal physical exam (Visit 2, 3, 4, 6 only) 6. Full physical examination, including assessment of pubertal status, injection site inspection, and thorough skeletal physical exam (Visit 5 only) 7. Qualitative assessment of changes of sleep and snoring pattern 8. Weight 9. Standing height and sitting height only (Visit 2, 3, 4, 6 only) 10. All anthropometric measurements (Visit 5 only) 11. Radiographic assessment of bone a. AP standing lower extremity X-ray (Visit 4 only) b. AP and lateral spine X-ray (Visit 4 only) 12. 12-lead ECG (Visit 2, 3, and 5 only) 13. Study drug and diary dispensing 14. Blood collection for the following laboratory assessments: a. Chemistry b. Hematology c. Lipid panel (Visit 3 and 6 only) d. 25(OH) Vitamin D (Visit 5 only) e. Pharmacokinetics f. Biomarkers (except Visit 3) g. Anti-drug antibodies (except Visit 3) 15. Urine collection (Visit 4, 5, and 6 only) 16. CCI [redacted] (Visits 3, 4, 5, and 6 only)

	Visit windows for all visits after Visit 1 may be increased due to extenuating circumstances such as Covid-19 travel restrictions, with the approval of the Medical Monitor. At Visit 2 (Week 4) and Visit 5 (Week 26), blood collection for pharmacokinetics must be at trough level. Therefore, study drug cannot be administered within 6 days prior to these visits. Visit 2, 3, 4, and 6 may be conducted remotely with assistance from the home health nurse (HHN), at the discretion of the Investigator. A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. Radiographic assessments at Visit 4 may be conducted remotely (e.g. at a community imaging center). Visit 5 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 5 must be conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. A physical assessment will be performed by the HHN under the remote supervision of the Investigator. **Visit 7 (Week 52 ±7 days) or ET Visit:** This visit will serve as the last visit in the Randomized Period and the first visit in the Open-Label Extension Period. At Visit 7, blood collection for pharmacokinetics must be at trough level. Therefore, study drug cannot be administered within 6 days prior to the visit. For participants who do not roll over to the Open-Label Extension, no further dose of study drug will be administered. Visit 7 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 7 is conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. A physical assessment will be performed by the HHN under the remote supervision of the Investigator. The following will be performed: 1. PRO/ObsRO validation battery 2. Review changes in concomitant medications 3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC) 4. Vital signs measurement (Temperature, HR, BP) 5. Full physical examination including assessment of pubertal status, injection site inspection, and thorough skeletal physical exam 6. Qualitative assessment of changes of sleep and snoring pattern 7. Weight 8. All anthropometric measurements

	9. Radiographic assessment of bone a. Left hand and wrist Bone age X-ray b. DXA c. AP Standing lower extremity X-ray d. AP and lateral spine X-ray 10. 12-lead ECG 11. Blood collection for the following laboratory assessments: a. Chemistry b. Hematology c. 25(OH) Vitamin D d. Lipid panel e. Pharmacokinetics f. Biomarkers g. Anti-drug antibodies 12. Urine collection 13. CCI Radiographic assessments at Visit 7 may be conducted remotely (e.g. at a community imaging center). Alternatively, radiologic assessments may be deferred until the participant is able to travel to the site. Radiographic assessments may not be required at Visit 7, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to Visit 7. Immediately following completion of 52 weeks in the Randomized Period, all participants, including those randomized to placebo, may continue into the Open-Label Extension Period to receive TransCon CNP if they fulfill the rollover criteria (see Section 8.1.3). If the Investigator or Medical Monitor has concerns about continuing the participant in the Open-Label Extension Period (e.g. potential safety concerns or emergent fulfillment of holding/stopping criteria) participant may end treatment at the end of the Randomized Period. For those participants not rolling over to the Open-Label Extension Period, a follow-up visit should be scheduled after 5 weeks (please see section below on follow-up visit). **Follow-Up Visit (Week 57 ±7 days):** Participants who are not continuing in the Open-Label Extension Period will attend a follow-up visit 5 weeks after Visit 7 to review any adverse events, to collect blood samples for assessment of anti-drug antibodies and answer any questions. The Follow-up visit may be conducted remotely (e.g. at the participant's home) by the HHN at the discretion of the investigator to minimize the risk of exposure to an infection during a pandemic, or due to other restrictions that prevent the participant from being able to travel to the site for the blood collection.

	OPEN-LABEL EXTENSION PERIOD VISITS: **Visit 7 (Week 52 ±7 days)** For participants continuing in the Open-Label Extension Period, all Visit 7 assessments for the Open-Label Extension Period must be done immediately following completion of the Visit 7 assessments for the Randomized Period. Prior to any protocol related activities for the Open-Label Extension Period, signed informed consent will be obtained for each potential participant in accordance with GCP and regional regulatory requirements. The format and content of the ICF must be approved by the appropriate institutional review board/ethics committee (IRB/EC) prior to implementation. During the Open-Label Extension Period, the Investigator should ascertain an individual's risk for becoming pregnant or fathering a child, and take appropriate steps for participants that attain reproductive potential during participation in the trial (see Appendix 6). After completion of all scheduled assessments for the Randomized Period, the following will be performed: 1. Informed consent 2. Assessment of childbearing potential according to Appendix 6 3. Urinary hCG test for females of childbearing potential (according to Appendix 6) 4. Study drug and diary dispensing For participants who received placebo during the Randomized Period, this will be the first dose of TransCon CNP, and in order to maintain the blind, all participants must undergo the same safety monitoring. Study drug must be administered on-site and participants will be monitored for at least 2 hours in the clinic after injection for any acute reactions. Visual inspection of the injection site and vital signs measurements (Temperature, HR, and BP) will be performed at 1 hour and 2 hours after injection. Participants should be monitored longer as clinically indicated based on any clinically significant changes that emerge during the 2 hours. For participants who weigh ≥11 kg, the following will also be performed after injection of study drug: • Blood collection for pharmacokinetic analyses at approximately 8, 24, and 48 hours after injection • Orthostatic vital signs (HR and BP) at rest (preferably supine) and upon standing prior to blood collection at approximately 8, 24, and 48 hours after injection • Inspection of injection site at approximately 8, 24, and 48 hours after injection

	• ECG collection at approximately 48 hours after injection prior to PK blood collection 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). Assessments at 24 hours and 48 hours after injection, including orthostatic vital signs, ECG collection, blood collection, and injection site assessment may be conducted remotely by HHN. **Phone Visit (Week 54 ±3 days):** All participants will be contacted by phone during Week 54 (±3 days) 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. **Visit 8 (± 3 days), 9, 10, 11, 12, 13, 14, 15, 16/ET (Week 56, 65, 78, 91, 104, 117, 130, 143, 156 (±7 days):** The following will be performed: 1. PRO/ObsRO validation battery (Visit 12, 16/ET) 2. Subset of PRO/ObsRO validation battery (Visit 10 and 14) 3. Review changes in concomitant medications 4. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC) 5. Vital sign measurements (Temperature, HR, BP) 6. Weight 7. Standing height and sitting height (Visit 8, 9, 11, 13, and 15) 8. All anthropometric measurements (Visit 10, 12, 14, and 16/ET) 9. Full physical examination, injection site inspection, and thorough skeletal exam (Visit 10, 12, 14, and 16/ET) 10. Limited physical examination, injection site inspection, and thorough skeletal exam (Visit 8, 9, 11, 13, and 15) 11. Assessment of pubertal status and childbearing potential according to Appendix 6 12. Qualitative assessment of changes of sleep and snoring pattern 13. Radiographic assessments a. X-ray of left hand and wrist for bone age (Visit 12 and 16/ET) b. Anterior-posterior (AP) standing lower extremity X-ray (Visit 9, 12, 13, and 16/ET) c. Dual-energy X-ray absorptiometry (DXA) for bone mineral density (participants 5 years and older only) (Visit 12 and 16/ET) d. Anterior-posterior and lateral spine X-ray (Visit 9, 12, 13, and 16/ET)

	14. 12-lead ECG (Visit 8, 10, 12, 14 and 16/ET and Visit 9 and 11 if dose is escalated at the visit) 15. Blood collection for the following laboratory assessments a. Chemistry b. Hematology c. 25(OH) Vitamin D (Visit, 10, 12, 14, and 16/ET) d. Lipid panel (Visit 10, 12, 14, and 16/ET) e. Pharmacokinetics (Visit 8, 10, 12, 14, and 16/ET and Visit 9 and 11 if dose is escalated at the visit) f. Anti-drug antibodies g. Biomarkers 16. Urine collection 17. Urine collection for Human Chorionic Gonadotropin (hCG) for females of childbearing potential only (see Appendix 6) 18. Study drug and diary dispensing (Visit 8, 9, 10, 11, 12, 13, 14, and 15) 19. CCI (Visit 9, 10, 11, 12, 13, 14, 15, and 16/ET) Visit 8, 9, 11, 13 and 15 may be conducted remotely with assistance from the home health nurse (HHN), at the discretion of the Investigator. Pubertal assessments will be deferred until the next on-site visit. A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. Scheduled radiographic assessments at Visit 9 and 13 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 also be conducted remotely (e.g. at a community imaging center). Visit 10, 12, 14 and 16/ET may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. A physical assessment will be performed by the HHN under the remote supervision of the Investigator, but the pubertal assessment will be deferred until the next on-site visit. Radiographic assessments at Visit 9, 12, 13 and 16/ET may be conducted remotely (e.g. at a community imaging center). Alternatively, radiologic assessments may be deferred until the participant is able to travel to the site. Radiographic assessments may not be required at Visit 16/ET, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to Visit 16/ET. During the Open-Label Extension Period, the Investigator should ascertain an individual's risk for becoming pregnant or fathering a child and take appropriate steps for participants that attain reproductive potential during participation in the trial. This should be captured in the eCRF. 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 Appendix 6). Evaluation of childbearing potential and inclusion of related safety measures like pregnancy testing will be included throughout the Open-Label Extension Period (see Appendix 6). It is not deemed necessary to include these measures in the Randomized Period because if a child progressed from Tanner 1 at baseline to reproductive potential in less than one year it would be considered pathologic pubertal tempo and would lead to study drug discontinuation under Stopping Rules (see Section 9.6). Immediately following the completion of treatment in the Open-Label Extension period (Visit 16), participants may be offered participation in a separate Long-Term Open-Label Extension Study (ASND0039). **Follow-Up Visit Open-Label Extension (Week 161 ±7 days):** Participants will attend a follow-up visit 5 weeks after Visit 16 to review any adverse events, to collect blood samples for assessment of anti-drug antibodies and answer any questions. The Follow-up visit may be conducted remotely (e.g. at the participant's home) by the HHN at the discretion of the investigator to minimize the risk of exposure to an infection during a pandemic, or due to other restrictions that prevent the participant from being able to travel to the site for the blood collection. The follow-up visit is not applicable for participants who will continue in the separate Long-Term Open-Label Extension Study (ASND0039). **Study Drug Dosing:** TransCon CNP (or placebo) will be dosed at 6 to 100 µg CNP/kg/week, and if adequate safety is demonstrated at 100 µg CNP/kg/week, dosing may advance to a higher dose cohort based on emerging data. CCI [redacted] CCI The initial volume of study drug (TransCon CNP or placebo) administered will be calculated using the weight measurement obtained at Visit 1. The dose volume will be adjusted at each visit based on the participant's weight at the corresponding visits. Study drug will be dispensed for weekly administration by the caregiver, except for the first dose administered at the trial site. **Data Monitoring Committee Meetings for Cohort Initiation and Dose Escalation in the Open-Label Extension Period** Data monitoring committee meetings will be held by the Sponsor upon review of the following data to assess whether the next cohort should be initiated as planned: 1. Initiation of Cohort 2: Cohort 1 data with a minimum of 12 weeks of follow up for all participants

	2. 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 3. 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 An independent Data Monitoring Committee (DMC) will attend each DMC meeting to provide recommendations on the action to be taken (i.e. proceed to the next dose cohort as planned, modify the dose of the next cohort, or stop dose escalation). The DMC will be provided with the following unblinded data at each DMC meeting: 1. Summary of safety data including but not limited to AEs, vital signs, and laboratory findings 2. Details of SAEs and AEs leading to discontinuation of study drug 3. Summary of anthropometric measurements of cohorts that completed at least 26 weeks 4. Other relevant available data at the request of the DMC, including available PK data Following the Data Monitoring Committee meeting, the Sponsor will take into consideration the recommendation of the DMC to decide to either proceed to the next dose level as planned, modify the dose of the next cohort, or stop dose escalation for the Randomized Period. 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 Data Monitoring Committee meeting will be reconvened. Another DMC meeting will be held upon completion of 26 weeks of treatment (Visit 5) for the all participants in Cohort 4 to assess whether additional higher dose levels (up to 200 µg CNP/kg/week) should be investigated based on emerging data. After review of the data and consultation with the DMC, the Sponsor will decide whether a higher dose level should be investigated. The DMC will also make a recommendation regarding dose escalation for 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. If one serious adverse drug reaction or two severe adverse drug reactions occur at any time during a particular cohort, dose escalation

	will be halted. Additionally, an urgent DMC meeting will be called to determine whether dosing should be halted in that cohort or across the entire trial. If deemed appropriate after review of all available safety data, the DMC may recommend that dose escalation be re-started. If the DMC does not feel that enough data is available to make a recommendation, they may defer a decision and recommend a time at which the data should be re-evaluated. Additionally, the DMC will be notified, and a meeting may be called for each incident of study drug discontinuation for reasons related to safety. If dose escalation is discontinued prior to initiating the Cohort 4, participants to be enrolled in the cohorts not yet filled may receive the highest tolerated dose level investigated (or placebo), instead of the planned higher doses. The decision to complete all four planned cohorts will be made by the Sponsor after review of available data and consultation with the DMC. In addition, ad hoc DMC meetings may be called by the Sponsor at any time for review of newly identified safety concerns.
INVESTIGATIONAL PRODUCT	**TransCon CNP Drug Product** TransCon CNP is a long-acting essentially inactive prodrug CCI [redacted] CCI [redacted] CCI TransCon CNP releases active CNP via auto-cleavage of the TransCon Linker in a controlled manner based on physiologic pH and temperature. As such, the TransCon technology is designed to provide sustained exposure of active CNP over 7 days, allowing an optimal pharmacokinetic profile for use in ACH. The drug product formulation containing TransCon CNP is a lyophilized powder in a single-use vial, i.e. TransCon CNP 3.9 mg CCI [redacted] Prior to use, the lyophilized powder must be reconstituted with sterile water for injection from a prefilled syringe. CCI [redacted] This solution will be administered by SC injection via syringe and needle.
REFERENCE PRODUCT(S)	Reference product will be supplied as one of two placebos: • Placebo for TransCon CNP drug product • sWfI (sterile water for injection) Placebo for TransCon CNP drug product Placebo for TransCon CNP drug product contains the same excipients as TransCon CNP drug product but does not contain TransCon CNP. Prior to use, the lyophilized powder must be reconstituted with sterile water for injection from a prefilled syringe. This solution will be administered by SC injection via syringe and needle.

	sWfI Placebo for TransCon CNP drug product consists of sWfI. The sWfI is supplied in the same prefilled syringe as the one used for reconstitution of the lyophilized powder of the Placebo for TransCon CNP drug product. The procedure for preparation and administration of sWfI Placebo for TransCon CNP drug product is the same as for Placebo for TransCon CNP drug product, only the vial with excipients will be replaced with an empty sterile vial. The diluent (sWfI) is injected into the empty vial and the dosing volume of sWfI will be drawn from the vial into the injection syringe and administered SC. If Placebo for TransCon CNP drug product is not available, sWfI Placebo for TransCon CNP drug product will be used until Placebo for TransCon CNP drug product becomes available. Placebo for TransCon CNP drug product will be available prior to the start of Cohort 2, so this procedure will only be utilized in Cohort 1. When Placebo for TransCon CNP drug product is available for Cohort 1, study drug will be prepared and administered by a caregiver (after proper training). Total dose volume for participants in Cohort 1 is expected to be ≤ 0.05ml (based on 95th percentile weight of 32.5 kg for children with ACH at 10.5 years of age). At such low volumes, risk of possible discomfort associated with hypotonicity is minimal and does not pose a significant safety concern. The dose of Cohort 1 is 6 µg CNP/kg/week (0.006 mg/kg/week) and the concentration of reconstituted study drug is 3.6 mg CNP/mL. Therefore, study drug will be administered at 0.006/3.6 = 0.0017mL/kg.
TREATMENT REGIMEN	Until Placebo containing the excipients become available, every dose of TransCon CNP or placebo will be prepared and administered by an unblinded site staff or home healthcare service. In order to maintain the blind, study drug will be prepared out of sight of the investigator, caregiver, and the participant. Once Placebo for TransCon CNP becomes available, study drug should be administered by the caregiver. The injections will be given SC once weekly (approximately every 7 days). The dose (volume) of study drug will be adjusted according to the participant's weight at each visit. For the first four weeks of study drug administration by the caregiver, once weekly home healthcare service will be offered to accommodate home administration of study drug. Extended support might be offered until participants/parents/caregivers are comfortable to take over administration of the study drug. Each participant will receive their assigned cohort dose for 52 weeks in the Randomized Period, after which they may roll over to the Open-Label Extension Period where all participants will receive TransCon CNP.

BLINDING	This trial consists of a 52-week randomized, double-blind, randomized, placebo-controlled treatment period. Participants will be randomized to either TransCon CNP or placebo in 3:1 ratio within each cohort. Once all participants enrolled in a dose cohort have completed (or withdrawn from) their Randomized Period and the database has been locked, the treatment allocation for that dose cohort will be unblinded. The Randomized Period will be followed by a 104-week Open-Label Extension treatment period where all participants will receive TransCon CNP.
TRIAL AND TREATMENT DURATION	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 additional 104 weeks of treatment in the Open-Label Extension Period) and a 5-week follow-up period.
STOPPING RULES	The investigator or Medical Monitor (and, if needed, with DMC review) may temporarily hold or stop the dosing of study drug to a participant at any time during the trial. For participants that discontinue study drug for reasons related to safety, unblinding of the treatment assignment for the participant may occur if deemed necessary by the Sponsor to assess a potential safety signal or by the investigator to provide adequate medical care to the participant. In case of medical emergency, the investigator will have direct access to unblinding of the treatment through the Interactive web response system. Examples of conditions or symptoms that may warrant holding or stopping study drug at the investigator's or Medical Monitor's discretion include: 1. Severe fracture of long bones or growth plates regardless of causality 2. Evidence of symptomatic persistent orthostatic intolerance, lasting over 24 hours not explained by other probable causes. Orthostatic hypotension is defined as decrease in SBP of ≥20 mmHg (Stewart 2018). Accompanying tachycardia is defined as change of heart rate increment of ≥40 bpm and absolute orthostatic HR ≥130 bpm (for ages 13 years and younger) (Singer 2012) 3. Skeletal abnormalities typically not associated with ACH, growth or other concurrent medical conditions, such as a. Scoliosis b. Severe hip pain c. Findings from thorough skeletal exam requiring imaging or consultation with orthopedics specialist

	d. Clinically relevant findings on radiologic assessments (new onset or worsening of tibial bowing, joint abnormalities at the elbows, evidence of slipped capital femoral epiphysis) 4. A severe or serious adverse reaction 5. QTc value > 500 msec, or an extension > 60 msec from baseline in absence of possible causes other than the study drug 6. Diagnosis of heart disease requiring pharmaceutical or surgical intervention to maintain heart function 7. Any other sign that warrants holding or discontinuing study drug at the discretion of the investigator or Medical Monitor The investigator, with Sponsor Medical Monitor notification, must stop study drug for an individual participant in the presence of the following symptoms at any time during the trial: 1. Closed epiphysis (bone age >14.0 years for females or >16.0 years for males) 2. Slipped capital femoral epiphysis 3. Pregnancy, intention of becoming pregnant, and females who become of childbearing potential and who do not use highly effective contraceptive measures. Highly effective contraceptive measures are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly (see Appendix 6). **If study drug is held or discontinued due to safety concerns, approval by the Medical Monitor is required prior to resumption of study drug. Consideration of dose changes due to safety concerns may occur on an individual basis.** Any participant who discontinues study drug should be encouraged to remain in the trial and attend all subsequent trial visits and complete all assessments. If, however, trial participation is fully discontinued for withdrawal of consent, an ET Visit should be performed.
CRITERIA FOR EVALUATION	**Safety Endpoints** The following safety endpoints will be assessed for both blinded 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 – AP standing lower extremity X-ray

	– AP and lateral spine X-ray • Incidence of anti-drug antibodies **Efficacy Endpoints** Primary endpoint • AHV as measured at 52 weeks of weekly TransCon CNP treatment or placebo Secondary endpoints Change in upper to lower body segment ratio as measured at 52 weeks of weekly TransCon CNP treatment or placebo Exploratory Endpoints CCI [redacted]
	Pharmacokinetic Endpoints • Plasma concentration of Total CNP • Plasma concentration of Free CNP • Plasma concentration of mPEG and mPEG-linker

STATISTICAL METHODS	Details of applicable statistical methods will be provided in a Statistical Analysis Plan. The Full Analysis Set will include all randomized participants 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. Participants will be analyzed according to study treatment as randomized. The Safety Analysis Set will include all randomized participants who have received at least one dose of investigational product. Participants will be analyzed according to study treatment as treated. The efficacy analyses will be based on the Full Analysis Set and safety analyses will be based on the Safety Analysis Set. In general, analysis will be done by dose levels, and placebo participants will be pooled. Data from clinical assessments will be summarized using descriptive statistics. Categorical data will be presented using counts and percentages of participants. Continuous variables will be presented using number of participants, mean, standard deviation (SD), standard error (SE), median, minimum and maximum. Statistical significance is defined as $P < 0.05$ (2-sided). For the primary efficacy endpoint, AHV at Week 52, the primary analysis is ANCOVA model with the AHV at Week 52 as the response variable, treatment (dose groups and placebo) as factors, baseline age, sex, and baseline height SDS as covariates. The similar ANCOVA model, with the baseline of the corresponding parameter as a covariate, will be applied to secondary and exploratory efficacy endpoints. As a sensitivity analysis for the primary efficacy endpoint, AHV at Week 52, 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. Once the highest tolerated dose is established, the following sequential testing procedure 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. Descriptive analysis for safety will mainly include the incidence and type of TEAEs, safety laboratory values, vital signs, radiographic findings, ECG parameters and antibody parameters.
SAMPLE SIZE DETERMINATION	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.

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µg	Microgram
CCI	[redacted]
ACH	achondroplasia
AE	adverse event
AEM	Achondroplasia Experience Measure
AHV	Annualized height velocity
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Anterior-posterior
CCI	[redacted]
AST	Aspartate aminotransferase
BMD	bone mineral density
BMI	body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Cº	Celsius
CFR	Code of Federal Regulations
CCI	[redacted]
cGMP	Cyclic guanosine monophosphate
cm	Centimeter
Cmax	Maximum plasma drug concentration
CMC	Cervical medullary compression
CNP	C-type natriuretic peptide
COVID	Corona Virus Disease
CRF	Case report form
CRO	contract research organization
CTX-I	C-terminal cross-linked telopeptide of type I collagen
CV	cardiovascular
DMC	Data Monitoring Committee
DXA	dual-energy X-ray absorptiometry
EC	Ethics Committee
ECG	electrocardiogram
eCRF	Electronic case report form
EDC	electronic data capture
ER	Emergency room

ET	Early termination
Fº	Fahrenheit
FDA	United States Food and Drug Administration
FGFR3	fibroblast growth factor receptor type 3
G380R	glycine-to-arginine substitution at codon 380
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
GU	Genitourinary
HbA1c	Hemoglobin A1c
hCG	Human Chorionic Gonadotropin
HDL	High-density lipoprotein
HEENT	Head, Eyes, Ears, Nose, and Throat
hGH	Human growth hormone
HHN	Home health nurse
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IM	Investigator meeting
IND	Investigational new drug
IRB	Institutional Review Board
IWRS	Interactive web response system
Kg	Kilogram
LDL	Low-density lipoprotein
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
NHS	Natural History Study
NPR-B	Natriuretic peptide receptor-B
NPR-C	Natriuretic peptide receptor-C
mPEG	methoxypolyethylene glycol
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTproCNP	amino-terminal propeptide of C-type natriuretic peptide
NYHA	New York Heart Association Functional Classification
ObsRO	observer-reported outcome

OLE	Open-Label Extension
PINP	propeptide of type I procollagen, N-terminal
PEG	polyethylene glycol
PK	pharmacokinetics
PR	PR interval of ECG
PRO	patient-reported outcome
QoL	quality of life
QRS	duration of ventricular muscle depolarization of ECG
QT	duration of ventricular depolarization and repolarization of ECG
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia's formula
RBC	Red blood cell
SAD	single ascending dose
SADDAN	Severe achondroplasia with developmental delay and acanthosis nigricans
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDS	Standard Deviation Score
SE	standard error
SF-36	36-Item Short Form Survey
SIV	Site initiation visit
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
sWFI	Sterile water for injection
$t_{1/2}$	terminal elimination half-life
TEAE	Treatment-emergent adverse event
TENS	Toxic epidermal necrolysis
T_{max}	time of maximum observed concentration
URI	upper respiratory infection
UV	Unscheduled visit
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

5. INTRODUCTION

5.1. BACKGROUND AND RATIONALE

5.1.1. Achondroplasia

Achondroplasia (ACH) is the most common skeletal dysplasia and the most frequent form of short-limbed dwarfism (Horton 2007). The condition occurs with a frequency of 1 in 10,000 to 30,000 live births, affecting 250,000 men and women equally worldwide (Horton 2007, Laederich 2010). Although a heritable condition, more than 80% of cases of ACH are due to a sporadic mutation (Horton 2007).

ACH results in severe skeletal complications that lead to numerous comorbidities at various developmental stages. Cervico-medullary compression resulting from foramen magnum stenosis is thought to be the major contributing factor to fatal cardiorespiratory arrest in infants with ACH (Horton 2007). Additionally, a newborn with ACH may suffer from a small cranial-cervical junction leading to hydrocephalus requiring shunting (Horton 2007). Mid-facial hypoplasia with relative hypertrophy of the adenoids and tonsils, short Eustachian tubes, and hypoglossal canal stenosis in infants and young children may lead to chronic otitis media and subsequent hearing loss, speech delays, and obstructive sleep apnea. Older children and adults suffer from premature synchondroses closure of the vertebrae and ossification center fusion leading to spinal stenosis with subsequent neurogenic claudication (Horton 2007). Due to short arms and limited range of motion of the joints, individuals with ACH have difficulty with personal care, such as dressing and personal hygiene, and require therapy to cope with the limitations (Unger 2017). Bowing of the legs can lead to difficulty walking and chronic knee pain.

5.1.2. Current Standard Therapy for ACH

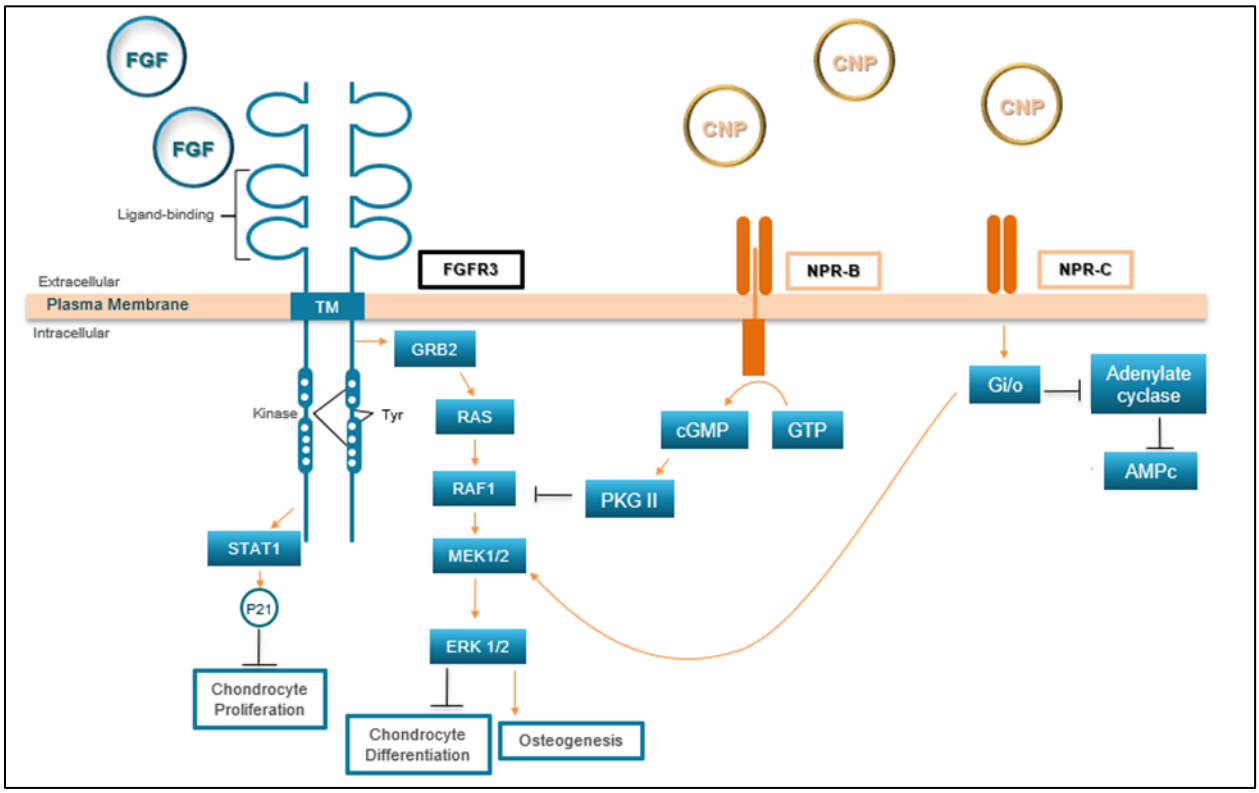
No effective medicinal product is available for treatment of ACH. All existing interventions are intended to alleviate specific comorbidities of the condition, and do not address the underlying pathophysiology (Trotter 2005, Horton 2007, Wright 2012, Ireland 2014). Cervico-medullary decompression is performed in infants and young children to treat central sleep apnea and alleviate neurological complications from spinal cord compression (Ho 2004). Newborns with ACH may also suffer from hydrocephalus requiring ventricular shunting. Adolescents and adults with lumbar stenosis may undergo laminectomy (Carlisle 2011). Challenges associated with height and reach may be alleviated by limb lengthening surgery, but the procedure comes with significant pain and morbidity over many months (Ornitz 2017, Unger 2017).

As none of the available therapies address the underlying pathophysiology of ACH, individuals with the condition undergo multiple surgeries and other interventions throughout their lives. A clear unmet medical need exists for an effective therapy to treat ACH.

5.1.3. Fibroblast Growth Factor Receptor Type 3

ACH is caused by a gain-of-function autosomal dominant mutation in the fibroblast growth factor receptor type 3 (FGFR3) gene with 100% penetrance. In cartilage, FGFR3 activation negatively regulates growth by inhibiting proliferation and terminal differentiation of growth plate chondrocytes, thereby reducing the rate of cartilage formation and turnover necessary for bone elongation.

Figure 1: Schematic Overview of the Interactions Between the Intracellular Pathways of the Fibroblast-Growth-Factor-Receptor 3 (FGFR3) and the C-Type Natriuretic Peptide (CNP) Receptors [Natriuretic peptide receptor-B (NPR-B) and -C (NPR-C)] in Bone Growth



Adapted from (*Peake 2014*, *Ornitz 2015*); FGF; Fibroblast Growth Factor

FGFR3 is a tyrosine-kinase receptor activating signal transducer and activator of transcription 1 (STAT1) and the mitogen-activated protein kinase (MAPK)-pathway [RAS-RAF-MEK-ERK], which both have inhibiting effects on endochondral ossification (chondrocyte proliferation and differentiation, respectively) (Figure 1).

5.1.4. C-type Natriuretic Peptide

CNP influences growth by some of the same intracellular signaling pathways as FGFR3, mediated through its receptors NPR-B and NPR-C (Figure 1). NPR-B mediates an increase in cyclic guanosine monophosphate (cGMP), substantiated to evoke an inhibition of RAF, thus blocking the MAPK-activity (Miyazawa 2002, Krejci 2005) resulting in increased growth, evident in animal models and humans overexpressing CNP (Yasoda 2004, Bocciardi 2007, Hannema 2013). On the other hand, absence of CNP or a non-functional NPR-B receptor result in dwarfism (Chusho 2001, Nakao 2015). The diminished growth in CNP-deficient rats can be rescued by continuous SC CNP administration (Hirota 2018), providing evidence that exogenous CNP can reach chondrocyte NPR-B receptors.

The NPR-C receptor is an important receptor for CNP with a lower affinity for CNP relative to NPR-B (Koller 1991, Potter 2006). NPR-C deficiency leads to increased growth (Colvin 1996, Matsukawa 1999). On the other hand, NPR-C mediates an intracellular signal that counteracts the NPR-B mediated signal (Figure 1). This is especially believed to be the case at supra-physiological CNP plasma concentration (Peake 2014).

Thus, the mechanism of action of CNP is believed to be via inhibition of the downstream signaling pathway of the FGFR3, thereby counteracting the overactivation of the FGFR3 pathway, characteristic for ACH, and thus restoring normal chondrogenesis (Laederich 2010).

In clinical trials in ACH children employing daily administration of vosoritide (a synthetic analogue of CNP), the impact on bone growth, measured as annualized height velocity (AHV), amounts to an additional 1-2 cm per year (BioMarin 2018) , from a baseline average growth velocity of approximately 5 cm/year (Hoover-Fong 2008, BioMarin 2018).

5.1.5. Impact of ACH on Well-Being and Functioning in Children with the Condition and Their Caregivers

Little is known about the impact of ACH on the functioning and well-being of children or the impact of caring for these children on their caregivers because much of the research conducted has focused on adults. There is evidence that children with ACH have lower functioning and impaired quality of life (QoL), possibly associated with lower self-esteem and social stigmatization; and 36-Item Short Form Survey (SF-36) scores, for both the Physical and Mental components, have been shown to be below national means (Ireland 2011, Dogba 2014, Wigg 2016, Dhiman 2017, Matsushita 2019). Further, this impairment in QoL is greater compared to children with short stature due to growth hormone deficiency or idiopathic short stature (Sommer 2017). Unfortunately, to date there are no measures that specifically assess these impacts on the daily functioning and well-being of the child with ACH.

Evidence for the impact on functioning and well-being for caregivers' of children with ACH is even more scarce, with a literature search on the topic identifying only 1 publication suggesting that caregivers' future outlook for their children with ACH focused on over-coming economic-occupational fears, and doubts concerning their ability to settle down and rear a family (Cacciaguerra 1981). Additionally, anecdotal evidence, including caregiver testimonials at the 2018 FDA public advisory committee meeting on ACH, suggests a substantial impact on caregivers and highlights the need to further understand the experience of these caregivers (FDA 2018).

Additionally, there is no current information about the participant/caregiver treatment experience of participation in an ACH clinical trial. As new treatments for this condition are developed it will be critical to better understand this experience.

5.2. RELEVANT FINDINGS FROM NONCLINICAL STUDIES

Please refer to the current version of the TransCon CNP Investigator's Brochure for a full discussion of nonclinical data.

In animal studies, TransCon CNP has shown the expected pharmacological effects on cartilage homeostasis and bone growth.

Cardiovascular (CV) changes (decreased blood pressure, increased heart rate (HR) and the heart rate corrected QT [QTc] interval) were observed in cynomolgus monkeys at doses of ≥300 µg CNP/kg but did not result in any clinical signs; the QTc increases were not biologically significant. The CV no observed adverse effect level in cynomolgus monkeys was 100 µg CNP/kg. In the pivotal repeat-dose toxicity studies in juvenile animals with a normal FGFR3 pathway, the no observed adverse effect level (NOAEL) for off-target effects after weekly SC administrations was the highest dose tested (up to 4000 µg CNP/kg/wk in rats). The repeat-dose toxicity studies were conducted in juvenile animals with an intact FGFR3-pathway and a normal balance between FGFR3 activation and CNP mediated suppression of the FGFR3-pathway. When administering CNP to intact animals, this balance is disturbed and skeletal overgrowth, eventually leading to adverse exaggerated pharmacology can be observed. The only adverse findings observed were related to CNP's pharmacological effect on the physeal chondrocytes.

5.3. CLINICAL EXPERIENCE

In the Phase 1, randomized, first-in-human, double-blind, placebo-controlled SAD trial, TransCon CNP was given by SC injection to healthy adult male participants. The primary objective was to determine the safety and tolerability of single-ascending SC doses of TransCon CNP. Other objectives were to evaluate the PK properties and exploratory biomarkers after administration of TransCon CNP. The trial was conducted under GCP, EC, and Declaration of Helsinki guidelines.

TransCon CNP was generally well tolerated as single ascending doses in healthy male adults. No serious AEs were reported, and no participant was withdrawn due to an AE. Dose levels up to 150 µg CNP/kg were investigated with no dose limiting toxicities.

No clinically significant trends were observed in clinical laboratory assessments, vital sign measurements, ECG parameters, or physical examination findings. Continuous ECG monitoring via Holter monitor revealed no clinically relevant effects on any of the studied ECG parameters, including heart rate or PR, QRS, and QT intervals at all investigated dose levels.

Potential adverse immune response upon exposure to TransCon CNP was evaluated. By using population derived assay cut points, all samples were confirmed negative for anti-CNP antibodies. In addition, individual changes in anti-PEG antibody levels were <3 fold compared to individual predose levels and were not considered clinically relevant.

Pharmacokinetic parameters were generally consistent with the target profile. Exposure, as assessed by C_{max} and AUC, of Total CNP, Free CNP-38, mPEG. and mPEG-linker increased proportionally with dose administered. A slow rise to peak concentrations were observed for all analytes (median T_{max} ranging from 45 to 66 hours post dose for Free CNP), with long and dose-independent elimination half-lives (t½ was 112 − 128 hours for Free CNP and 137 − 163 hours for Total CNP).

The effect of TransCon CNP on cGMP levels was dose dependent, and the data supports administration of TransCon CNP as a way to deliver active CNP in a sustained manner.

Endogenous CNP biosynthesis did not appear to be affected by single administration of TransCon CNP, as evidenced by no changes in plasma NTproCNP levels irrespective of CNP dose level.

5.4. TRIAL RATIONALE

Because of the short half-life of native CNP (2-3 minutes), continuous IV administration is required to restore bone growth in ACH mice (Yasoda 2009). Proof-of-principle for a mutated CNP analogue (vosoritide) with increased resistance to degradation by neutral endopeptidase has been obtained in the nonclinical setting. Daily administration of CNP to mice, with phenotypical traits similar to those observed in individuals with ACH, suggests that the daily administration of the CNP analogue vosoritide is capable of improving the major phenotypical dwarfism traits (Lorget 2012, Wendt 2015). In clinical trials in ACH children employing daily administration of vosoritide, the impact on bone growth, measured as AHV, amounts to an additional 1-2 cm per year (BioMarin 2018), from a baseline average growth velocity of approximately 5 cm/year (Hoover-Fong 2008, BioMarin 2018).

TransCon technology is designed to provide sustained exposure of active CNP. Applying the TransCon technology to CNP results in a mean apparent half-life of Free CNP of approximately 120 h in human adult volunteers. This is in contrast to the short systemic half-life of endogenous CNP in humans of only 2 to 3 minutes (Hunt 1994), and the half-life of vosoritide of 20-23 minutes (BioMarin 2018). The aim of TransCon CNP therapy is to treat the underlying pathophysiology of ACH by inhibiting the effects of constitutive FGFR3 overactivation 24 hours a day, aiming to ameliorate and prevent the comorbidities of ACH.

A study in a mouse model of ACH (FGFR3 gain of function mutation) demonstrated that TransCon CNP exposure was able to modify synchondrosis closure and long-bone growth-plate cartilage homeostasis. In a 6-month pharmacology study in healthy juvenile monkeys an increase in long bone growth was observed.

The data from the non-IND Phase 1 clinical trial (TransCon CNP TCC-101) demonstrated the ability of TransCon CNP to sustain elevated plasma levels of CNP with a weekly SC injection.

TransCon CNP is intended to promote growth of bones by acting on the chondrocytes within the growth plates. Therefore, clinical trials to assess the efficacy of TransCon CNP are conducted in children with open growth plates.

5.5. SUMMARY OF IMPORTANT RISKS AND POTENTIAL BENEFITS

5.5.1. Important Risks

TransCon CNP has not been investigated in individuals with ACH, and therefore the risks are unknown. In the Phase 1 clinical trial investigating single doses of TransCon CNP up to 150 µg CNP/kg in healthy adult male participants, TransCon CNP was generally well tolerated. In the general toxicity studies with healthy juvenile animals, no off-target (non-bone related) adverse findings were observed. The only significant adverse findings were related to the expected pharmacology of CNP on bone growth and are regarded to be a consequence of the exaggerated pharmacology when dosing animals without the activating FGFR3 mutation to counterbalance the effect of exogenous CNP administration.

5.5.2. Potential Risks

The following effects are considered potential risks with the use of TransCon CNP in children with ACH:

5.5.2.1. Cardiovascular Changes

Decreased blood pressure, increased heart rate (HR), and increased heart rate corrected QT (QTc) interval were observed in cynomolgus monkeys at doses of ≥300 µg CNP/kg. The changes did not result in any clinical signs, and the QTc interval increases were not biologically significant (Ando 2005). Throughout the non-clinical studies, a no observed effect limit (NOEL) for cardiovascular (CV) findings of 100 µg CNP/kg/wk was established. The predicted steady state Total CNP C_{max} at 6 µg CNP/kg/wk in the pediatric population is 22 to 23-fold lower than the observed C_{max} at the NOEL dose (100 µg CNP/kg/wk) in cynomolgus monkeys. Hypotensive effects were reported to correlate with high peak plasma CNP concentrations in adults administered exogenous CNP (Igaki 1998). However, this correlation was not observed in the phase 1 clinical trial, TCC-101 (tested up to 150 µg CNP/kg), likely due to the much lower C_{max} and peak-to-trough ratio with TransCon CNP, and no clinically relevant effects on the studied ECG parameters were found.

5.5.2.2. Adverse Bone Overgrowth

TransCon CNP has not been tested in children with ACH and, therefore, whether adverse bone overgrowth could occur is unknown. Mutations leading to an overproduction of CNP in people without activating mutations in FGFR3 result in skeletal overgrowth, including long hands and feet, scoliosis and ankle valgus deformity (Bocciardi 2007, Moncla 2007, Tassano 2013, Ko 2015).

In the repeat-dose toxicity studies of TransCon CNP in healthy juvenile animals without an activating mutation in FGFR3, an exaggerated effect related to CNP's biology on the growth plate was observed. Skeletal overgrowth and sequelae thereof such as physeal clefting, physeal fractures (Salter-Harris Type 1) and bone deformities were found. When administering CNP to animals without the ACH mutation, the balance between the activity of FGFR3 and CNP is disturbed. In the context of ACH, in which FGFR3 is overactivated, sustained increase in CNP exposure is expected to modulate/decrease FGFR3 signaling and promote a more physiologic balance between the two pathways. The aim of treatment with TransCon CNP is to normalize the effect of constitutively overactivated FGFR3.

5.5.3. Potential Benefits

Clinical trials of TransCon CNP in children with ACH have not been conducted. Based on the published studies of CNP administration in mouse models of ACH (Lorget 2012, Wendt 2015) and nonclinical studies using TransCon CNP, treatment with TransCon CNP may promote proportional growth of the long bones and alleviate the comorbidities associated with premature closure of the synchondroses in children with ACH. Body disproportionality is a hallmark of ACH that leads to common comorbidities that may limit functioning and well-being, as well as caregiver burden, such as short limbs, joint and back pain, and limited range of motion (Horton 2007, Ireland 2014, Unger 2017). Premature closure of the synchondroses contribute to hydrocephalus, spinal stenosis, ear infections, hearing problems, and respiratory problems.

The PK profile observed for TransCon CNP in healthy adult male participants (Trial TCC-101) showed dose-proportional increases in C_{max}, with apparent $t_{1/2}$ of Free CNP ranging from 112 to 128 h. TransCon CNP has the potential to provide full 7-day (168-h) CNP coverage at expected therapeutic ranges. Delivery of CNP via the TransCon technology is expected to provide the following benefits:

- Maximize growth-promoting effects of CNP by maintaining CNP levels in circulation at therapeutic levels for the entire duration between doses.
- Minimize potential non-skeletal effects of CNP, such as hypotensive and natriuretic effects, by reducing the fluctuations between peak and trough levels. Hypotensive effects have been reported to correlate with high peak plasma CNP concentrations in adults administered exogenous CNP (Igaki 1998), but this correlation was not observed in the Phase 1 clinical trial (Trial TCC-101) at doses up to 150 µg CNP/kg. Results of nonclinical studies have not indicated a natriuretic potential at the studied dose levels.

6. OBJECTIVES

6.1. 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 AHV

6.2. 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

6.3. EXPLORATORY OBJECTIVES

CCI

CCI

7. TRIAL DESIGN

7.1. OVERALL TRIAL DESIGN AND PLAN

This trial 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 this extension period, participants may receive the highest dose level of TransCon CNP that has been reviewed and recommended by the Data Monitoring Committee (DMC) for safety and has passed DMC safety review.

The total duration of the randomized trial period for an individual participant is:

For participants who do not continue in the Open-Label Extension Period: Up to approximately 61 weeks (including approximately 4 weeks of screening plus 52 weeks of treatment, and a 5 weeks follow-up period).

For participants who continue in the Open-Label Extension Periods: Up to approximately 165 weeks (up to approximately 4 weeks of screening plus 156 weeks of treatment, including 52 weeks of placebo-controlled treatment period followed by an additional 104 weeks of treatment in the Open-Label Extension Period and a 5 weeks follow-up period).

This is summarized in the scheme below:

Trial Design Scheme

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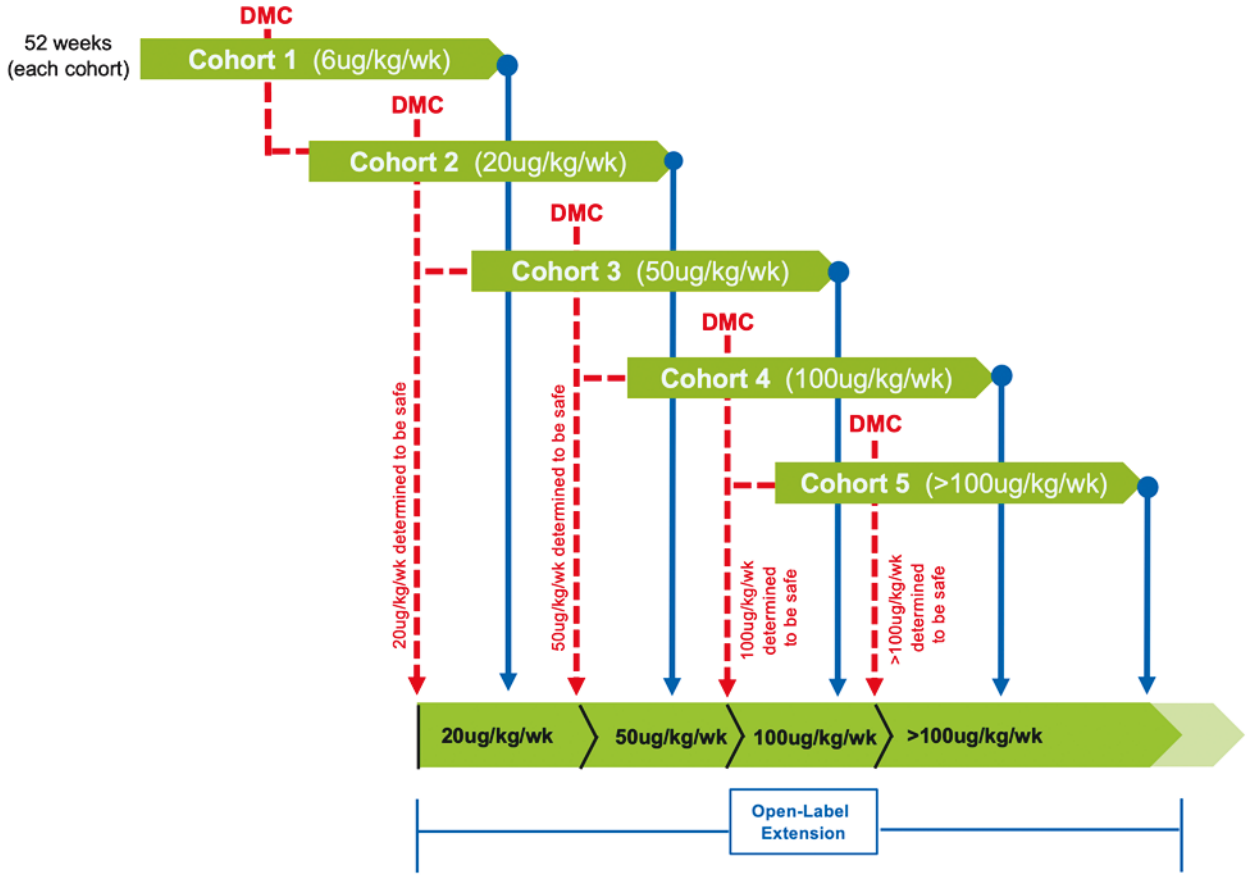
Figure 2: Trial Design Scheme



(Figure 2) Trial design scheme in the Randomized and Open-Label Extension period. In the Randomized Period, participants in each cohort will receive their allocated cohort dose for 52 weeks, after which they are rolled over into the Open-Label Extension. The initiation of a new, subsequent cohort in the Randomized Period is gated by a DMC that reviews 3 months of safety data of the current cohort to determine if the dose is safe, after which the DMC can recommend to proceed with the next cohort (including dose escalation).

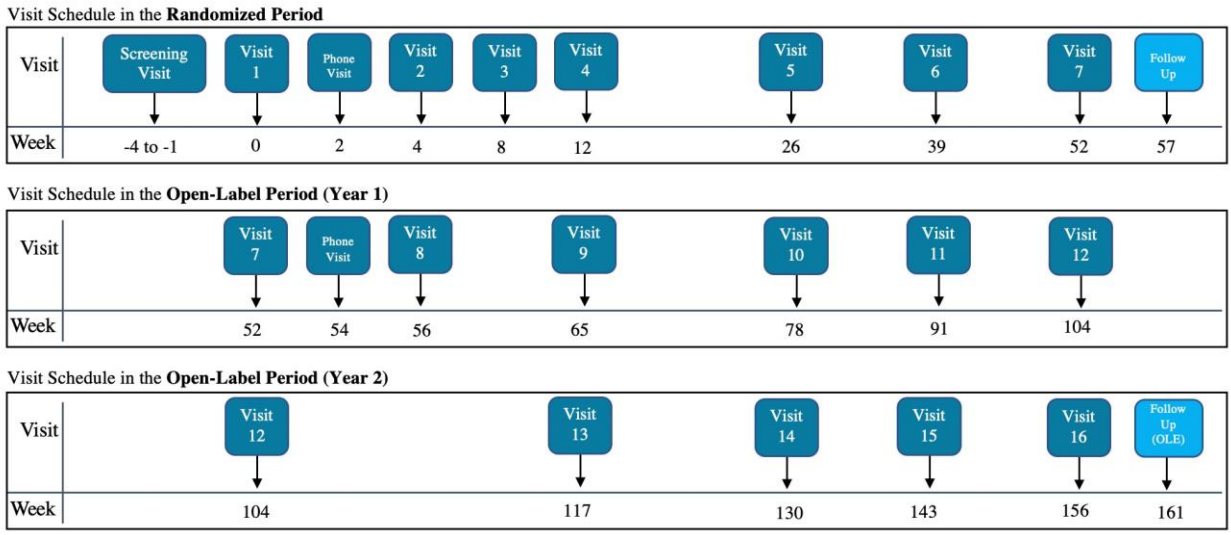
In the Open-Label Extension Period, participants may receive the highest dose level of TransCon CNP that has been reviewed and recommended by the Data Monitoring Committee (DMC) for safety and has passed DMC safety review.

- **Screening Period:** Up to approximately 4 weeks
- **Randomized Treatment Period:** 52 weeks
- **Open-Label Extension Period:** 104 weeks

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, if needed, 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 dropouts due to COVID-19.

Visit Schedule Diagram in the Randomized and Open-Label Extension Periods:



7.1.1. Measures Taken to Maximize Study Integrity and Minimize Bias

The randomized, double-blinded, placebo-controlled period of this trial is included to minimize bias in the assessment of the effect and safety of TransCon CNP. Participants will be randomized to either TransCon CNP or placebo in 3:1 ratio within each cohort.

Once all participants enrolled in a dose cohort have completed (or withdrawn from) their Randomized Period and the database has been locked, the treatment allocation for that dose cohort will be unblinded.

This Randomized Period will be followed by a 104-week Open-Label Extension treatment period where all participants will receive TransCon CNP.

Participant visits should be performed at approximately the same time of day for all visits. Also, assessments should be performed in a similar fashion at each visit. Additionally, all efforts will be made to keep missing data to a minimum, including the following:

- Investigators will be trained about the importance of participant retention
- Investigators will be instructed to encourage participants to complete all scheduled visits, including any participants who discontinue the study drug early

- The Informed Consent Form (ICF) will include a statement educating participants about the scientific importance of their data even if the participant discontinues study drug early
- Special efforts will be made to provide assistance to participants/families who might discontinue due to travel or cost barriers, such as offers of transportation to the clinic
- All study visits have visit windows to allow flexibility for clinic attendance (See Appendix 1 and Appendix 2: Schedule of Events in the Randomized and Open-Label Extension Period, respectively)
- Every effort will be made to maintain contact with participants or other family members

7.2. TRIAL SITES

The trial will be conducted at approximately 35 sites worldwide.

8. PARTICIPANT POPULATION

Minimum of sixty (60) male and female prepubertal children with ACH, age 2 to 10 years, inclusive.

8.1. ELIGIBILITY CRITERIA

8.1.1. Inclusion Criteria

1. Clinical diagnosis of ACH with genetic confirmation (See Section 11.11)
2. Age between 2 to 10 years old (inclusive) at Screening Visit
3. Prepubertal (Stage 1 breasts for girls or testicular volume < 4ml for boys) at Screening Visit (See Section 11.3)
4. Able to stand without assistance
5. Caregiver willing and able to administer subcutaneous injections of study drug
6. Written, signed informed consent of the parent(s) or legal guardian(s) of the participant and written assent of the participant as required by the institutional review board/human research ethics committee/independent ethics committee (IRB/HREC/IEC)

8.1.2. Exclusion Criteria

1. Clinically significant findings at Screening that:
   - are expected to require surgical intervention during participation in the trial or
   - are musculoskeletal in nature, such as Salter-Harris fractures and severe hip pain or
   - otherwise are considered by investigator or Medical Monitor to make a participant unfit to receive study drug or undergo trial related procedures
2. Have received treatment (>3 months) of human growth hormone (hGH) or other medications to affect stature or body proportionality at any time
3. Have received any dose of medications intended to affect stature or body proportionality within the previous 6 months of Screening Visit

4. Have received any study drug or device intended to affect stature or body proportionality at any time
5. History or presence of injury or disease of the growth plate(s), other than ACH, that affects growth potential of long bones
6. History of any bone-related surgery that affects growth potential of long bones, such as orthopedic reconstructive surgery and osteotomy (Limb-lengthening with full recovery is allowed with a minimum of 12 months of bone healing. Foramen magnum decompression and laminectomy with full recovery are allowed with minimum of 6 months of bone healing. History of 8 plate epiphysiodesis is allowed, but the plates must have been removed prior to Screening with minimum 4 weeks of healing.)
7. Have a form of skeletal dysplasia other than ACH or known medical conditions that result in short stature or abnormal growth [such as severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), hypochondroplasia, growth hormone deficiency, Turner syndrome, pseudoachondroplasia, inflammatory bowel disease, chronic renal insufficiency, active celiac disease[1], Vitamin D deficiency[2], untreated hypothyroidism[3], poorly controlled diabetes mellitus (HbA1c ≥8.0%) or diabetic complications[4]]

   [1]Celiac disease responsive to a gluten-free diet is allowed.
   [2]Vitamin D deficiency or insufficiency treated with supplementation is allowed. Vitamin D deficiency is defined as 25(OH)D level <20ng/mL (<49.9 nmol/L). Vitamin D insufficiency is defined as 25(OH)D level 20-30ng/mL (49.92 -74.86 nmol/L). Participants with Vitamin D deficiency or insufficiency must be on Vitamin D regimen before randomization.
   [3]Participants with hypothyroidism must be clinically euthyroid for 3 months prior to Screening Visit and, in the opinion of the investigator, have achieved any catch-up growth expected from thyroxine replacement
   [4]Participants with diabetes mellitus must have been on stable medication regimen for 3 months prior to randomization (dose adjustments are allowed but addition or discontinuation of medications in this time period is disallowed)
8. History or presence of malignant disease, other than basal cell epithelioma/carcinoma or completely resected squamous skin cancer with no recurrence for 12 months per medical records
9. History or presence of the following:
   - Chronic anemia (resolved iron deficiency anemia is allowed)
   - Significant cardiovascular disease per the judgement of the investigator, such as congenital heart disease (uncomplicated patent ductus arteriosus and atrial or ventricular septal defect with repair are allowed), aortic insufficiency, clinically significant arrhythmias, congestive heart failure with NYHA class II and above, or other conditions that impair regulation of blood pressure or heart rate
   - Condition that impacts hemodynamic stability (such as autonomic dysfunction, orthostatic intolerance)
   - History of chronic renal insufficiency

- Chronic or recurrent illness that can affect hydration or volume status. This may include conditions associated with decreased nutritional intake or increased volume loss.
- Bone fracture within 6 months prior to Screening Visit (within 2 months for fracture of digits)
- Any disease or condition that, in the opinion of the investigator, may make the participant unlikely to fully complete the trial, may confound interpretation of trial results, or presents undue risk from the receiving study drug

10. Child has significant electrocardiogram abnormalities, including evidence of a previous myocardial infarction, left ventricular hypertrophy, flat T waves (particularly in the inferior leads) or more than minor non-specific ST-T wave changes or:
    - QRS >90 milliseconds (msec)
    - QT interval corrected using Fridericia's formula (QTcF) >440 msec
    - PR interval >170 msec
    - Complete right or left bundle branch block
11. Requires, or anticipated to require, chronic (> 4 weeks) or repeated (more than twice per year) treatment with oral corticosteroids during participation in the trial (low and mid-dose inhaled corticosteroids are allowed. High-dose inhaled corticosteroids are not allowed.). See Appendix 5 for definition of high doses of inhaled corticosteroids.
12. Use of medication known to prolong the QT/QTc interval within 7 days or 5 half-lives (whichever is longer) prior to the Screening Visit (see https://crediblemeds.org/ for the list of medications that are known to prolong the QT/QTc interval. Note: Only medications on the Known Risk list are excluded, not those on the Possible or Conditional Risk lists)
13. Ongoing treatment with any medication that affects blood pressure or heart rate
14. Known hypersensitivity to the components of the study drug [trehalose, tris(hydroxymethyl)aminomethane, succinate and PEG]
15. Any other reason that in the opinion of the investigator would prevent the child from complying with the trial requirements or completing the trial

8.1.3. Rollover Criteria for Open-Label Extension Period

Participants are eligible for the Open-Label Extension Period if they fulfill the following rollover criteria:

1. Have completed the 52 weeks randomized treatment period
2. Written, signed informed consent of the parent(s) or legal guardian(s) of the participant and written assent of the participant as required by the institutional review board/human research ethics committee/independent ethics committee (IRB/HREC/IEC) to continue into the Open-Label Extension (OLE) Period
3. Do not fulfill any of the holding/stopping study drug conditions or symptoms (see Section 9.6)

8.2. PREMATURE PARTICIPANT WITHDRAWAL

Premature participant withdrawal occurs when an enrolled participant ceases participation in the trial, regardless of the circumstances, prior to the expected completion of the trial.

In the case of premature participant withdrawal, the investigator should schedule an Early Termination (ET) Visit to collect data, particularly AE follow-up data (if applicable), and to collect blood for final laboratory evaluations. This visit should contain all appropriate assessments and the reason(s) for trial discontinuation should be documented.

The investigator/site staff should make every attempt to contact the participant to arrange the appropriate follow-up assessment(s) for such participants.

Participants may voluntarily withdraw consent to participate in the study for any reason at any time.

8.2.1. Study Drug Discontinuation and Participant Withdrawal

8.2.1.1. Study Drug Discontinuation

Unless informed consent is withdrawn*, participants who permanently discontinue study drug should:

- Attend all subsequent visits up to Visit 7 if discontinued during the Randomized Period, and up to Visit 16 if discontinued during the Open-Label Extension Period. Additionally, ET Visit should be completed as soon as possible after discontinuation of study medication.

** If the participant is not willing to attend all subsequent trial visits, an ET Visit should be scheduled and this should be considered a withdrawal of consent from further participation in the trial.*

See Section 10.1.5 for details on ET Visit.

8.3. PARTICIPANT REPLACEMENT CRITERIA

Participants who terminate early are not expected to be replaced.

9. TREATMENTS

9.1. INVESTIGATIONAL PRODUCT

TransCon CNP is a long-acting essentially inactive prodrug [redacted] TransCon CNP releases active CNP via auto-cleavage of the TransCon Linker in a controlled manner based on physiologic pH and temperature. As such, the TransCon technology is designed to provide sustained exposure of circulating CNP over 7 days, allowing an optimal pharmacokinetic profile for use in ACH.

The drug product formulation containing TransCon CNP is a lyophilized powder in a single-use vial, CCI [redacted]. Prior to use, the lyophilized powder must be reconstituted with sterile water for injection from a prefilled syringe. CCI [redacted] This solution will be administered by SC injection via syringe and needle.

9.1.1. Labeling

All study drug will be labeled according to Good Manufacturing Practice (GMP) and local regulatory requirements. The labels are trial-specific and carry unique identification pack numbers. Participants will be provided with dosing and storage instructions.

9.1.2. Accountability, Storage, and Dispensing

Investigator will be responsible for study drug, ancillary supplies, and associated procedures, exercising accepted medical and pharmaceutical practices.

Study drug must be kept in a locked, temperature-controlled, and temperature-monitored area with limited access and stored according to its labeling. Investigator or dedicated trial staff must evaluate the storage temperature and inform Ascendis Pharma immediately if study drug has been stored outside the specified conditions on the label. TransCon CNP must be stored at 2°C to 8°C and protected from light. The prefilled syringe with sterile Water for Injection (sWfI) (diluent) must be stored at 2°C to 30°C.

The trial will use an internet-based interactive web response system (IWRS) to capture drug inventory and accountability data, including receipt of study drug and supplies by the site, treatment assignment for each participant, distribution to participants, return to the site from participants, and return to the Sponsor (or destruction with the Sponsor's approval). The IWRS system complies with all applicable regulatory requirements for record keeping and record retention in clinical trials [21 CFR Part 11 and ICH E6 (R2) GCP].

Investigator will be responsible for ensuring accountability and reconciliation of study drug.

Site staff will provide training on proper storage to each participant at Visit 1. Once Placebo for TransCon CNP drug product becomes available, this training will also include a review of the Instructions for Use (IFU) and on-site administration of the first dose of study drug by the caregiver. A copy of the IFU will be provided to the participants to take home. For participants that begin participation in the trial prior to the Placebo for TransCon CNP drug product becoming available, site staff will provide training on study drug administration at the next visit following availability of Placebo for TransCon CNP drug product.

NOTE: Under no circumstances will the investigator allow study drugs to be used for other than as directed by this protocol.

See Pharmacy Manual and IFU for further details.

9.2. REFERENCE PRODUCT

Reference product will be supplied as one of two placebos:

- Placebo for TransCon CNP drug product
- sWfI Placebo for TransCon CNP drug product

Placebo for TransCon CNP drug product contains the same excipients as TransCon CNP drug product but does not contain TransCon CNP. Prior to use, the lyophilized powder must be reconstituted with sWfI from a prefilled syringe. This solution will be administered by SC injection via syringe and needle.

sWfI Placebo for TransCon CNP drug product consists of sWfI. The sWfI is supplied in the same prefilled syringe as the one used for reconstitution of the lyophilized powder of the Placebo for TransCon CNP drug product. The procedure for preparation and administration of sWfI Placebo for TransCon CNP drug product is the same as for Placebo for TransCon CNP drug product, only the vial with excipients will be replaced with an empty, sterile vial. The diluent (sWfI) is injected into the empty vial and the dosing volume of sWfI will be drawn from the vial into the injection syringe and administered SC.

If Placebo for TransCon CNP drug product is not available, sWfI Placebo for TransCon CNP drug product will be used until Placebo for TransCon CNP drug product becomes available. Placebo for TransCon CNP drug product will be available prior to the start of Cohort 2, so this procedure will only be utilized in Cohort 1. When Placebo for TransCon CNP drug product is available for Cohort 1, study drug will be prepared and administered by a caregiver (after proper training). Total dose volume for participants in Cohort 1 is expected to be ≤ 0.05ml (based on 95th percentile weight of 32.5 kg for children with ACH at 10.5 years of age). At such low volumes, risk of possible discomfort associated with hypotonicity is minimal and does not pose a significant safety concern.

The dose of Cohort 1 is 6 µg CNP/kg/week (0.006 mg/kg/week) and the concentration of reconstituted study drug is 3.6 mg CNP/mL. Therefore, study drug will be administered at 0.006/3.6 = 0.0017mL/kg.

The 5%ile for weight for a 2-year-old female with achondroplasia is approximately 9kg and the 95%ile for a 10-year-old male with achondroplasia is approximately 30kg (Hoover-Fong 2007). Therefore, the anticipated dose range is approximately 0.0017×9 = 0.015mL to 0.0017×30 = 0.05mL. As study drug will be administered using insulin syringes, volumes will be rounded to the nearest unit (0.01mL). Further details regarding dose volume is provided in the Pharmacy Manual.

9.3. TREATMENT ADMINISTERED

Until Placebo for TransCon CNP becomes available, every dose of study drug will be prepared and administered by an unblinded site staff or home healthcare service. In order to maintain the blind, study drug will be prepared out of sight of the investigator, caregiver and the participant. When Placebo for TransCon CNP is available, study drug should be administered by the caregiver. The injections will be given SC once weekly (approximately every 7 days). The initial volume of study drug (TransCon CNP or placebo) administered will be calculated using the weight measurement obtained at Visit 1. The dose (volume) of study drug will be adjusted

according to the participant's weight at each visit. Study drug will be dispensed for weekly administration by the caregiver, except for the first dose administered at the trial site. The last dose of study drug in the Randomized Period will be administered at least 6 days prior to Visit 7.

For the first four weeks of study drug administration by the caregiver, once weekly home healthcare service will be offered to accommodate home administration of study drug. Extended support might be offered until participants/caregivers are comfortable to take over administration of the study drug.

Each participant will receive their assigned cohort dose for 52 weeks in the Randomized Period, after which they may roll over to the Open-Label Extension Period where all participants will receive TransCon CNP.

In the Open-Label Extension Period, participants may receive the highest dose level of TransCon CNP that has been reviewed and recommended by the Data Monitoring Committee (DMC) for safety and has passed DMC safety review.

Each injection will have a volume ≤750 µL and is to be administered by the caregiver (following training by study staff). Participants may participate in the administration of study drug if deemed developmentally appropriate by the investigator and supervised by the caregiver. Study drug should always be drawn up by caregiver or healthcare professional. One dose may need to be administered as 2 or more injections depending on the dose volume. There are a total of 8 possible injection areas: right abdomen, left abdomen, right anterior thigh, left anterior thigh, right buttocks, left buttocks, right posterior upper arm, and left posterior upper arm, with multiple possible sites within each of these 8 injection areas. Participants should be instructed to rotate injection sites. If multiple injections are required to give one dose, each injection should be administered at different injection area.

All presentations of study drug are provided in a single-use vial.

9.4. SELECTION OF TRIAL DOSES

TransCon CNP is an inactive prodrug. The Phase 1 clinical trial with TransCon CNP demonstrated that a dose range up to 150 µg CNP/kg was well-tolerated in healthy adult male volunteers. Plasma concentration of Free CNP, the active form of drug, reached a C_{max} of approximately 40 pmol/L after single injection of 150 µg CNP/kg in adult males, which is approximately 20-fold higher than endogenous levels seen in children with ACH. With a half-life of ~120 h, free CNP levels in plasma were sustained above anticipated effective threshold for 7 days following administration without affecting production of endogenous CNP.

Based on the available non-clinical safety data with a NOAEL of 30 µg CNP/kg/wk in the 26-week cynomolgus monkey toxicity study and the only adverse effect seen in the chronic toxicity studies being related to exaggerated pharmacology in animals with a normal FGFR3 pathway, a safety factor of 5, based on dose-levels, was considered acceptable. This results in a starting dose of 6 µg CNP/kg/wk.

In individuals with ACH, CNP levels are normal or marginally elevated (Olney 2015). Additionally, it has been demonstrated that a high FGFR3 activity in chondrocytes can de-sensitize the NPR-B receptors towards CNP activation (Robinson 2017, Shuhaibar 2017). As FGFR3 is constitutively active in ACH individuals, this could potentially induce tissue resistance to CNP activation of NPR-B receptors. Higher exposure to CNP may thus be needed to

sufficiently suppress the FGFR3-pathway in children with ACH. Because the NOAEL was established in animals without the activating FGFR3 mutation, CNP exposures above the non-clinical NOAELs of 30 µg CNP/kg/week may be needed and tolerated in children with ACH.

The starting dose is substantially below the NOEL for cardiovascular changes in cynomolgus monkeys (100 µg CNP/kg) and the highest dose in the clinical Phase 1 trial (TCC-101) where extensive cardiovascular monitoring was included and none of the cardiovascular findings in the non-clinical studies were observed.

Additionally, simulation estimations of steady state exposure in the anticipated weight range (~10 to 35 kg) of the ACH children in the proposed TransCon CNP TCC-201 trial have been performed based on Phase 1 data in adults and subsequent allometric scaling to the paediatric population. The modelling showed that 6 µg CNP/kg/week dose is expected to result in a plasma Free CNP-38 C_{max} at steady state of ~ 0.77 – 1.1 pM. This range overlaps with endogenous plasma CNP levels of 1-3 pM, and thus represents a conservative choice for starting dose in a dose escalation trial.

Maximum dose level of 200 µg CNP/kg/week was set based on the same simulation estimation of steady state exposure, which predicted a comparable Free CNP-38 Cmax between a child weighing 35 kg (approximately 95th percentile for weight in a 11-year-old child with ACH) receiving weekly dose of 200 µg CNP/kg at steady state and the mean Free CNP-38 Cmax that was observed after single dose of 150 µg CNP/kg in healthy adults in TCC-101. Free CNP 38 C_{max} is predicted to be lower in smaller children (e.g. 2 year old child with ACH) when administered the same dose level. The dose levels to be investigated in TransCon CNP TCC-201 trial are designed to investigate exposure levels previously tested and shown to be safe and well-tolerated in healthy adult males. As PK data become available from TCC-201, the data will be reviewed to ensure children are not overexposed to TransCon CNP. Prior to determining if cohort 5 should be initiated at a dose > 100 µg CNP/kg/week, the safety data and height velocity at 6 months in cohort 4 for all participants will be assessed, in addition to all data from prior cohorts. The dose level of Cohort 5 will be determined taking into consideration the updated PK model that will incorporate the available PK data from TCC-201 to ensure exposure to Free CNP-38 does not exceed levels observed in TCC-101.

9.5. TREATMENT ASSIGNMENT

9.5.1. Treatment Assignment During Randomized Period

At Visit 1, participants will be randomized to TransCon CNP or placebo in a 3:1 ratio in one of the following cohorts:

Cohort 1: TransCon CNP 6 µg CNP/kg/week or placebo

Cohort 2: TransCon CNP 20 µg CNP/kg/week or placebo

Cohort 3: TransCon CNP 50 µg CNP/kg/week or placebo

Cohort 4: TransCon CNP 100 µg CNP/kg/week or placebo

Cohort 5: TransCon CNP > 100 µg CNP/kg/week* or placebo

*Up to 200 µg CNP/kg/week, if needed, at a dose to be determined based on emerging data

Each participant will receive their assigned cohort dose for 52 weeks in the Randomized Period, after which they may roll over to the Open-Label Extension Period where all participants will receive TransCon CNP.

9.5.2. Dose Escalation

Data Monitoring Committee 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

An independent Data Monitoring Committee (DMC) will attend each meeting to provide recommendations on the action to be taken (i.e. proceed to the next dose level as planned, modify the dose of the next cohort, or stop dose escalation).

The DMC will be provided with the following unblinded data at each Data Monitoring Committee meeting:

1. Summary of safety data including but not limited to AEs, vital signs, and laboratory findings
2. Details of SAEs and AEs leading to discontinuation of study drug
3. Summary of anthropometric measurements of cohorts that completed at least 26 weeks
4. Other relevant available data at the request of the DMC, including available PK data

Following the Data Monitoring Committee 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 be 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 to assess whether additional higher dose levels (up to 200 µg CNP/kg/week) should be investigated based on emerging data. After review of the data and consultation with the DMC, the Sponsor will decide whether a higher dose level should be investigated.

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.

If one serious adverse drug reaction or two severe adverse drug reactions occur in a particular cohort, dose escalation will be halted. Additionally, an urgent DMC meeting will be called to determine whether dosing should be halted in that cohort or across the entire trial. If deemed appropriate after review of all available safety data, the DMC may recommend that dose escalation be re-started. If the DMC does not feel that enough data is available to make a recommendation, they may defer a decision and recommend a time at which the data should be re-evaluated.

Additionally, the DMC will be notified and a meeting may be called for each incident of study drug discontinuation for reasons related to safety.

If dose escalation is discontinued prior to initiating the 4th cohort, participants to be enrolled in the cohorts not yet filled may receive the highest tolerated dose level investigated (or placebo), instead of the planned higher doses. The decision to complete all four planned cohorts will be made by the Sponsor after review of available data and consultation with the DMC.

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

Refer to the DMC charter for further details.

9.6. HOLDING/STOPPING STUDY DRUG

The investigator or Medical Monitor (and, if needed, with DMC review) may temporarily hold or stop the dosing of study drug to a participant at any time during the trial. For participants that discontinue study drug for reasons related to safety, unblinding of the treatment assignment for the participant may occur if deemed necessary by the Sponsor to assess a potential safety signal or by the investigator to provide adequate medical care to the participant. In case of medical emergency, the investigator will have direct access to unblinding of the treatment through the Interactive web response system. Examples of conditions or symptoms that may warrant holding or stopping study drug at the investigator's or Medical Monitor's discretion include:

1. Severe fracture of long bones or growth plates regardless of causality
2. Evidence of symptomatic persistent orthostatic intolerance, lasting over 24 hours not explained by other probable causes. Orthostatic hypotension is defined as decrease in SBP of ≥20 mmHg (Stewart 2018). Accompanying tachycardia is defined as change of heart rate increment of ≥40 bpm and absolute orthostatic HR ≥130 bpm (for ages 13 years and younger) (Singer 2012)
3. Skeletal abnormalities typically not associated with ACH, growth or other concurrent medical conditions, such as
    - Scoliosis
    - Severe hip pain
    - Findings from thorough skeletal exam requiring imaging or consultation with orthopedics specialist

- Clinically relevant findings on radiologic assessments (new onset or worsening of tibial bowing, joint abnormalities at the elbows, evidence of slipped capital femoral epiphysis)

4. A severe or serious adverse reaction
5. QTc value > 500 msec, or an extension > 60 msec from baseline in absence of possible causes other than the study drug
6. Diagnosis of heart disease requiring pharmaceutical or surgical intervention to maintain heart function
7. Any other sign that warrants holding or discontinuing study drug at the discretion of the investigator or Medical Monitor

The investigator, with Sponsor Medical Monitor notification, must stop study drug for an individual participant in the presence of the following symptoms at any time during the trial:

1. Closed epiphysis (bone age >14.0 years for females or >16.0 years for males)
2. Slipped capital femoral epiphysis
3. Pregnancy, intention of becoming pregnant, and females who become of childbearing potential and who do not use highly effective contraceptive measures. Highly effective contraceptive measures are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly (see Appendix 6).

If study drug is held or discontinued due to safety concerns, approval by the Medical Monitor is required prior to resumption of study drug. Consideration of dose changes due to safety concerns may occur on an individual basis.

Any participant who discontinues study drug should be encouraged to remain in the trial and attend all subsequent trial visits and complete all assessments. However, if trial participation is fully discontinued, an ET Visit should be performed.

9.7. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications include all prescription or over-the-counter medications, vitamins and herbal/nutritional supplements.

Prior medication is considered any therapy/medication(s) that the participant has taken prior to the Screening Visit and will be recorded on the appropriate eCRF page. At minimum, all medications taken within 90 days prior to Screening Visit should be recorded. Additionally, medications taken at any time prior to signing the informed consent that affect stature must be reported, such as hGH and chronic oral corticosteroid use, regardless of when the medication was last taken.

Concomitant medication is considered any medication other than the study drug that is administered after signing the informed consent up until the last completed trial visit. Any change in documented, permitted concomitant medication being taken at the beginning of the clinical trial must be recorded in the eCRF.

Medications that are considered necessary for the children's welfare may be given at the discretion of the investigator. The administration of medication must be recorded in the

appropriate source document and on the case report form (CRF) for the duration of participation in the trial.

9.7.1. Prohibited Therapies

The following medications are prohibited throughout the trial:

- hGH or other medicinal products known to promote growth of long bones

In case of any questions regarding current or prior medication, Sponsor Medical Monitor should be contacted.

If use of a prohibited medication becomes necessary, administration of study drug may be discontinued at the discretion of the Investigator and Sponsor Medical Monitor. The participant should be encouraged to complete all scheduled visits per protocol.

10. TRIAL PROCEDURES

10.1. TRIAL DURATION

The total duration of the trial for an individual participant is approximately 165 weeks.

- **Screening Period:** Up to approximately 4 weeks
- **Randomized Treatment Period:** 52 weeks and for participants who do not continue in the Open-Label Extension Period a follow-up period of 5 weeks.
- **Open-Label Extension Period**: 104 weeks and a follow-up period of 5 weeks.

All visits for each participant should be scheduled at approximately the same time of day.

10.1.1. Trial Periods and Visits

See Appendix 1 and Appendix 2 for Schedules of Events.

Following the Screening Visit, each participant attends:

- Visit 1 (Randomization/Week 0). The visit will be the date of randomization.
- Phone Visit (Week 2) ±3 days. This visit will occur 11 to 17 days after Visit 1.
- Visit 2 (Week 4) ±3 days (trough visit, pre-dose). The visit will occur 25 to 31 days after Visit 1.
- Visit 3 (Week 8) ±7 days (any time). The visit will occur 49 to 63 days after Visit 1.
- Visit 4 (Week 12) ±7 days (any time). The visit will occur 77 to 91 days after Visit 1.
- Visit 5 (Week 26) ±7 days (trough visit, pre-dose). The visit will occur 175 to 189 days after Visit 1.
- Visit 6 (Week 39) ±7 days (any time). The visit will occur 266 to 280 days after Visit 1.
- Visit 7 (Week 52) ±7 days (trough visit, pre-dose). The visit will occur 357 to 371 days after Visit 1.

- Follow-up Visit (Week 57) ±7 days. The visit will occur 393 – 407 days after Visit 1. Only for participants not continuing in the Open-Label Extension Period.

Open-Label Extension Period:

- Visit 7 (Week 52) ±7 days. The visit will occur 357 to 371 days after Visit 1. The visit must be conducted on the same day as Visit 7 in the Randomized Period.
- Phone Visit (Week 54) ±3 days. This visit will occur 375 to 381 days after Visit 7.
- Visit 8 (Week 56) ±3 days (any time). The visit will occur 389 to 395 days after Visit 1.
- Visit 9 (Week 65) ±7 days (any time). The visit will occur 448 to 462 days after Visit 1.
- Visit 10 (Week 78) ±7 days (any time). The visit will occur 539 to 553 days after Visit 1.
- Visit 11 (Week 91) ±7 days (any time). The visit will occur 630 to 644 days after Visit 1.
- Visit 12 (Week 104) ±7 days (any time). The visit will occur 721 to 735 days after Visit 1.
- Visit 13 (Week 117) ±7 days (any time). The visit will occur 812 to 826 days after Visit 1.
- Visit 14 (Week 130) ±7 days (any time). The visit will occur 903 to 917 days after Visit 1.
- Visit 15 (Week 143) ±7 days (any time). The visit will occur 994 to 1008 days after Visit 1.
- Visit 16 (Week 156) ±7 days (any time). The visit will occur 1085 to 1099 days after Visit 1.
- Follow-up Visit (Week 161) ±7 days. The visit will occur 1120 – 1134 days after Visit 1.

Visit windows for all visits after Visit 1 may be increased due to extenuating circumstances such as Covid-19 travel restrictions, with the approval of the Medical Monitor.

10.1.2. Screening Visit (approximately Week -4 to -1)

The Screening Visit may occur up to approximately 4 weeks prior to randomization, during which clinical data will be collected and screening procedures will be performed to determine eligibility. The Screening Visit window may be extended at the discretion of the Medical Monitor.

Prior to any protocol related activities, screening procedures, or assignment of a Participant Number, informed consent will be obtained from each potential participant in accordance with GCP and regional regulatory requirements. The format and content of the ICF must be approved by the appropriate institutional review board/ethics committee (IRB/EC) prior to implementation.

The following must be performed during the Screening Period:

1. PRO/ObsRO validation battery
2. Verification of eligibility
3. Demographics (date of birth, age at screening, biological sex, ethnicity, race)
4. Medical history including family history of ACH, age of diagnosis, date of diagnosis (if available), type of mutation, and historical anthropometric measurements, as available
5. Prior and concomitant medications
6. Vital sign measurements (Temperature, HR, BP)
7. Full physical examination, including assessment of pubertal status and thorough skeletal exam
8. Baseline qualitative assessment of sleep and snoring pattern (clinical assessment for monitoring)
9. Weight
10. Standing height
11. Sitting height
12. 12-lead ECG
13. Genetic confirmation of ACH (if not done previously). See Section 11.11.
14. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. TSH
    c. Hemoglobin A1c
    d. Hematology
    e. Lipid panel
    f. 25(OH) Vitamin D
    g. Anti-drug antibodies
    h. Biomarkers
15. Urine collection
16. CCI [redacted]

NOTE: PRO/ObsRO validation battery 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. The PRO/ObsROs should be completed at the visit if possible. If the same caregiver is unable to attend a particular visit, an alternate caregiver may complete the PRO/ObsROs at the visit.

The CCI [redacted] should be completed by the investigator after all clinical assessments are completed.

Screening Visit may be conducted remotely (e.g. at the participant's home), at the discretion of the investigator, to minimize the risk of exposure to an infection during a pandemic or due to other restrictions that prevent the participant from being able to travel to the site. In such an event, consent may be obtained remotely as allowed by the applicable IRB/EC requirements, and the Investigator will conduct the scheduled assessments remotely with assistance from the home health nurse (HHN) who will be with the participant.

If the PRO/ObsRO validation battery cannot be completed during the Screening Visit due to the visit being conducted remotely, the battery should be completed separately at approximately 14 days prior to Visit 1, up to 7 days prior to Visit 1.

All anthropometric measurements per medical records for up to one year prior to Screening Visit should be collected. If measurement(s) are not available within one year, the last available measurement(s) prior to Screening Visit should be collected. Method of measurement (standing vs recumbent, wall-mounted vs free-standing stadiometer in medical clinic vs other setting) should also be recorded.

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.

Qualitative assessment of sleep and snoring pattern should include questions about neck hyperextension during sleep, loud and irregular snoring, glottal stops, observed sleep apnea, deep compensatory sighs, self-arousals, secondary enuresis, night-time emesis, morning headaches, daytime somnolence, or changes in school performance or behavior (Pauli 2019). See Section 11.4 for details.

For the assessment of pubertal status, boys will be assessed for testis volumes, and girls for breast development according to Tanner stages (Tanner 1976). 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 (Emmanuel 2019). Tanner stage progression during the course of the trial will not impact study treatment. See Appendix 3 for details.

In case the Screening Visit is conducted remotely, full physical exam including pubertal assessment and thorough skeletal exam, may be conducted at Visit 1 before administration of study drug, with the understanding that an exam consistent with Tanner stage ≥ 2 is exclusionary. If the full physical exam and thorough skeletal exam are done pre-dose at Visit 1; an additional thorough skeletal exam and limited symptom directed physical exam at Visit 1 are not required

The analysis of anti-drug antibodies may only be conducted after randomization and is not required for eligibility verification.

Upon confirmation of eligibility, the participant will be randomized following Medical Monitor or designee confirmation.

If unavailable from medical records, genetic test for ACH will be performed. The test may be performed at any time after signing the consent and before Visit 1. Further testing may be pursued on an individual basis as indicated. Mutations other than those resulting in G380R substitution in FGFR3 may be used as genetic confirmation of ACH, pending review of Medical Monitor.

Participants who sign the informed consent form but do not meet one or more eligibility criteria (including withdrawing of consent) prior to first study drug dosing will be considered screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography and screen failure details (eligibility criteria).

The decision to rescreen will be made on a case by case basis after discussion with Medical Monitor, including which screening procedures may not need repeating. Rescreened participants will receive a new Screening ID upon rescreening if they have not previously participated in ACHieve study (TCC-NHS-01). Participants that participated in ACHieve will not be given a new Screening ID if they are Rescreened. For all re-screened participants, the reason for the initial screen failure must be documented.

See Section 11 for further details on procedures listed above.

10.1.3. Randomized Treatment Period (Week 0 to Week 52) and Open-Label Extension Period (Week 52 – Week 156)

During the Treatment Period, participants are randomized in a 3:1 ratio of TransCon CNP to placebo. The dose is dependent on the cohort the participant is enrolled into:

- Cohort 1: TransCon CNP 6 µg CNP/kg/week (Estimated 9 on TransCon CNP, 3 on placebo)
- Cohort 2: TransCon CNP 20 µg CNP/kg/week (Estimated ≥9 on TransCon CNP, ≥3 on placebo)
- Cohort 3: TransCon CNP 50 µg CNP/kg/week (Estimated ≥9 on TransCon CNP, ≥3 on placebo)
- Cohort 4: TransCon CNP 100 µg CNP/kg/week (Estimated ≥9 on TransCon CNP, ≥3 on placebo)
- Cohort 5*: TransCon CNP >100 µg CNP/kg/week (Estimated ≥9 on TransCon CNP, ≥3 on placebo)

* Up to 200 µg CNP/kg/week, if needed, at a dose to be determined based on emerging data

NOTE: Participants remain on the same dose of study drug throughout the 52 week Treatment Period

During the Open-Label Extension Period, all participants receive TransCon CNP at the highest dose determined to be safe by DMC based on the data from the Randomized Period.

10.1.3.1. Visit 1 (Randomization/Week 0)

Participants meeting all entry criteria will return to the clinic for Visit 1.

The following will be performed prior to randomization and study drug administration:

1. Subset of PRO/ObsRO validation battery
2. Review changes in medical history
3. Review of concomitant medications
4. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
5. Vital sign measurements (Temperature, HR, BP), including orthostatic HR and BP
6. Limited symptom-directed physical examination (at investigator's discretion), injection site inspection, and thorough skeletal exam
7. Qualitative assessment of changes of sleep and snoring pattern
8. Weight
9. All anthropometric measurements
10. Radiographic assessment of bone
    a. Left hand and wrist bone age X-ray
    b. Dual-energy X-ray absorptiometry (DXA)
    c. Anterior-posterior (AP) Standing lower extremity X-ray
    d. AP and lateral spine X-ray
11. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. Pharmacokinetics
    d. Biomarkers
    e. Anti-drug antibodies
12. CCI
13. After completion of these assessment, participants can proceed to randomization and study drug administration:
    a. Randomization
    b. Study drug administration at site and diary dispensing

If for any reason the PRO/ObsRO validation battery for the Screening Visit was not completed prior to Visit 1, the same battery should be completed during Visit 1 prior to study drug administration in lieu of the subset scheduled for Visit 1.

Orthostatic vital signs (HR and BP) will be taken at rest (preferably supine) and upon standing. Orthostatic hypotension is defined as decrease in SBP of ≥ 20 mmHg (Stewart 2018). Accompanying tachycardia is defined as change of heart rate increment of ≥40 bpm and absolute orthostatic HR ≥130 bpm (for ages 13 years and younger) (Singer 2012).

Limited symptom-directed physical examination of other systems should be performed at the discretion of the investigator to verify no clinically relevant changes have occurred since the Screening Visit. Injection site must be visually inspected prior to dosing.

If the Screening Visit was conducted remotely, full physical examination, including pubertal status assessment, must be performed at Visit 1 before administration of study drug. Additional thorough physical exam and limited symptom directed physical exam are not required.

Thorough skeletal physical exam will be performed and additional imaging assessments may be conducted as clinically indicated based on the physical exam findings.

Anthropometric measurements should be taken following the Anthropometric Parameter Manual. For any anthropometric parameters that could not be measured during the visit, the reason must be documented.

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

Bone age using X-ray imaging will be assessed in the left hand and wrist for all participants unless a medical reason prohibits.

DXA will be performed only for participants aged 5 years and older.

The first dose of study drug will be administered on-site to provide training to the caregiver on study drug administration. Participant will be monitored for at least 2 hours in the clinic after injection for any acute reactions. Visual inspection of the injection site and vital signs measurements (Temperature, HR, and BP) will be performed at 1 hour and 2 hours after injection. Participants should be monitored longer as clinically indicated based on any clinically significant changes that emerge during the 2 hours.

For participants who weigh ≥11 kg, the following will also be performed after injection of study drug:

- Blood collection for pharmacokinetic analyses at approximately 8, 24, and 48 hours after injection
- Orthostatic vital signs (HR and BP) at rest (preferably supine) and upon standing prior to blood collection at approximately 8, 24, and 48 hours after injection
- Inspection of injection site at approximately 8, 24, and 48 hours after injection
- ECG collection at approximately 48 hours after injection prior to PK blood collection

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). Assessments at 24 hours and 48 hours after injection, including orthostatic vital signs, ECG collection, blood collection, and injection site assessment may be conducted remotely by HHN.

10.1.3.2. Phone Visit (Week 2 ±3 days)

All participants will be contacted by phone during Week 2 (±3 days) 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.

10.1.3.3. Visit 2 (Week 4 ±3 days)

At Visit 2, blood collection for pharmacokinetics must be at trough level. Therefore, study drug cannot be administered within 6 days prior to the visit. Study drug may be administered after all blood collection is completed. Visit 2 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight.

The following will be performed:

1. Review changes in concomitant medications
2. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
3. Vital sign measurements (Temperature, HR, BP)
4. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
5. Qualitative assessment of changes of sleep and snoring pattern
6. Weight
7. Standing height and sitting height only
8. 12-lead ECG
9. Study drug and diary dispensing
10. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. Pharmacokinetics
    d. Biomarkers
    e. Anti-drug antibodies

10.1.3.4. Visit 3 (Week 8 ±7 days)

Visit 3 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight.

The following will be performed:

1. Subset of PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, BP, HR)
5. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
6. Qualitative assessment of changes of sleep and snoring pattern
7. Weight
8. Standing height and sitting height only
9. 12-lead ECG
10. Study drug and diary dispensing
11. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. Lipid panel
    d. Pharmacokinetics
12. CCI

10.1.3.5. Visit 4 (Week 12 ±7 days):

Visit 4 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight.

The following will be performed:

1. Subset of PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, BP, HR)
5. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
6. Qualitative assessment of changes of sleep and snoring pattern
7. Weight
8. Standing height and sitting height only

9. Radiographic assessment of bone
    a. AP standing lower extremity X-ray
    b. AP and lateral spine X-ray
10. Study drug and diary dispensing
11. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. Pharmacokinetics
    d. Biomarkers
    e. Anti-drug antibodies
12. Urine collection
13. CCI

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 at Visit 4 may be conducted remotely (e.g. at a community imaging center).

10.1.3.6. Visit 5 (Week 26 ±7 days):

At Visit 5, blood collection for pharmacokinetics must be at trough level. Therefore, study drug cannot be administered within 6 days prior to the visit. Study drug may be administered after all blood collection is completed. Visit 5 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 5 is conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight, but full anthropometric measurements will be deferred until the participant is able to travel to the site. A physical assessment will be performed by the HHN under the remote supervision of the Investigator, but the pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Subset of PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, HR, BP)
5. Full physical examination, including assessment of pubertal status, injection site inspection, and thorough skeletal physical exam
6. Qualitative assessment of changes of sleep and snoring pattern
7. Weight
8. All anthropometric measurements
9. 12-lead ECG

10. Study drug and diary dispensing
11. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. 25(OH) Vitamin D
    d. Pharmacokinetics
    e. Biomarkers
    f. Anti-drug antibodies
12. Urine collection
13. CCI

10.1.3.7. Visit 6 (Week 39 ±7 days):

Visit 6 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight.

The following will be performed:

1. Subset of PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, HR, BP)
5. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
6. Qualitative assessment of changes of sleep and snoring pattern
7. Weight
8. Standing height and sitting height only
9. Study drug and diary dispensing
10. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. Lipid panel
    d. Pharmacokinetics
    e. Biomarkers
    f. Anti-drug antibodies
11. Urine collection
12. CCI

10.1.3.8. Visit 7 (Week 52 ±7 days) or ET Visit:

This visit will serve as the last visit in the Randomized Period and the first visit in the Open-Label Extension Period.

At Visit 7, blood collection for pharmacokinetics must be at trough level. Therefore, study drug cannot be administered within 6 days prior to the visit. For participants who do not roll over to the Open-Label Extension Period, no further dose of study drug will be administered.
Visit 7 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 7 is conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. A physical assessment will be performed by the HHN under the remote supervision of the Investigator.

The following will be performed:

1. PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital signs measurement (Temperature, HR, BP)
5. Full physical examination including assessment of pubertal status, injection site inspection, and thorough skeletal physical exam
6. Qualitative assessment of changes of sleep and snoring pattern
7. Weight
8. All anthropometric measurements
9. Radiographic assessment of bone
    a. Left hand and wrist Bone age X-ray
    b. DXA
    c. AP Standing lower extremity X-ray
    d. AP and lateral spine X-ray
10. 12-lead ECG
11. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. 25(OH) Vitamin D
    d. Lipid panel
    e. Pharmacokinetics
    f. Biomarkers
    g. Anti-drug antibodies
12. Urine collection
13. CCI

Radiographic assessments at Visit 7 may be conducted remotely (e.g. at a community imaging center). Alternatively, radiologic assessments may be deferred until the participant is able to travel to the site. Radiographic assessments may not be required at Visit 7, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to Visit 7.

Immediately following completion of 52 weeks in the Randomized Period, all participants, including those randomized to placebo, may continue into the Open-Label Extension Period to receive TransCon CNP if they fulfill the rollover criteria (see Section 8.1.3). If the Investigator or Medical Monitor has concerns about continuing the participant in the Open-Label Extension Period (e.g. potential safety concerns or emergent fulfillment of holding/stopping criteria) participant may end treatment at the end of the Randomized Period.

10.1.3.9. Follow-up Visit (Week 57 ±7 days): For Participants Not Continuing in the Open-Label Extension

Participants who are not continuing in the Open-Label Extension Period will attend a follow-up visit 5 weeks after Visit 7 to review any adverse events, to collect blood samples for assessment of anti-drug antibodies and answer any questions. The Follow-up visit may be conducted remotely (e.g. at the participant's home) by the HHN at the discretion of the investigator to minimize the risk of exposure to an infection during a pandemic, or due to other restrictions that prevent the participant from being able to travel to the site for the blood collection.

OPEN-LABEL EXTENSION PERIOD VISITS:

10.1.3.10. Visit 7 (Week 52 ±7 days):

For participants continuing in the Open-Label Extension Period, all Visit 7 assessments for the Open-Label Extension Period must be done immediately following the Visit 7 assessments for the Randomized Period.

Prior to any protocol related activities for the Open-Label Extension Period, signed informed consent will be obtained for each potential participant in accordance with GCP and regional regulatory requirements. The format and content of the ICF must be approved by the appropriate institutional review board/ethics committee (IRB/EC) prior to implementation.

During the Open-Label Extension Period, the Investigator should ascertain an individual's risk for becoming pregnant or fathering a child and take appropriate steps for participants that attain reproductive potential during participation in the trial. This should be captured in the eCRF. 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 Appendix 6).

After completion of all scheduled assessments for the Randomized Period, the following will be performed:

1. Informed consent
2. Assessment of childbearing potential according to Appendix 6
3. Urinary hCG test (for females of childbearing potential according to Appendix 6)

4. Study drug and diary dispensing

For participants who received placebo during the Randomized Period, this will be the first dose of TransCon CNP, and in order to maintain the blind, all participants must undergo the same safety monitoring. Study drug must be administered on-site and participants will be monitored for at least 2 hours in the clinic after injection for any acute reactions. Visual inspection of the injection site and vital signs measurements (Temperature, HR, and BP) will be performed at 1 hour and 2 hours after injection. Participants should be monitored longer as clinically indicated based on any clinically significant changes that emerge during the 2 hours.

For participants who weigh ≥11 kg, the following will also be performed after injection of study drug:

- Blood collection for pharmacokinetic analyses at approximately 8, 24, and 48 hours after injection
- Orthostatic vital signs (HR and BP) at rest (preferably supine) and upon standing prior to blood collection at approximately 8, 24, and 48 hours after injection
- Inspection of injection site at approximately 8, 24, and 48 hours after injection
- ECG collection at approximately 48 hours after injection prior to PK blood collection

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). Assessments at 24 hours and 48 hours after injection, including orthostatic vital signs, ECG collection, blood collection, and injection site assessment may be conducted remotely by HHN.

10.1.3.11. Phone Visit (Week 54 ±3 days):

All participants will be contacted by phone during Week 54 (±3 days) 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.

10.1.3.12. Visit 8 (Week 56 ±3 days):

Visit 8 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. Pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Review changes in concomitant medications
2. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
3. Vital sign measurements (Temperature, HR, BP)
4. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
5. Qualitative assessment of sleep and snoring pattern
6. Assessment of pubertal status and childbearing potential according to Appendix 6

7. Weight
8. Standing height and sitting height
9. 12-lead ECG
10. Blood collection for the following laboratory assessments
    a. Chemistry
    b. Hematology
    c. Pharmacokinetics
    d. Biomarkers
    e. Anti-drug antibodies
11. Urine collection (including hCG test for females of childbearing potential (according to Appendix 6)
12. Study drug and diary dispensing

10.1.3.13. Visit 9 (Week 65) ±7 Days

Visit 9 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. Pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Review changes in concomitant medications
2. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
3. Vital sign measurements (Temperature, HR, BP)
4. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
5. Qualitative assessment of sleep and snoring pattern
6. Assessment of pubertal status and childbearing potential according to Appendix 6
7. Standing height and sitting height
8. 12-lead ECG *
9. Weight
10. Radiographic assessments
    a. Anterior-posterior (AP) standing lower extremity X-ray
    b. Anterior-posterior and lateral spine X-ray
11. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. Pharmacokinetics *
    d. Biomarkers

e. Anti-drug antibodies

12. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)
13. CCI
14. Study drug and diary dispensing
15. 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 at Visit 9 may be conducted remotely (e.g. at a community imaging center).

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

10.1.3.14. Visit 10 (Week 78) ±7 Days

Visit 10 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 10 is conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight, but full anthropometric measurements will be deferred until the participant is able to travel to the site. A physical assessment will be performed by the HHN under the remote supervision of the Investigator, but the pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Subset of PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, HR, BP)
5. All anthropometric measurements
6. 12-lead ECG
7. Full physical examination, injection site inspection, and thorough skeletal physical exam
8. Qualitative assessment of sleep and snoring pattern
9. Assessment of pubertal status and childbearing potential according to Appendix 6
10. Weight
11. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. 25(OH) Vitamin D
    d. Lipid panel
    e. Pharmacokinetics
    f. Biomarkers

g. Anti-drug antibodies

12. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)
13. CCI
14. Study drug and diary dispensing

10.1.3.15. Visit 11 (Week 91) ±7 Days

Visit 11 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. Pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Review changes in concomitant medications
2. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
3. Vital sign measurements (Temperature, HR, BP)
4. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
5. Qualitative assessment of sleep and snoring pattern
6. Assessment of pubertal status and childbearing potential according to Appendix 6
7. Standing height and sitting height
8. 12-lead ECG *
9. Weight
10. Blood collection for the following laboratory assessments:
    a. Chemistry
    b. Hematology
    c. Pharmacokinetics *
    d. Biomarkers
    e. Anti-drug antibodies
11. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)
12. CCI
13. Study drug and diary dispensing

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

10.1.3.16. Visit 12 (Week 104) ±7 Days

Visit 12 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 12 is conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight, but full anthropometric measurements will be deferred until the participant is able to travel to the site. A physical assessment will be performed by the HHN under the remote supervision of the Investigator, but the pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, HR, BP)
5. All anthropometric measurements
6. Full physical examination, injection site inspection, and thorough skeletal physical exam
7. Qualitative assessment of sleep and snoring pattern
8. Assessment of pubertal status and childbearing potential according to Appendix 6
9. Weight
10. Radiographic assessments
    a. X-ray of left hand and wrist for bone age
    b. Dual-energy X-ray absorptiometry (DXA) for bone mineral density (participants 5 years and older only)
    c. Anterior-posterior and lateral spine X-ray
    d. Anterior-posterior (AP) standing lower extremity X-ray
11. 12-lead ECG
12. Blood collection for the following laboratory assessments
    a. Chemistry
    b. Hematology
    c. 25(OH) Vitamin D
    d. Lipid panel
    e. Pharmacokinetics
    f. Biomarkers
    g. Anti-drug antibodies
13. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)

14. CCI

15. Study drug and diary dispensing

Radiographic assessments at Visit 12 may be conducted remotely (e.g. at a community imaging center). Alternatively, radiologic assessments may be deferred until the participant is able to travel to the site.

10.1.3.17. Visit 13 (Week 117) ±7 Days

Visit 13 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. Pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Review changes in concomitant medications
2. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
3. Vital sign measurements (Temperature, HR, BP)
4. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
5. Qualitative assessment of sleep and snoring pattern
6. Assessment of pubertal status and childbearing potential according to Appendix 6
7. Standing height and sitting height
8. Weight
9. Radiographic assessments
    a. Anterior-posterior (AP) standing lower extremity X-ray
    b. Anterior-posterior and lateral spine X-ray
10. Blood collection for the following laboratory assessments
    a. Chemistry
    b. Hematology
    c. Biomarkers
    d. Anti-drug antibodies
11. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)
12. CCI
13. Study drug and diary dispensing
14. 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 at Visit 13 may be conducted remotely (e.g. at a community imaging center).

10.1.3.18. Visit 14 (Week 130) ±7 Days

Visit 14 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 14 is conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight, but full anthropometric measurements will be deferred until the participant is able to travel to the site. A physical assessment will be performed by the HHN under the remote supervision of the Investigator, but the pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Subset of PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, HR, BP)
5. All anthropometric measurements
6. Full physical examination, injection site inspection, and thorough skeletal physical exam
7. Qualitative assessment of sleep and snoring pattern
8. Assessment of pubertal status and childbearing potential according to Appendix 6
9. Weight
10. 12-lead ECG
11. Blood collection for the following laboratory assessments
    a. Chemistry
    b. Hematology
    c. 25(OH) Vitamin D
    d. Lipid panel
    e. Pharmacokinetics
    f. Biomarkers
    g. Anti-drug antibodies
12. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)
13. CCI
14. Study drug and diary dispensing

10.1.3.19. Visit 15 (Week 143) ±7 Days

Visit 15 may be conducted remotely with assistance from the home health nurse (HHN). A portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. Pubertal assessment will be deferred until the next on-site visit.

The following will be performed:

1. Review changes in concomitant medications
2. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
3. Vital sign measurements (Temperature, HR, BP)
4. Limited, symptom-directed physical examination at investigator's discretion, injection site inspection, and thorough skeletal physical exam
5. Qualitative assessment of sleep and snoring pattern
6. Assessment of pubertal status and childbearing potential according to Appendix 6
7. Standing height and sitting height
8. Weight
9. Blood collection for the following laboratory assessments
    a. Chemistry
    b. Hematology
    c. Biomarkers
    d. Anti-drug antibodies
10. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)
11. CCI
12. Study drug and diary dispensing

10.1.3.20. Visit 16 (Week 156) ±7 Days/Early Termination Visit

No further dose of study drug will be administered after Visit 16. Visits 16 may only be conducted remotely when regional/institutional restrictions prohibit site visits (e.g. facility closed due to pandemic). If Visit 16 is conducted remotely, a portable stadiometer will be used to measure standing and sitting height and a portable scale to measure weight. A physical assessment will be performed by the HHN under the remote supervision of the Investigator.

The following will be performed:

1. PRO/ObsRO validation battery
2. Review changes in concomitant medications
3. Review adverse events (including review of ACH comorbidities based on age, including risk of sleep apnea and CMC)
4. Vital sign measurements (Temperature, HR, BP)
5. All anthropometric measurements
6. Full physical examination, injection site inspection, and thorough skeletal physical exam
7. Qualitative assessment of sleep and snoring pattern

8. Assessment of pubertal status and childbearing potential according to Appendix 6
9. Weight
10. 12-lead ECG
11. Radiographic assessments
    a. X-ray of left hand and wrist for bone age
    b. Dual-energy X-ray absorptiometry (DXA) for bone mineral density (participants 5 years and older only)
    c. Anterior-posterior and lateral spine X-ray
    d. Anterior-posterior (AP) standing lower extremity X-ray
12. Blood collection for the following laboratory assessments
    a. Chemistry
    b. Hematology
    c. 25(OH) Vitamin D
    d. Lipid panel
    e. Pharmacokinetics
    f. Biomarkers
    g. Anti-drug antibodies
13. Urine collection (including hCG test for females of childbearing potential according to Appendix 6)
14. CCI

Radiographic assessments at Visit 16 may be conducted remotely (e.g. at a community imaging center). Alternatively, radiologic assessments may be deferred until the participant is able to travel to the site. Radiographic assessments may not be required at Visit 16, with Medical Monitor/Medical Expert approval, if the same assessments were conducted within approximately 3 months prior to Visit 16.

Immediately following completion of treatment in the study at Visit 16, all participants may be offered to continue in a separate long-Term Open-Label _Extension Study (ASND0039) if they fulfill the eligibility criteria for the study. In the separate study, participants will continue to receive TransCon CNP. If the Investigator or Medical Monitor has concerns about continuing the participant in the separate Long-Term Open-Label Extension Study (e.g. potential safety concerns or emergent fulfillment of holding/stopping criteria), the participant will end treatment with TransCon CNP.

10.1.3.21. Follow-Up Visit (Week 161 ±7 days):

Participants who will not continue in the separate Long-Term Open-Label Extension Study (ASND0039), will attend a follow-up visit 5 weeks after Visit 16 to review any adverse events, to collect blood samples for assessment of anti-drug antibodies and answer any questions. The Follow-up visit may be conducted remotely (e.g. at the participant's home) by the HHN at the discretion of the investigator to minimize the risk of exposure to an infection during a pandemic, or due to other restrictions that prevent the participant from being able to travel to the site for the blood collection.

10.1.4. Unscheduled Visits (UV)

Unscheduled Visits are those visits that occur between regularly scheduled visits at investigator discretion to manage an already documented AE, assess a potential AE, abnormal/alarming laboratory values, and/or clinical findings. Unscheduled Visits may be conducted remotely with assistance from the home health nurse (HHN). Only focused assessments (guided by the reason for the visit) will occur at these visits. In such cases, the participant's caregiver will be contacted to arrange an UV.

10.1.5. Early Termination (ET) Visits

ET Visits are performed for any early termination/withdrawal of a participant from this clinical trial. This does not apply to participants who have discontinued study drug but consented to continue trial visits. The structure and assessments of the ET Visit should as much as possible be similar to Visit 7 if performed during the Randomized Period and Visit 16 if performed during the Open-Label Extension Period. Radiographic assessments may not be required, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to the ET Visit.

11. ASSESSMENTS

11.1. VITAL SIGN MEASUREMENTS

Participants should rest for at least 5 minutes before vital sign measurement and vital signs should be taken prior to any blood draws. The following vital signs should be measured:

- Heart Rate (measured in beats per minute)
- Blood Pressure (seated BP will be taken measured in mm Hg)
- Temperature [measured in degrees Celsius (°C) or Fahrenheit (°F)]

All vital signs above must be measured at all visits. Orthostatic HR and systolic/diastolic BP will also be measured at Visit 1 prior to administration of study drug when the participant is at rest for 5 minutes (preferably supine) and again after standing at 3 minutes for assessment of orthostatic hypotension. Orthostatic hypotension is defined as decrease in SBP of ≥ 20 mmHg (Stewart 2018). Accompanying tachycardia is defined as change of heart rate increment of ≥40 bpm and absolute orthostatic HR ≥130 bpm (for ages 13 years and younger) (Singer 2012). Additionally, at Visit 1 and Visit 7 (in the Open-Label Extension Period), 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 (at Visit 1 in the Randomized Period and Visit 7 in the Open-Label Extension Period), orthostatic systolic/diastolic BP and HR will be measured prior to each PK blood collection.

11.2. ELECTROCARDIOGRAM (ECG)

An ECG must be collected at Screening and Visits 1, 2, 3, 5, and 7/ET in the Randomized Period, and at Visits 8, 10, 12, 14, and 16/ET in the Open-Label Extension. In addition, ECGs will be collected at Visits 9 and 11 if the dose is escalated at the visit. This schedule allows any child who switches from placebo to study drug to have ECGs performed in the same schedule as those who began study drug treatment in the Randomized Period. At Visit 1 on the Randomized Period and Visit 7 in the Open-Label Extension Period, ECG will be collected only at approximately 48 hours after the first dose for participants that undergo blood collection for PK analysis at that time. Standard 12-lead ECG will be recorded when the participant is in a resting state, prior to blood collection if scheduled at the same time. ECGs will be read centrally. If adequate tracing is unable to be collected at the site, external ECGs may be allowed for safety monitoring.

11.3. PHYSICAL EXAMINATIONS

Full physical examination must be performed at the Screening Visit, Visit 5 (Week 26), Visit 7 (Week 52)/ET, and in the Open-Label Extension Period Visit 10 (Week 78), Visit 12 (Week 104), Visit 14 (week 130), and Visit 16/ET (week 156) and includes assessment of all major body systems including general appearance, HEENT, Neck (including thyroid), Lung/pulmonary, Chest, CV, Abdomen, Back, GU, Neurological, Extremities, and Skin.

At the Screening Visit, Visit 5, and at Visit 7/ET in the Randomized Period and at all visits in the Open-Label Extension Period, physical examination must also include an assessment of pubertal status. Boys will be assessed for testis volumes, and girls for breast development according to Tanner stages (Tanner 1976). Pubic hair rating will also be recorded according to Tanner stages but will not be used to assess eligibility. At randomization, 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 (Emmanuel 2019). Tanner stage progression during the course of the trial will not impact study treatment. See Appendix 3 for details. In the Open-Label Extension Period, assessment for child-bearing potential will also be performed, if applicable (see Appendix 6).

At all other on-site visits, limited physical examination should be performed. Limited, symptom-directed physical examination should include assessment of all major body systems (as listed above) at the investigator's discretion.

Physical examination should include a visual inspection of the injection sites at every visit. At Visit 1 in the Randomized Period and Visit 7 in the Open-Label Extension Period, visual inspection of the injection site must be performed prior to injection of study drug 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. Clinically significant findings should be assessed for whether they qualify as AEs as defined in Section 12 Adverse Event Assessment and Reporting.

Additionally, thorough skeletal physical exam will be performed at all visits in both the Randomized Period and the Open-Label Extension Period 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. Such findings should be assessed for whether they qualify as AEs as defined in Section 12 Adverse Event Assessment and Reporting.

11.4. QUALITATIVE ASSESSMENT OF SLEEP AND SNORING PATTERN

Qualitative assessment of sleep and snoring pattern is required at all visits in both the Randomized Period and the Open-Label Extension Period, and a sleep study considered if any changes are noted. Assessment should include questions about neck hyperextension during sleep, loud and irregular snoring, glottal stops, observed sleep apnea, deep compensatory sighs, self-arousals, secondary enuresis, night-time emesis, morning headaches, daytime somnolence, or changes in school performance or behavior (Pauli 2019). Such findings should be assessed for whether they qualify as AEs as defined in Section 12 Adverse Event Assessment and Reporting.

11.5. ANTHROPOMETRIC MEASUREMENTS

Anthropometric measurements, including weight, should be taken following the procedures described in the Anthropometric Parameter Manual. All individuals involved in anthropometry measurements must have a documented record of understanding of the manual prior to taking measurements for the trial. Refer to the anthropometric measurement manual for detailed instructions.

11.6. PRO/OBSRO VALIDATION BATTERY

Three child/parent experience measures are currently being developed and are collectively referred to as the Achondroplasia Experience Measures (AEMs). They consist of:

The Validation Battery consists of the AEMs and other questionnaires needed for the psychometric testing. The Validation Battery must be completed at the Screening Visit and Visit 7/ET in the Randomized Period, and at Visits 12 and 16/ET in the Open-Label Extension Period. Completion of the Validation Battery is expected to take approximately 30-45 minutes. If the PRO/ObsRO validation battery cannot be completed during the Screening Visit due to the visit being conducted remotely, the battery should be completed separately at approximately 14 days prior to Visit 1, up to 7 days prior to Visit 1. If for any reason the PRO/ObsRO validation battery for the Screening Visit was not completed prior to Visit 1, the same battery should be completed during Visit 1 prior to study drug administration in lieu of the subset scheduled for Visit 1. A subset of the Validation Battery must also be completed at Visits 1, 3, 4, 5, and 6 in the Randomized Period, and at Visits 10 and 14 in the Open-Label Extension Period.

The measures in the validation battery are Generic Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy SF Upper Extremity, Global Health and SF Depressive Symptoms, Satisfaction with Life Scale – Child (SWLS-C), Pediatric Quality of Life Inventory (PedsQL), CCI , Growth Hormone Deficiency-Child Impact Measure (GHD-CIM), DISABKIDS Chronic Generic Module (DCGM-37), Sheehan Disability Scale, CCI , Parent Experience of Child Illness (PECI), Activity Impairment Assessment (AIA), Perceived Stress Scale (PSS), CCI and Endicott Work Productivity Scale (EWPS), Euroqol 5-Dimensional Questionnaire Youth Proxy version 1 (EQ-5D-Y Proxy1), and a resource utilization questionnaire.

NOTE: 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. The PRO/ObsRO **validation batteries** should be completed at the visit if possible. If the same caregiver is unable to attend a particular visit, an alternate caregiver may complete the PRO/ObsRO **validation batteries** at the visit. All PRO/ObsROs should be done when scheduled even if the same meaures where not completed at Screening Visit and/or Visit 1.

Refer to the PRO/ObsRO Validation Battery and instructions for further details.

In countries where these PRO/ObsRO batteries are available, all participants will be expected to complete the PRO/ObsRO **validation batteries**. For Cohort 1, completion of the PRO/ObsRO **validation batteries** is expected for participants from sites in US.

11.7. CCI

CCI

11.8. RADIOGRAPHIC ASSESSMENT OF BONE

The type and frequency of radiographic assessments has been carefully chosen to minimize exposure to radiation for the trial participants as shown below. Total exposure during the trial is expected to be approximately 7.4 mSv/participant.

Randomized Period:

- AP standing lower extremity X-ray 3 times over 12 months – 0.18 mSv
- AP and lateral lumbar spine X-ray 3 times over 12 months – 3.0 mSv
- Bone age of left hand and wrist 2 times over 12 months – 0.002 mSv
- DXA 2 times over 12 months – 0.002 mSv

Open-Label Extension Period:

- AP standing lower extremity X-ray 4 times over 24 months – 0.24 mSv
- AP and lateral lumbar spine X-ray 4 times over 24 months – 4.0 mSv
- Bone age of left hand and wrist 2 times over 24 months – 0.002 mSv
- DXA 2 times over 24 months – 0.002 mSv

Radiographic assessments may not be required at Visit 1 with Medical Monitor approval, if the assessments were conducted within approximately 3 months prior to Visit 1. 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.

On Visit 4 in the Randomized Period and Visits 9, 12 and 13 in the Open-Label Extension Period, 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. They may also be conducted remotely (e.g. at a community imaging center).

Radiographic assessments at Visit 7/ET and 16/ET may be conducted remotely (e.g. at a community imaging center). Alternatively, radiologic assessments may be deferred until the participant is able to travel to the site. Radiographic assessments may not be required at Visit 7/ET and 16/ET, with Medical Monitor approval, if the same assessments were conducted within approximately 3 months prior to Visit 7 or Visit 16/ET, respectively.

Refer to the radiographic assessment manual for details of the procedures for the radiographic assessment of bone.

11.8.1. Hand and Wrist X-ray

Hand and wrist X-ray imaging will be conducted at Visit 1, Visit 7/ET, and in Visits 12 and 16/ET (in the Open-Label Extension Period). The assessment will be in the left hand and wrist for all participants unless a medical reason prohibits, in which case the right hand and wrist may be used. Images will be used to assess bone age and bone growth.

11.8.2. Anterior-posterior (AP) Standing Lower Extremity X-ray

Standing X-ray films of lower extremity along the AP axis will be collected at Visit 1, 4 and 7/ET in the Randomized Period, and Visit 9, 12, 13, 16/ET in the Open-Label Extension Period. Standing lower extremity X-ray will be used to monitor changes in varus deformities, bone growth and possible adverse changes in growth plates.

11.8.3. Dual-energy X-ray Absorptiometry (DXA)

DXA will be performed at Visit 1, and Visit 7/ET in the Randomized Period and Visits 12 and 16/ET (in the Open-Label Extension Period). The assessment will be done only for participants aged 5 years and older. DXA will be used to assess any changes in bone mineral density (BMD).

11.8.4. Anterior-posterior and Lateral Spine X-ray

X-ray of the spine, along the AP and lateral axes, will be taken at Visit 1, 4, and 7/ET in the Randomized Period and at Visits 9, 12, 13, 16/ET in the Open-Label Extension Period. Spine X-ray will be used to monitor any changes in kyphosis, lordosis, scoliosis, and morphology of vertebral bodies.

11.9. WEEKLY DIARY

Participants/caregivers are trained on the weekly diary during Visit 1 and instructed to return the diary at every visit for site staff review as part of concomitant medication review, adverse event review and study drug compliance. Diary must be completed from Visit 1 until completion of Visit 7/ET Visit in the Randomized Period, and from Visit 7 in the Open-Label Extension Period until completion of Visit 16/ET.

Participants/caregivers will be required to complete a weekly diary to capture the following:

- Study drug, starting at Visit 1 (dose, administration date and time, and injection location)
- Changes to concomitant medications
- Changes to the participant's health or well-being, including any procedures, ER visits, and hospitalizations.

11.10. ADVERSE EVENT REVIEW

At each visit, the participant and/or caregiver should be asked about the following to assess for any potential AEs:

- General well-being
- Any changes to health or medications since the previous visit; specifically, any ear infections or sleep apnea or neurological symptoms suggestive of cord compression
- Symptoms of hypotension such as dizziness, headache, lightheadedness, blurry vision, and loss of consciousness since the previous visit
- Emergency/urgent care visits or hospitalizations since the previous visit

At each visit, site staff will review diary with the participant and the caregiver, and any data related to changes in health or medications should be further assessed for potential AEs.

Additionally, changes from baseline noted during a physical examination should be assessed for potential AEs.

Additional assessments, including a physical examination or additional laboratory assessment, may be performed at the discretion of the investigator even if not required at the specific study visit or if an UV must be scheduled.

See Section 12 for details on reporting AEs.

11.11. LABORATORY ASSESSMENTS

Safety labs and immunogenicity samples are important for safety assessment in this trial. Samples for immunogenicity (antibody measurements) are stored for up to 8 years after the end of the trial in order to make additional antibody tests and characterizations possible at the request of health authorities. All other samples will be destroyed no later than the end of the trial.

The objective of the PK assessments is to understand the relation between exposure and biologic activity. Pediatric blood volume limit guidelines were utilized to minimize blood collection volumes and assay technologies were chosen that are capable of sensitively detecting analytes using the lowest possible volume of blood for analysis.

The TCC-201 trial has been designed to minimize deviations from the normally conducted procedures for the diagnosis and treatment of ACH. To reduce stress and pain and at the same time ensure safety of the children that participate in TCC-201, sparse sampling of PK blood collection is employed and the volume of blood to be drawn at each trial visit will be restricted based on the weight of the child at each visit following the recommendations published by the European Commission titled “Ethical considerations for clinical trials on medicinal products conducted with minors”, dated 18 September 2017. See Appendix 4 for details.

The following laboratory assessments are performed. See Appendix 1 and Appendix 2 for the Schedule of Events.

1. **Genetic confirmation of ACH**

If unavailable from medical records, a blood sample will be collected and used to identify the FGFR3 mutation for ACH. The test may be performed at any time after signing the consent and before Visit 1. The central lab will test for the G380R substitution in FGFR3 (i.e. G to A transition or G to C transversion at nucleotide 1138 of *FGFR3* gene), but further testing may be pursued on an individual basis as indicated. Other mutations may be used as genetic confirmation of ACH, pending review of Medical Monitor.

2. **Chemistry**

   a. Sodium
   b. Potassium
   c. Chloride
   d. Bicarbonate
   e. Magnesium
   f. Phosphate
   g. Calcium
   h. Glucose
   i. Alkaline Phosphatase

j. Aspartate Aminotransferase (AST)
k. Alanine Aminotransferase (ALT)
l. Creatinine
m. Creatine Phosphokinase
a. Albumin
b. Direct Bilirubin
c. Total Bilirubin
d. BUN
e. Gamma Glutamyl Transferase
f. Lactate Dehydrogenase
g. Total Protein
h. Uric Acid

3. **Thyroid stimulating hormone (TSH)**
4. **Hemoglobin A1c (HbA1c)**
5. **Hematology**
   a. Hemoglobin
   b. Hematocrit
   c. RBC Count
   d. WBC Count
   e. Differential Cell Count
   f. Platelet Count
6. **Lipid panel**
   a. Total cholesterol
   b. LDL
   c. HDL
   d. Triglycerides
7. **25(OH) Vitamin D**
8. **Urinalysis Panel**
9. **Urine Chemistry**
   a. Urine Calcium
   b. Urine Creatinine
   c. Urine Phosphate
10. **PK Assessments**
    a. Free CNP
    b. Total CNP
    c. mPEG and mPEG-linker
11. **Biomarkers (blood)**
    a. Exploratory biomarkers of pharmacodynamic response to treatment with TransCon CNP, [redacted]

12. **Immunogenicity Assessments**

    a. Anti-drug antibodies

11.12. TREATMENT PERIOD ADMINISTRATION

The first dose of study drug will be administered by the caregiver in the clinic, and the participant will be observed for at least 2 hours for assessment of adverse reactions. Caregiver will administer all subsequent weekly doses of study drug for 52 weeks during the Randomized Period plus 104 weeks during the Open-Label Extension Period. The last dose of randomized study drug will be administered at least 6 days prior to Visit 7 (Week 52). At each visit, injection sites should be examined, and injection site rotation should be reinforced.

12. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING

12.1. ADVERSE EVENTS

12.1.1. Definition

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the participant that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with achondroplasia that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events Definition

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e. the AE cause or leads to death).
- It is life threatening (i.e. the AE, in the view of the investigator, places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form or was allowed to continue, might have caused death).
- It requires or prolongs inpatient hospitalization (see Section 12.3.3).
- It results in persistent or significant disability/incapacity (i.e. the AE results in substantial disruption of the participant's ability to conduct normal life functions).

- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug.
- It is considered a significant medical event by the investigator based on medical judgment (e.g. may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g. rated as mild, moderate, or severe according to Table 1; see Section 12.2.2.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e. no more than 24 hours after learning of the event; see Section 12.4.2 for reporting instructions).

Special Situation Definition

Special situations are non-standard medical conditions that provide valuable information (e.g. clinical, safety) about a medicinal product, even when they do not occur in association with an adverse event or medical condition. Examples of special situations include and should all be captured in the eCRF:

- Pregnancy
- Breastfeeding
- Overdose
- Drug abuse
- Misuse
- Off label use
- Occupational exposure
- Lack of therapeutic efficacy
- Medication error

The Medical Monitor will review all safety information on an ongoing basis. The key safety data will also be reviewed periodically by Data Monitoring Committee (DMC) in accordance with its governing charter).

12.2. METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to Ascendis Pharma, in accordance with FDA CFR 312.32 (IND Safety Reports) and ICH E6.

12.2.1. Adverse Event Reporting Period

The Adverse Event Reporting Period is the period requiring reporting of AEs and SAEs for any patients exposed to the study drug and/or study related procedures. Reporting period begins from the time informed consent is obtained and ends at the last study visit. After this period, investigators should only report SAEs that are attributed to prior study treatment.

12.2.2. Severity, Causality, and Outcome Assessment

12.2.2.1. Severity Rating

Assessment of Severity of Adverse Events

The World Health Organization (WHO) toxicity grading scale will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 1: Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 12.1.1).

12.2.2.2. Causality Rating

All AEs and SAEs whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means must be reported appropriately.

Each reported AE or SAE must be described by its duration (i.e. start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken. To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Related (Yes) – There is a plausible temporal relationship between the onset of the AE and administration of the study drug. The AE cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies. The AE follows a known pattern of response to the study drug or with similar treatments. And/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.

Not Related (No) – Evidence exists that the AE has an etiology other than the study drug (e.g. preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication). The AE has no plausible temporal relationship to study drug administration (e.g. cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the current Investigator Brochure (IB). There are no events that are considered to be expected for assessment of Serious Adverse Reactions based on the reference safety information in the current version of the IB. Unexpected adverse events are those not listed in the current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or IB (For example, under this definition, hepatic necrosis would be unexpected if the P.I. or IB only referred to elevated hepatic enzymes or hepatitis). In the case of TransCon CNP, all events are considered to be unexpected.

12.2.2.3. Outcome Assessment

Participants will be followed until AEs have either resolved, participants have returned to their baseline status, or participants are deemed stable or commensurate with ongoing disease processes. One of five outcomes listed below must be recorded:

Recovered/Resolved – The event has stopped. The stop date of the event must be recorded.

Recovering/Resolving – The participant is clearly recovering from an event. The event is not yet completely resolved.

Not Recovered/Not Resolved – The event is still ongoing. (Could include stable and commensurate with ongoing disease processes).

Recovered/Resolved with Sequelae – The event has reached a state where no further changes are expected, and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.

The stop date of the event must be recorded. In case of SAE, the sequelae should be specified.

Fatal – The participant has died as a consequence of the event. Date of death is recorded as stop date for the AE.

Unknown – Unknown to investigator, e.g. participant lost to follow up.

12.3. PROCEDURES FOR ELICITING, RECORDING AND REPORTING ADVERSE EVENTS

12.3.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all participant evaluation time points should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

12.3.2. Recording Procedures for All Adverse Events

All AEs will be documented in response to question about the participant's well-being and whether any possible changes in well-being have occurred since the previous visit. Additionally, at each visit, site staff will review participant diary data with the participant/caregiver, to determine if diary entries reflect any AEs.

AEs, including SAEs, will be documented through to the end of the participation in the trial. All AEs must be recorded on the appropriate eCRF. AEs either observed by the investigator or reported by the participant must be recorded regardless of causality. For any participant who withdraws from treatment, correspondence with the participant's caregiver (e.g. phone call, email) will be conducted at least 5 weeks after final dose to evaluate for AEs. The following attributes must be documented for each reported AE:

- Subject ID
- Description
- Onset date (if AE was present on Day 1, include whether onset was prior to or after the first dose of the study drug)
- Resolution date, if applicable
- Severity
- Causality (relationship to the study drug)
- Outcome
- Action taken
- Determination of "seriousness criteria" (whether serious or not serious)

Any pre-existing condition, medical history, signs, symptoms, and illnesses present at the Screening visit will be captured as baseline (preexisting) events, if appropriate, to assure that any change(s) in these experiences during the trial also are recorded as an AE and a complete safety profile is obtained. An event that occurs after signing of ICF but prior to the first study drug administration will be reported as a non–treatment-emergent AE. Any new or worsening pre-existing medical conditions that occurs from the time of the first study drug administration until the last study visit will be recorded as an AE.

Routine titration of chronic, concomitant medications will not be considered to meet the criteria for AEs.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviation (e.g. hypertension for elevated BP that persists and requires chronic treatment and follow-up, or increased blood pressure for elevated blood pressure that occurs for a limited time and does not persist or require ongoing treatment).

An accidental overdose is not an AE if there are no signs or symptoms. Any undesirable medical occurrence resulting from an accidental overdose is an AE and should be recorded and reported on the appropriate eCRF. Regardless of classification as an AE or not, all overdoses should be documented, and the participant(s) monitored. Since accidental overdoses with the study drug

could have serious clinical consequences and/or represent a compliance issue, they should be reported to the Medical Monitor immediately and evaluated by the Sponsor.

12.3.3. Specific Instructions for Recording Adverse Events

Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g. dosage modification or titration, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g. potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g. significant increase of alkaline phosphatase and bilirubin associated with cholestasis), only the diagnosis (i.e. cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g. "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g. high blood pressure), only the diagnosis (i.e. hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available as separate AEs. If a diagnosis is subsequently established, it should be reported as follow-up information.

Injection Related Reaction

Each sign or symptoms will be recorded as a separate adverse event on the adverse event eCRF.

Adverse events that occur during or within 24 hours after study drug administration, should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g. record hypertension and dyspnea as separate events rather than a diagnosis of infusion related reaction or anaphylactic reaction).

Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a participant is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g. "more frequent headaches").

Pregnancy

If a female participant becomes pregnant while receiving the study drug or within 5 weeks after the last dose of study drug, or if the female partner of a male study participant becomes pregnant while the study participant is receiving the study drug or within 5 weeks, a Pregnancy report should be completed and expeditiously submitted to Ascendis Pharma within 24 hours. Follow-up to obtain the outcome of the pregnancy should also occur and the outcome reported to Ascendis Pharma. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female participant exposed to the study drug should be expeditiously reported as an SAE. Additional information regarding pregnancy can be found in Appendix 6.

Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

12.4. SERIOUS ADVERSE EVENTS (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

12.4.1. Non-Serious Adverse Events Leading to Discontinuation

If situation permits, non-serious events (including laboratory abnormalities and pregnancies) that may require permanent discontinuation of study drug should be discussed with the Medical Monitor prior to making any final decision.

12.4.2. Reporting

All initial and follow-up information regarding SAEs and Special Situations reporting must be reported by the investigator to the Sponsor or its representatives within 24 hours of discovery, including those related to protocol-mandated procedures and regardless of suspected causality.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 12.1.1 for seriousness criteria), severity (see Section 12.2.2.1), and causality (see Section 12.2.2.2).

Reporting must not be delayed by waiting for additional information. The minimum information required for reporting an SAE and Special Situations are the AE term (diagnosis), patient, study drug, reporter, and the investigator's initial causality assessment. Additional information must be reported to the Sponsor or its representatives as a follow-up report. All SAEs and Pregnancies (including follow-up information) must be submitted via:

safety.ascendispharma.com

SAEs and Special Situations information is collected and reported via SAE Forms provided by the Sponsor or its representative. Pregnancy information is collected and reported via Pregnancy Forms provided by the Sponsor or its representative. The Sponsor (or its representatives) is responsible for reporting within the time frame required by applicable regulations all SAEs qualifying as SUSARs to:

- Investigators
- Central IRBs/HRECs/IECs (if applicable)
- National ethics committees (if applicable)
- Appropriate regulatory authorities

It is the investigators' responsibility to comply with the requirements of their local IRB/HREC/IEC for reporting SUSARs, other SAEs, and any new and/or relevant safety information provided by the Sponsor or its representatives. At minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

13. SAFETY MONITORING

The Sponsor will conduct an ongoing review of all trial data, with particular attention given to laboratory findings, AEs, and concomitant medications. Any important safety trends or other findings considered related to the study drug will be reported to the investigators and to regulatory authorities. In particular, the Sponsor will notify investigators and regulatory authorities of AEs that:

- Fulfill the criteria for SUSARs.
- Occur at a meaningfully greater frequency than described in the current Investigator's Brochure or Reference Safety Information.

Any AE that occurs during the clinical trial must be monitored and followed up until:

- It has resolved or receded
- Pathology laboratory findings have returned to normal
- Steady-state has been achieved
- It has been shown to be unrelated to the study drug and/or trial related procedure

Details will be described in the Safety Management Plan.

14. STATISTICS

14.1. GENERAL

Details of applicable statistical methods will be provided in a statistical analysis plan (SAP) which will be finalized before database lock. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record.

In general, analyses will be done by dose cohort, and placebo participants will be pooled as placebo group. Data from clinical assessments will be summarized using descriptive statistics. Categorical data will be presented using counts and percentages of participants. Continuous variables will be presented using number of participants, mean, standard deviation (SD), standard error (SE), median, minimum and maximum. Statistical significance is defined as $P < 0.05$ (2-sided).

14.2. ENDPOINTS

14.2.1. Safety Endpoints

The following safety endpoints will be assessed for both blinded 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
  - AP standing lower extremity X-ray
  - AP and lateral spine X-ray
- Incidence of antibodies against drug

14.2.2. Efficacy Endpoints

Primary Endpoint:

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

Secondary Endpoints:

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

Exploratory Endpoints:

14.2.3. Pharmacokinetic Endpoints

- Plasma concentration of Total CNP
- Plasma concentration of Free CNP
- Plasma concentration of mPEG and mPEG-linker

14.3. STATISTICAL ANALYSIS

The Full Analysis Set will include all randomized participants 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. Participants will be analyzed according to study treatment as randomized. The Safety Analysis Set will include all randomized participants who have received at least one dose of investigational product. Participants will be analyzed according to study treatment as treated. The efficacy analyses will be based on the Full Analysis Set and safety analyses will be based on the Safety Analysis Set.

In general, analysis will be done by dose levels, and placebo participants will be pooled. Data from clinical assessments will be summarized using descriptive statistics. Categorical data will be presented using counts and percentages of participants. Continuous variables will be presented using number of participants, mean, standard deviation (SD), standard error (SE), median, minimum and maximum.

For the primary efficacy endpoint, AHV at Week 52, the primary analysis is ANCOVA model with the AHV at Week 52 as the response variable, treatment (dose groups and placebo) as factors, baseline age, sex, and baseline height SDS as covariates. The similar ANCOVA model, with the baseline of the corresponding parameter as a covariate, will be applied to secondary and exploratory efficacy endpoints. As a sensitivity analysis for the primary efficacy endpoint, AHV at Week 52, 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.

Once the highest tolerated dose is established, the following sequential testing procedure 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.

Reporting of the safety data is descriptive and will mainly include the incidence and type of adverse events, laboratory changes, vital signs, radiographic findings, 12-lead ECG parameters and incidence of anti-drug antibodies. Abnormal laboratory data and abnormal physical examinations will be listed as appropriate.

Refer to SAP for details.

All participants who will receive the study drug and for whom the primary PK data are considered sufficient and interpretable will be included in the PK analysis. The PK parameters and their statistical evaluation will be included in the Clinical Study Report or as an appendix. Potential impact of any anti-drug antibodies detected will be included in the evaluation.

Refer to PK Analysis Plan for details.

14.4. 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.

14.5. 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.

14.6. SIGNIFICANCE

Statistical significance is defined as $P < 0.05$ (2-sided).

15. TRIAL CONDUCT

15.1. SITE INITIATION

Prior to participation, investigational sites and investigators will be evaluated for appropriate qualifications and ability to execute the trial. Each investigational site must undergo appropriate training on the trial protocol and ancillary trial procedures and documents through participation in a Site Initiation Visit (SIV) or Investigator Meeting (IM). Protocol and GCP training must take place before any participants are enrolled at a site. SIVs and IMs will include, but may not be limited to, study drug preparation and administration procedures, data collection requirements, and participant eligibility requirements.

15.2. DATA HANDLING AND RECORD KEEPING

15.2.1. Collection of Data

Data will be collected in the eCRF. The eCRF is an integral part of the trial and subsequent reports. It must be used to capture trial-specific data collected and must be kept current to reflect participant status during the course of the trial. Only a Participant Identification Number will be used to identify the participant. The investigator must keep a separate Participant Identification Code List with participant names and medical record numbers or other personal identifier(s).

The trial will use an Internet-based remote data entry system to collect clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 (R2) GCP. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The system is configured based on the requirements from the Sponsor. Source documents are to be retained to enable a reconstruction and evaluation of the trial. Source documents include the site files and trial worksheets provided by the Sponsor. Data will be recorded in the trial worksheets as appropriate to complete and/or clarify the source data.

The design of the computerized system complies with all the applicable regulatory requirements for record keeping and record retention in clinical trials [21 CFR Part 11 and ICH E6 (R2) GCP]. Clinical investigators must retain either the original or a certified copy of all source documents, including query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly provides a means to locate and read the prior information. All changes to

the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

15.2.2. Coding Dictionaries

Prior and concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). See Data Management Plan for details.

15.2.3. Data Handling

eCRFs should be completed in a timely manner to enable the Sponsor or designee to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock, the investigator will use her/his log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or sponsor, who routinely review the data for completeness, correctness, and consistency. The site is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and by providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Sponsor will provide the site with a certified copy of the electronic CRFs submitted by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 15.2.1.

15.2.4. Direct Access to Source Data/Documents

The investigator/trial site is to provide direct access to source data/documents for trial-related monitoring, audits, IRB/EC review, and regulatory inspection. This includes access to Electronic Medical Record system and any other electronic systems containing source data or trial-related documents.

15.2.5. Record Keeping

The investigator is responsible for maintaining adequate records to fully document the conduct of the trial consistent with that noted in ICH E6 (R2), including but not limited to the following:

1. All versions of the Investigator's Brochure
2. Signed Protocol and Amendments in effect during the conduct of the trial
3. Signed ICFs
4. Source documents, including adequate case histories, questionnaires, and participant diaries
5. Signed, dated, and completed eCRFs and documentation of data corrections
6. Notification of SAEs and related reports
7. Dated and documented IRB/EC approvals and approval by regulatory authorities, as required

8. Normal laboratory reference ranges
9. Laboratory certifications
10. Curricula Vitae of all clinical investigators
11. Completed Forms FDA 1572, as applicable
12. SIV documentation
13. Delegation of Authority Log
14. Participant Screening & Enrollment Log(s)
15. Participant Identification Code List
16. Study drug accountability documentation
17. Signed agreements between involved parties
18. Relevant communication, including that related to monitor site visits (e.g. letters, meeting notes, notes from telephone calls)
19. Interim, annual, or final reports to IRBs/ECs and regulatory authorities, as required
20. Audit certificate(s), if applicable

15.3. DATA QUALITY CONTROL

15.3.1. Monitoring Procedures

The Sponsor and/or its representative may make periodic visits to the investigational site to assess compliance with trial procedures and regulatory requirements; to ensure that the safety, welfare, and privacy of participants are being protected; and to verify the accuracy and integrity of the trial data. In addition, independent Quality Assurance site audits may be conducted as verification of the quality and compliance of trial conduct.

The Sponsor and/or its representative will periodically review the trial data to ensure that data are being appropriately collected and reported. Queries and corrections will be made as needed.

15.3.2. Data Management

Sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and CRO's standard operating procedures (SOPs). A comprehensive data management plan will be developed including a data management overview, database development, validation and maintenance, data entry and processing, external data transfer, data validation and archive, and medical coding processes. Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

15.4. AUDITING PROCEDURES

In addition to the routine monitoring , a GCP Quality Assurance audit may be initiated by the Sponsor. The investigator must ensure that participants/caregivers are aware of and consent to personal information being reviewed during the data verification process as a part of monitoring/auditing/inspection by the Sponsor, properly authorized agents of the Sponsor, or competent authorities. In addition, participation and personal information is treated as strictly confidential to the extent that applicable law permits and to which it is not publicly available. The purpose of audits and inspections is to evaluate compliance with the principles of GCP, international and local regulatory requirements, and the trial protocol. The audit or inspection may include, for example, a review of all source documents, drug records, original clinic medical notes, and some or all of the facilities used in the trial.

The audits may be conducted by the Sponsor or Sponsor's selected agent in accordance with Sponsor's SOP or SOPs of the selected and properly authorized agent. A competent authority may also wish to conduct an inspection during the trial or after its completion. If an inspection is requested by a competent authority, the investigator must inform the Sponsor immediately that this request has been made. The investigator and his/her institution will permit all monitoring, audits, and regulatory inspections, providing direct access to source data.

15.5. LABORATORY QUALITY STANDARDS

Laboratory tests or evaluations for safety described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the central laboratories. Some blood samples may be used for laboratory test validation.

The safety laboratories must provide a list of reference ranges for applicable analyses. The methods employed for each assay should be available on request. Any change in the laboratory procedures, reference values, etc., during the trial must promptly be communicated to the Sponsor. The laboratories may also be audited by the Sponsor or by competent authorities.

15.6. TRIAL TERMINATION OR COMPLETION

The investigator should notify the IRB/EC in writing of the completion or early termination of the trial. Completion of the trial is defined as the completion of the last participant's last visit. Upon trial completion or termination, applicable regulatory reporting requirements will be followed. The Sponsor reserves the right to terminate the trial at any time for any reason. The Sponsor may stop this trial at a particular site for any of the following reasons:

- The site cannot enroll an adequate number of participants
- Serious and/or persistent non-compliance with the protocol or clinical trial conduct
- Careless or premeditated false documentation in the electronic case report form (eCRF)
- Inadequate cooperation with the investigator
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation

15.7. CHANGES TO THE PROTOCOL

Changes in any portion of this protocol must be documented in the form of an amendment from the Sponsor and must be approved by the investigational site's IRB/EC and regulatory authorities, as required, before the amendment is implemented. However, in the event of apparent immediate hazard to a participant, a deviation from the protocol is allowed to eliminate the hazard. In this case, the deviation and the reason for it must be promptly reported as required by regional regulations to the applicable IRB/EC and regulatory authorities, along with a proposed protocol amendment if appropriate.

Protocol amendments may only be made with prior written approval of the Sponsor and/or its representative and documented approval or favorable opinion from applicable regulatory authorities or regional IRB/EC, as required. The investigator must send a copy of the documented approval to the Sponsor and/or its representative.

15.8. OTHER CHANGES IN TRIAL CONDUCT

Changes in trial conduct are not permitted. Any unforeseen changes in trial conduct will be recorded in the clinical study report.

15.9. USE OF INFORMATION AND PUBLICATION

The data and information generated in this trial are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required prior to disclosing any information related to this trial. Publication of the results will be based on appropriate analyses and review of the complete data. Authorship will be determined based on ICMJE criteria. Publication of any data of this trial without prior Sponsor approval is not permitted.

16. ETHICAL AND LEGAL CONSIDERATIONS

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- GCPs as outlined in ICH E6 (R2) and regional regulations
- Regional participant data protection laws and regulations
- Other applicable regional and local regulations
- US Federal Regulations, as applicable

16.1. DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will attend each DMC meeting to provide recommendations on: (A) the action to be taken (i.e. proceed to the next dose level as planned, modify the dose of the next cohort, or stop dose escalation); and (B) the escalation of dose for cohorts in the extension based on review of unblinded data. The DMC may request to invite guests (on an as-needed basis) to DMC meetings for their expertise or may request advice from an ad hoc expert related to a specific safety concern. A guest/expert may be a specialist in a field where expertise is required. Refer to the DMC Charter for further details.

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

16.2. INFORMED CONSENT

The draft ICF must be reviewed by the Sponsor and/or its representative prior to submission to a regional IRB/EC for approval. A copy of the ICF approved by the review board must be forwarded to the Sponsor and/or its representative.

The ICF (and Participant Information Sheet, if applicable) documents the trial-specific information the investigator provides to the participant and the participant's agreement to participate. The investigator or designee will fully explain in layman's terms the nature of the trial along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The ICF and Participant Information Sheet must be appropriately signed and dated before the participant undergoes any trial-related procedure. The original and any amended signed and dated ICFs and participant information sheets must be retained at the trial site with a copy of each provided to the participant.

16.2.1. Subject Identification Card

Participants will be provided with a Subject Identification Card containing the following information:

- Subject number
- Participation status: that he/she is participating in a clinical study.
- That the study includes a treatment regimen with TransCon CNP.
- The name and phone number of the Investigator.
- Name of main Sponsor / local Sponsor / CRO (note: as required by local regulations)

The participant will be instructed to carry the card at all times during the participation in the study and asked to return the Subject Information Card at the end-of-trial visit.

16.3. IRB/EC APPROVALS

The Principal Investigator at each site is responsible for obtaining approval from the appropriate regional IRB/EC for the final protocol, Sponsor-approved ICF and participant information sheet (if applicable), and any advertisements to recruit participants. Written approval of these documents must be obtained from the committee before any participant is enrolled at a trial site. The IRB/EC must comply with all applicable ICH E6 GCP requirements, as well as all regional and local requirements.

The Principal Investigator is also responsible for the following interactions with the regional IRB/EC:

1. Obtaining review board approval for any protocol amendments and ICF revisions before implementing the changes
2. Providing the review board with any required information before or during the trial

3. Submitting progress reports to the review board as required during the conduct of the trial, requesting continuing review and approval of the trial as needed and providing copies of all review board re-approvals and relevant communication to the Sponsor and/or its representative
4. Notifying the review board of all serious and unexpected AEs related to the study drug reported by the Sponsor and/or its representative, as required
5. Notifying the review board of the end of trial participation, in accordance with regional guidelines and regulations. End of trial is defined as last subject last visit.

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SIGNATURE OF AGREEMENT

In signing this protocol, the investigator agrees to:

1. Conduct the trial in accordance with the relevant, current protocol and make changes only after notifying the Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human participants
2. Comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice plus appropriate regional regulatory laws and requirements, including US Federal Regulations, as applicable
3. Personally conduct or supervise the described investigation
4. Inform any participants or persons used as controls that the study drugs are being used for investigational purposes
5. Ensure requirements relating to obtaining informed consent and regional ethical or institutional review board approval have been met
6. Report to the Sponsor or its representative any AEs that occur in the course of the investigations, as specified in Section 12
7. Read and understand the Investigator's Brochure, including potential risks and side effects of the study drug
8. Ensure all associates, colleagues, and employees assisting in the conduct of the trial are informed of their obligations in meeting their commitments
9. Maintain adequate and accurate records and make these available for inspection by the Sponsor and/or its representative or any regulatory agency authorized by law
10. Promptly report to the regional ethical or institutional review board all changes in research activity and all unanticipated problems involving risks to human participants or others
11. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements
12. Administer study drug only to participants who meet trial entry criteria and are enrolled in the trial and only according to the guidelines set forth in this protocol
13. Sign a Form 1572, as applicable

SIGNATURE OF AGREEMENT

I have read and understand the information in this clinical trial protocol, including the potential risks and side effects of the study drug, and agree to personally conduct or supervise the described investigation(s) in accordance with the relevant, current protocol(s) and will not deviate from the protocol, except when necessary to protect the safety, rights, or welfare of participants. I agree to inform all participants that the study drug is being used for experimental purposes, and I will ensure that the requirements related to obtaining informed consent are met. I agree to report to the Sponsor any adverse events that occur in the course of the investigation(s).

1. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments.
2. I will not make any changes in the research without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human participants.
3. I agree to maintain all information in this document and regarding the stud(ies) as confidential and to use it only for the purpose of conducting the stud(ies). I agree not to forward this document to any other party without the prior written authorization of the Sponsor.

Investigator:

Printed Name and Title: _____

Signature: _____

Date: _____

18. 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	
Hand and Wrist 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	

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**
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								

[a] 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 (Tanner 1976). 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 (Emmanuel 2019). Tanner stage progression during the course of the trial will not impact study treatment. See 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[q]**
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	
Hand and Wrist 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	
Urine collection	X		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[q]
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 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 (Tanner 1976). 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 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 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 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

[q] Only for participants not proceeding to the separate Long-Term Open-Label Extension Study (ASND0039).

APPENDIX 3. TANNER STAGING CRITERIA

(From Emmanuel 2019)

Below are the Tanner Stages described in detail for clinical reference. For all three sites of development, Tanner Stage 1 corresponds to the prepubertal form with progression to Tanner Stage 5, the final adult form. Breast and genital staging, as well as other physical markers of puberty such as height velocity, should be relied on more than pubic hair staging to assess pubertal development because of the independent maturation of adrenal axis.

Pubic Hair Scale (both males and females)

- Stage 1: No hair
- Stage 2: Downy hair
- Stage 3: Scant terminal hair
- Stage 4: Terminal hair that fills the entire triangle overlying the pubic region
- Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh

Female Breast Development Scale

- Stage 1: No glandular breast tissue palpable
- Stage 2: Breast bud palpable under areola (1st pubertal sign in females)
- Stage 3: Breast tissue palpable outside areola; no areolar development
- Stage 4: Areola elevated above contour of the breast, forming “double scoop” appearance
- Stage 5: Areolar mound recedes back into single breast contour with areolar hyperpigmentation, papillae development and nipple protrusion

Male External Genitalia Scale

- Stage 1: Testicular volume < 4 ml or long axis < 2.5 cm
- Stage 2: 4 ml-8 ml (or 2.5-3.3 cm long), 1st pubertal sign in males
- Stage 3: 9 ml-12 ml (or 3.4-4.0 cm long)
- Stage 4: 15-20 ml (or 4.1-4.5 cm long)
- Stage 5: > 20 ml (or > 4.5 cm long)

APPENDIX 4. BLOOD VOLUME DRAWN AT EACH VISIT

1. Blood Volume Drawn at Each Visit in the Randomized Period

	Blood Volume Drawn (ml)												
	Visit												
Weight (kg)	Screening (Week -4 to -1)	1 at Predose (W 0)	1 at 8h (W 0)	1 at 24h (W 0)	1 at 48h (W 0)	2 (W 4)	3 (W 8)	4 (W 12)	5 (W 26)	6 (W 39)	7 (W 52)	F-U Visit (W 57)[a]	Cumulative
6.0-9.9	5.5	5.0	0	0	0	5.0	6.0	5.0	5.5	5.0	5.0	2.0	**44**
10.0-10.9	9.5	9.0	0	0	0	9.0	6.0	9.0	9.5	9.0	9.0	2.0	**72**
11.0-13.9	9.5	9.0	2	2	3	10.0	6.0	10.0	10.5	10.0	10.0	2.0	**84**
14.0-15.9	12.5	9.0	2	2	3	13.0	6.0	13.0	13.5	13.0	13.0	2.0	**102**
16.0-16.9	12.5	10.0	2	2	3	13.0	6.0	13.0	13.5	13.0	13.0	2.0	**103**
17.0-17.9	12.5	10.0	2	3	3	13.0	6.0	13.0	13.5	13.0	13.0	2.0	**104**
18.0-20.9	12.5	10.0	3	3	3	13.0	6.0	13.0	13.5	13.0	13.0	2.0	**105**
≥21.0	12.5	13.0	3	3	3	13.0	6.0	13.0	13.5	13.0	13.0	2.0	**108**

[a] **Only for participants** who are not continuing in the Open-Label Extension Period

2. Blood Volume Drawn at Each Visit in the Open-Label Extension Period

Weight (kg)	7 at 8h (W 52)	7 at 24h (W 52)	7 at 48h (W 52)	8 (W 56)	9[a] (W 65)	10 (W 78)	11 (W 91)	12 (W 104)	13 (W 117)	14 (W 130)	15 (W 143)	16/ET (W 156)	F-U Visit OLE (W 161)	Cumulative
6.0-9.9	0	0	0	5.0	5.0 (3.0)	5.5	5.0 (3.0)	5.5	3.0	5.5	3.0	5.5	2.0	**45**
10.0-10.9	0	0	0	9.0	9.0	9.5	9.0	9.5	7.0	9.5	7.0	9.5	2.0	**81**
11.0-13.9	2	2	3	10.0	10.0 (9.0)	10.5	10.0 (9.0)	10.5	7.0	10.5	7.0	10.5	2.0	**95**
14.0-15.9	2	2	3	13.0	13.0	13.5	13.0	13.5	10.0	13.5	10.0	13.5	2.0	**122**
16.0-16.9	2	2	3	13.0	13.0	13.5	13.0	13.5	10.0	13.5	10.0	13.5	2.0	**122**
17.0-17.9	2	3	3	13.0	13.0	13.5	13.0	13.5	10.0	13.5	10.0	13.5	2.0	**123**
18.0-20.9	3	3	3	13.0	13.0	13.5	13.0	13.5	10.0	13.5	10.0	13.5	2.0	**124**
≥21.0	3	3	3	13.0	13.0	13.5	13.0	13.5	10.0	13.5	10.0	13.5	2.0	**124**

[a] In case of dose escalation at Visit 9 or 11, total blood volume includes additional blood sampling for pharmacokinetics. In case dose escalation is not done at the visits, the total blood volume is indicated in parenthesis

APPENDIX 5. DEFINITION OF HIGH DOSES OF INHALED CORTICOSTEROIDS

Dose of inhaled corticosteroids listed in the table below are considered high doses of inhaled corticosteroids and are not allowed to be used during participation in the TCC-201 trial.

Medication	**Daily Dose (µg)**
Beclometasone (CFC)	>400
Declometasone (HFA)	>200
Budesonide (DPI)	>400
Budesonide (nebules)	>1,000
Ciclesonide	>160
Fluticasone propionate (DPI)	>400
Fluticasone propionate (HFA)	>500
Mometasone	≥440
Triamcinolone	>1,200

APPENDIX 6. DEFINITION OF CHILDBEARING POTENTIAL AND CONTRACEPTIVE REQUIREMENTS

Participants are not expected to attain reproductive potential during the first year of the trial because progression from Tanner stage 1 to menarche within 12 months would be considered pathological and would lead to study drug discontinuation under Stopping Criteria #8. Abnormal pubertal development would be detected via full physical examination scheduled at Week 26, which includes Tanner staging, and such findings will be further investigated by the Investigator as clinically indicated.

However, during the open-label period, the Investigator should ascertain an individual's risk for becoming pregnant or fathering a child and take appropriate steps. This should be captured in the eCRF. 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.

If contraception is indicated, highly effective methods with a failure rate <1% per year are required. Abstinence is only considered an acceptable method of contraception if it is a pre-existing part of a participant's lifestyle. Symptom-thermal methods (basal body temperature in degrees Celsius (°C) or Fahrenheit (°F), cervical mucous, or calendar/rhythm) or withdrawal are not considered adequate forms of contraception for the purposes of this trial (Heads of Medicine Agencies CTFG 2020)

1) Definition of Female of Childbearing Potential and Fertility in Males

Female participants who are post-menarchal, regardless of amenorrhea of any duration, will be considered to be of childbearing potential unless they have had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Male participants at Tanner Stage 3 will be considered fertile, unless they have medically documented infertility.

2) Contraceptive Requirements for Females

Female participants requiring contraception must use a recommended highly effective method consistently during the trial and at least 5 weeks after the last dose of TransCon CNP (equal to 5 half-lives of TransCon CNP). Acceptable highly effective methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated
- with inhibition of ovulation: oral, intravaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]: oral, injectable, or implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

- Vasectomised partner[1]
- Sexual abstinence[2]

[1] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[2] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

3) Contraceptive Requirements for Male Participants (and their female partners)

Male participants requiring contraception must agree to consistently and correctly use a condom until 5 weeks after administration of the last dose of study medication. If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 5 weeks after administration of the last dose of study medication.

If applicable, male participants must agree to refrain from sperm donation for at least 5 weeks after the last dose of study medication.

4) Procedures to be Followed in the Event of Pregnancy

Participants will be instructed to notify the Investigator if they or their partner become pregnant at any time during the study, or if they become pregnant within 5 weeks of the last dose of study medication. Participants who become pregnant or who suspect that they are pregnant must report the information to the Investigator. Participants whose partner has become pregnant or suspects she is pregnant must report the information to the Investigator. All pregnancies (participants and their partners) should be followed up until resolution if possible.

Approval Signatures

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