CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:	ApproaCH: A Phase 2b, Multicenter, Double-Blind, Randomized, Placebo-controlled Trial evaluating Efficacy and Safety of Subcutaneous Doses of TransCon CNP Administered Once Weekly for 52 Weeks in Children with Achondroplasia followed by an Open Label Extension period
PROTOCOL NUMBER:	ASND0036
AMENDMENT NUMBER:	4
COMPOUND:	TransCon CNP
BRIEF TITLE:	A phase 2b clinical trial to evaluate efficacy and safety of weekly doses of TransCon CNP compared with placebo in participants with achondroplasia aged 2 to 11 years of age
PHASE:	2b
SPONSOR:	Ascendis Pharma Growth Disorders A/S Tuborg Boulevard 12 DK-2900 Hellerup, Denmark
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND ID 142685 EudraCT No: 2022-002954-25

SPONSOR COMMITMENT

Ascendis Pharma declares that all trial sites conducted under an IND for which an alternative FDA FORM 1572 is completed will be conducted in a country where the national regulatory authority is a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). As a member of the ICH, the country has implemented the ICH E6 Guideline for Good Clinical Practice (ICH E6) in regional and/or national legislation, norms, regulations, or competent authority administrative processes. Ascendis Pharma will obtain a signed commitment to follow the recommendations in ICH E6 from each investigator at the trial sites listed, by using the Alternative FDA FORM 1572. Additionally, Ascendis Pharma will comply with the terms of the Alternative FDA FORM 1572. Further, Ascendis Pharma will ensure that each investigator at the trial sites listed complies with the commitments contained in the Alternative FDA FORM 1572.

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1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Protocol Title:

ApproaCH (ASND0036): A Phase 2b, Multicenter, Double-Blind, Randomized, Placebo-controlled Trial evaluating Efficacy and Safety of Subcutaneous Doses of TransCon CNP Administered Once Weekly for 52 Weeks in Children with Achondroplasia followed by an Open Label Extension period.

Clinical Trial Rationale:

The present trial will provide data to support the regulatory approval of TransCon CNP (INN navepegritide), which is under development for treatment of children with achondroplasia (ACH). It is expected that the use of TransCon technology with C-type natriuretic peptide (CNP) will maintain the active CNP in circulation at steady therapeutic levels for the entire duration between doses, thereby maximizing the treatment potential while minimizing potential non-skeletal effects of CNP, such as hypotension and other natriuretic effects (see Section 2.2.3) occurring at peak exposure. Use of the TransCon CNP dosing allows for weekly subcutaneous (SC) dosing, thereby providing the basis for a good compliance and convenience and reducing patient and caregiver burden compared to daily injection.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
• To evaluate efficacy of TransCon CNP on growth	Annualized growth velocity (AGV) at Week 52
Secondary	
• To evaluate efficacy of TransCon CNP on growth	Change from baseline in height Z-score at Week 52
• To evaluate the treatment impact of TransCon CNP on spinal curvature	Change from baseline in thoracolumbar kyphosis (TLK) ACH-specific Z-score at Week 52
• To evaluate the treatment impact of TransCon CNP on health-related quality of life	Change from baseline in the Short Form 10 Physical Summary (SF-10 PHS) score at Week 52 Change from baseline in the following Achondroplasia Child Experience Measure (ACEM) scores at Week 52: • ACEM-Impact Measure – Physical Functioning (ACEM-PF) • ACEM-Impact Measure – Daily Living Functioning (ACEM-DF)

Objectives	**Endpoints**
	• Observed Signs Measure (ACEM-OSM)
Safety	
• To evaluate safety and tolerability of TransCon CNP	Incidence of treatment emergent adverse events (TEAEs), safety assessments (safety labs, vital signs, physical and skeletal examination, 12-lead electrocardiogram (ECG), Tanner staging, bone age based on X-ray, bone-related safety events (fracture, slipped capital femoral epiphysis, avascular necrosis and osteonecrosis). Tolerability and acceptability
Pharmacokinetics and ADA	
• To evaluate pharmacokinetic properties of TransCon CNP	Plasma concentrations of Total CNP, free CNP and methoxy polyethylene glycol (mPEG)
• To assess potential immunogenic response to TransCon CNP	Detection and characterisation of anti-drug antibodies (ADA)
Exploratory	
CCI	[redacted]

Objectives	Endpoints
CCI	

Objectives	Endpoints
CCI	

Brief Summary:

The purpose of this clinical trial is to evaluate efficacy and safety of once weekly SC doses of 100 µg CNP/kg compared to placebo on AGV after a 52-week randomized treatment period in children aged 2 to 11 years with genetically confirmed ACH. The double-blind, placebo-controlled treatment period is followed by an Open Label Extension (OLE) period of a 52-week duration.

Ideally, the participants will roll over from the observational study (ACHieve TCC-NHS-01 ACHieve). Prior to enrollment, participants must have a minimum of 6 months of observational period (collecting baseline data on anthropometric measurements and ACH-related complication assessments) from ACHieve TCC-NHS-01 or a minimum of 6 months historical height/length data and be confirmed by the medical monitor to be enrolled if not from ACHieve TCC-NHS-01.

Children who have severe ACH-related complications or significant risk factors that could affect growth or confound trial analysis will not be considered eligible for participation.

The trial consists of the following periods:

- **Screening period:** Up to 5 weeks
- **Double-Blind Treatment Period:** 52-week, double-blind (DB), randomized, placebo-controlled treatment period evaluating 100 µg CNP/kg/week or placebo (randomization ratio 2:1)
- **Open-Label Extension Period:** 52-week open-label extension (OLE) period in which all participants receive 100 µg CNP/kg/week
- **Follow-up period:** 5-week follow-up period (following last dose administered)

Route of administration of CNP or placebo is SC injections.

Dose regimen is once weekly administered in the clinic or at home.

Number of Participants:

In total, approximately 80 participants will be enrolled in a 2:1 randomization ratio.

The participants will be aged 2 to 11 years (inclusive, at the time of screening).

Treatment Groups and Duration:

Trial participants will receive either 100 µg CNP/kg/week or placebo for a 52-week double-blind, randomized treatment period followed by a 52-week OLE period where all participants will receive 100 µg CNP/kg/week. The treatment period of the trial has a total duration of 104 weeks.

Trial participants will be stratified by age and sex at the time of randomization as the following 3 categories:

Category 1: Aged < 5 years

Category 2: Aged ≥ 5 years and female

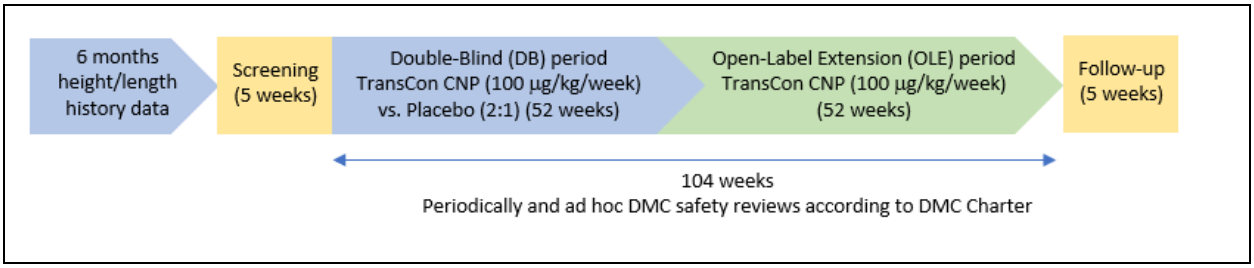
Category 3: Aged ≥ 5 years and male

Data Monitoring Committee (DMC):

A TransCon CNP DMC has been appointed for this clinical trial to monitor the safety data, and to make recommendations to the sponsor regarding the continuing or stopping of this clinical trial. The full scope of the TransCon CNP DMC roles and responsibilities will be outlined in the TransCon CNP DMC charter for the trial.

1.2. SCHEMA

Figure 1: Trial Design in the Double-Blind (DB) and Open Label Extension (OLE) Periods



1.3. SCHEDULE OF ACTIVITIES

1.3.1. Schedule of Activities in Double-Blind Period

Visit	Screening	1	Phone[b]	2	3	4	5	6[c] DB	ET[d]/ EoT	FU[e] DB
Week	**-**	**0**	**2**	**4**	**12**	**26**	**39**	**52**	**-**	**57**
Visit Window (days)	[-5w to 0][a]	-	±2	±3	±7	±7	±7	±7	-	±7
Informed Consent	X									
Demographics	X									
Verification of eligibility, incl. genetic test for ACH[f]	X									
Randomization		X								
Medical history/ Concomitant Illness	X	X								
Prior/Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X
Adverse events (AE)[g]		----------X ----------							X	X
Assessment of pubertal status[h]		X				X		X	X	
Physical and skeletal examination[i]	X[j]	X[j]		X[k]	X[j]	X[k]	X[k]	X[j]	X[j]	X[j]
Vital signs[l]	X	X[m]		X	X	X	X	X[m]	X	X
Body weight	X	X		X	X	X	X	X	X	X
Standing height, Upper body segment (sitting height) and Lower body segment		X			X	X	X	X	X	
Arm span, Upper leg length, Lower leg length, Upper arm length, and Lower arm length		X				X		X	X	
Head circumference		X						X	X	
12-lead ECG[n]	X	X			X	X		X	X	
X-ray for bone age and epiphyseal changes	X							X	X[o]	
CCI										
Pharmacokinetics[q]				X	X	X	X	X	X	
Clinical laboratory tests incl. urinalysis[r]	X[s]	X[s]		X	X	X[s]	X	X[s]	X[s]	
Urinary hCG test[t]	X	X		X	X	X	X	X	X	X
Anti-drug antibody		X		X	X	X	X	X	X	X
Exploratory biomarkers[u]		X		X	X	X	X	X		

Visit	Screening	1	Phone[b]	2	3	4	5	6[c] DB	ET[d]/ EoT	FU[e] DB
Week	**-**	**0**	**2**	**4**	**12**	**26**	**39**	**52**	**-**	**57**
Visit Window (days)	[-5w to 0][a]	-	±2	±3	±7	±7	±7	±7	-	±7
CCI										
Treatment acceptability assessment								X	X	
Qualitative Exit Phone Interviews[y]								X	X	
Investigational Medicinal Product (IMP) administration training and IFU hand-out		X		X	X	X	X		X	
Dispensing of IMP		X[z]		X	X	X	X			
Return of IMP to site				X	X	X	X	X	X	
Participant diary hand-out/reminder		X		X	X	X	X			
Participant diary review				X	X	X	X	X	X	

DB = double-blind; ET = early termination of IMP; EoT = End-of-Trial; FU = follow-up visit; w = week; OLE = open label extension

[a] Screening period must be initiated at least 2 weeks prior to first dosing as shipment of IMP is prompted when screening is initiated for a participant.

[b] All participants will be contacted by phone during Week 2 for follow-up. The trial staff will ask about the general well-being of the child, administration of trial drug procedures, record any AEs, record any concomitant medication changes, and answer any questions.

[c] All assessments at Visit 6 DB must be performed prior to the first dose administration of the OLE period. Visit 6 DB will be considered baseline for the OLE period, and assessments will not be repeated at Visit 6 OLE. For participants who have permanently discontinued IMP, Visit 6 DB will be the End-of-Trial visit as they cannot roll over to OLE.

[d] Applicable for participants permanently discontinuing IMP (see Section 7.1) and participants withdrawn from the trial (see Section 7.2). For participants who are withdrawn from the trial, the site should attempt at having the participant come in for the EoT visit and, if possible, the FU DB visit (if participant was on IMP at the time of withdrawal).

[e] Not applicable for participants proceeding to the OLE period and participants who permanently discontinue IMP.

[f] A blood sample will be collected and used to identify the most common FGFR3 variants unless documented evidence of genetic confirmation of the pathologic variant in FGFR3 gene is already available.

[g] Adverse events including ACH complications and manifestations are collected throughout the trial. All AEs that occur from the signing of the ICF until the initiation of trial treatment will be collected if deemed related to a trial procedure (see Section 8.4.1).

[h] Boys will be assessed for testis volumes, and girls for breast development according to Tanner stages (Tanner 1976). Tanner stage progression during the trial will not impact trial treatment.

[i] Skeletal physical examination includes palpating bone structure and joints for tenderness and mobility for all abnormal findings including those typically found in children with ACH.

[j] Physical examination includes assessments of all major body systems including general appearance, head, eyes, ears, nose, and throat (HEENT), neck (including thyroid), lung/pulmonary, chest, cardiovascular (CV), abdomen, back, genito-urinary, neurological, extremities, and skin. A visual inspection of injection site(s) must be performed, excluding Screening. On Visit 1, visual inspection of injection site(s) is done pre-dose and approx. 2 hours post-dose.

[k] A visual inspection of injection sites is mandatory, and an optional, limited, symptom-directed physical examination may be performed at the discretion of the investigator.

[l] Vital signs include body temperature, blood pressure (BP) (systolic/diastolic) and heart rate (HR). Vital signs are assessed at Visit 1 (pre-dose and approx. 2 hours post-dose), Visit 3 (24-72 hours post-dose), and Visit 6 DB. At other visits, the assessment can be done any time within the allowed visit window.

[m] Orthostatic vital signs (HR, BP) will be taken at rest (supine position) and upon standing at Visit 1 (pre-dose as well as 1- and 2-hours post-dose) and at Visit 6 DB. Assessment at Visit 6 DB is only applicable for participants proceeding to the OLE period.

[n] 12-lead ECG (single recording) will be assessed at Visit 1 (pre-dose), Visit 3 (24-72 hours post-dose) and Visit 4 (pre-dose). At other visits, the assessment can be done any time within the allowed visit window.

[o] For participants permanently discontinuing IMP and withdrawn participants, X-ray should only be performed if more than 3 months has passed since the last x-ray.

CCI [redacted]

[q] At Visit 3, blood for pharmacokinetic analysis must be drawn 24-72 hours post-dose. At Visit 4 and Visit 6 DB, blood must be drawn pre-dose (trough), and IMP administration cannot take place within 6 days prior to these visits. At Visits 2 and 5, blood can be drawn anytime within the allowed visit window.

[r] Blood samples for clinical laboratory tests for standard panel of blood biochemistry and hematology will be drawn (see Section 10.2 [Appendix 2]).

[s] Additional blood samples for lipids, 25(OH) Vitamin D, and thyroid stimulating hormone (TSH) will be drawn and urine for urinalysis will be collected. Blood sample for HbA1c is drawn at Screening only (see Section 10.2 [Appendix 2]). In addition, blood sample for genetic confirmation of ACH is collected at Screening, as applicable (see Section 10.2 [Appendix 2]).

[t] Urinary hCG test applicable for females of childbearing potential only.

[u] Blood samples for exploratory biomarkers of pharmacodynamic response to treatment will be drawn.

CCI [redacted]

[y] Phone exit interviews to occur with selected English-speaking caregivers of participants at 2 weeks post Visit 6 DB.

[z] First dose administration must take place at the clinic.

1.3.2. Schedule of Activities in the Open Label Extension Period

Visit	6[a] OLE	Phone[b]	7	8	9	10	11 EoT[c]	FU[c] OLE
Week	**52**	**54**	**56**	**64**	**78**	**91**	**104**	**109**
Visit Window (days)	-	±2	±3	±7	±7	±7	±7	±7
Prior/Concomitant medication and procedure		X	X	X	X	X	X	X
Adverse events[d]	----------	----------	----------	----------	X	----------	----------	X
Assessment of pubertal status[e]			X	X	X	X	X	
Physical and skeletal examination[f]			X[h]	X[h]	X[g]	X[h]	X[g]	X[g]
Vital signs[i]	X[j]		X	X	X	X	X	
Body Weight			X	X	X	X	X	
Standing height, Upper body segment (sitting height) and Lower body segment				X	X	X	X	
Arm span, Upper leg length, Lower leg length, Upper arm length, and Lower arm length					X		X	
Head circumference							X	
12-lead ECG[k]					X		X	
X-ray for bone age and epiphyseal changes							X[l]	
CCI								
Pharmacokinetics[n]			X	X	X	X	X	
Clinical laboratory tests incl. urinalysis[o]			X	X	X[p]	X	X[p]	
Urinary hCG test[q]			X	X	X	X	X	X
Anti-drug antibody			X	X	X	X	X	X
Exploratory biomarkers[r]			X	X	X	X	X	
CCI								

Visit	6[a] OLE	Phone[b]	7	8	9	10	11 EoT[c]	FU[c] OLE
Week	**52**	**54**	**56**	**64**	**78**	**91**	**104**	**109**
Visit Window (days)	-	±2	±3	±7	±7	±7	±7	±7
Treatment acceptability assessment							X	
IMP administration training and IFU hand-out	X		X	X	X	X		
Dispensing of IMP	X[w]		X	X	X	X		
Return of IMP to site			X	X	X	X	X	
Participant diary hand-out/reminder	X		X	X	X	X		
Participant diary review				X	X	X	X	

OLE = open label extension; EoT = end of trial; FU = follow-up visit; w = week

[a] All assessments at Visit 6 DB are performed prior to the first dose administration and considered baseline for the OLE period. All assessments at Visit 6 OLE are performed post-dose. No assessment performed at Visit 6 DB will be repeated at Visit 6 OLE.

[b] All participants will be contacted by phone during Week 54 for follow-up.

[c] If a participant is withdrawn from the trial, the site should attempt at having the participant come in for the EoT visit and, if possible, the FU OLE visit.

[d] Adverse events including ACH complications and manifestations are collected throughout the trial.

[e] Boys will be assessed for testis volumes, and girls for breast development according to Tanner stages. Tanner stage progression during the trial will not impact trial treatment.

[f] Skeletal physical examination includes palpating bone structure and joints for tenderness and mobility and other abnormal changes not normally found in children with ACH.

[g] Physical examination includes assessments of all major body systems including general appearance, HEENT, neck (including thyroid), lung/pulmonary, chest, CV, abdomen, back, genito-urinary, neurological, extremities, and skin. In addition, all visits will include a visual inspection of injection sites.

[h] A visual inspection of injection site(s) is mandatory. A limited, symptom-directed physical examination may be performed at discretion of the investigator.

[i] Vital signs include body temperature, BP (systolic/diastolic) and HR. At Visit 6 OLE, vital signs are assessed approx. 2-hours post-dose. At other visits, the assessment can be done any time within the allowed visit window.

[j] Orthostatic vital signs (HR, BP) will be taken at rest (supine position) and upon standing at Visit 6 OLE (1- and 2-hours post-dose). Note, pre-dose assessment is done at Visit 6 DB.

[k] 12-lead ECG (single recording) can be assessed at Visits 9 and 11 at any time within the allowed visit window.

[l] For participants permanently discontinuing IMP/withdrawn from the trial, X-ray should only be performed if more than 3 months since the last x-ray.

CCI [redacted]

[n] Blood samples for pharmacokinetics can be drawn anytime within the allowed visit window.

[o] Blood samples for clinical laboratory tests for standard panel of blood biochemistry and hematology will be drawn (see Section 10.2 [Appendix 2]).

[p] Additional blood samples for lipids, 25(OH) Vitamin D, and TSH will be drawn and urine for urinalysis will be collected (see Section 10.2 [Appendix 2]).

[q] Urinary hCG test applicable for females of childbearing potential only.

[r] Exploratory biomarkers of pharmacodynamic response to treatment.

[s] Observer Reported Outcome (ObsRO) measures must be completed by the same caregiver without assistance and should be completed prior to conducting any clinical assessments throughout the trial.

CCI

[redacted]

[w] First dose administration must take place at the clinic.

2. INTRODUCTION

Achondroplasia (ACH) is the most common skeletal dysplasia and the most frequent form of short-limbed dwarfism (Horton 2007). It occurs with a frequency of 1 in 10,000 to 30,000 live births, affecting 250,000 men and women equally worldwide (Horton 2007, Unger 2017). ACH is a debilitating condition, and the life expectancy of people with ACH is 10 years shorter than the general population (Hecht 1987, Wynn 2007).

Rhizomelic short stature is cardinal feature in ACH. The average adult height for men with ACH is 131±5.6 cm; for women, 124±5.9 cm. Body disproportionality includes shortened limbs, particularly of the proximal long bones. Other manifestations and complications include spinal curvature, joint and back pain, limited range of motion, frequent otitis media and hearing loss, sleep disturbances, all of which may limit function and well-being, as well as increase caregiver burden (Horton 2007, Ireland 2014, Unger 2017). Premature closure of the synchondroses contribute to hydrocephalus, spinal stenosis, and respiratory problems.

Obesity is a major problem in ACH (Hecht 1987). Excessive weight gain can manifest in early childhood. In adults, obesity can aggravate the morbidity associated with lumbar stenosis and contribute to nonspecific joint problems and possibly to early mortality from cardiovascular complications (Wynn 2007).

TransCon CNP (ACP-015) is under development for once weekly SC treatment of ACH in children.

2.1. CLINICAL TRIAL RATIONALE

Growth in children is a dynamic process influenced by numerous innate and external variables. The innate variables include factors such as familial potential, genetic variability, sex, overall health status, and circadian rhythms. The external variables that affect growth include intrauterine environment, nutrition, exercise, and seasonality with maximal growth in the spring and summer. These factors all contribute to the overall growth pattern (often in short bursts or spurts) of a person yielding their ultimate absolute end adult height. Skeletal dysplasia, such as ACH, occur as a result of aberrant bone growth in the spine and skull, and in the long bones of the arms and legs thereby resulting in marked short stature and associated complications and manifestations.

CNP is a paracrine regulator that plays a fundamental role in in cardiovascular homeostasis and bone growth by activating natriuretic peptide receptor B (Lumsden 2010). CNP exists in two predominant forms in humans, a 2.2kDa CNP-22 peptide, which is rapidly degraded in blood plasma by neutral endopeptidase (NEP) resulting in a short half-life of 2-3 minutes in human blood (Hunt 1994, Brandt 1997), and a 5.8kDa CNP-53 peptide (53 amino acids) which by virtue of its size is comparatively NEP resistant (Oefner 2000, Wendt 2015). Continuous IV administration of CNP-22 has been demonstrated to restore bone growth in ACH mice (Yasoda 2009). CNP-53 is the predominant form of CNP in tissues (Potter 2009).

Recently, a modified CNP peptide, vosoritide, has been granted approval for linear growth in children with ACH. Vosoritide comprises the 37 C terminal amino acids of CNP-53, with the addition of an N terminal proline-glycine motif, not found in wildtype CNP, which reportedly conveys NEP resistance (NDA 214938). Studies showed an average of 1.6 cm of additional height growth after 52 weeks of treatment with vosoritide. The long-term effect in linear growth

and the final adult height after treatment with vosoritide is still to be determined. Side effects from vosoritide use include decreased BP occurring shortly after SC administration of vosoritide and injection site reactions (Savarirayan 2020). Vosoritide has a half-life of approximately half an hour and is administered SC once-daily.

The present trial will provide data to support the regulatory approval of TransCon CNP. The TransCon™ (Transient Conjugation) technology is designed to provide sustained release of CNP (see Section 2.2) resulting in a low peak exposure of active CNP. It is expected that CNP levels in circulation will be maintained at steady therapeutic levels for the entire duration between doses, thereby maximizing the treatment potential while minimizing potential non-skeletal effects of CNP, such as hypotension and other potential natriuretic effects occurring at peak exposure. Use of TransCon™ technology also allows for weekly SC dosing, thereby decreasing injection frequency, allowing for good compliance and convenience, and reducing caregiver burden compared to daily injection.

2.2. BACKGROUND

2.2.1. Etiology

ACH is caused by gain-of-function autosomal dominant pathologic variants in the *fibroblast growth factor receptor-3* (*FGFR3*) gene which encodes FGFR3 protein (Horton 2007). FGFR3 protein is a factor that inhibits chondrocyte proliferation and differentiation in the long bone growth plate. The most common pathologic variant (98%), G380R, results in a substitution in the transmembrane domain of FGFR3 receptor. The majority of ACH cases (80%) are caused by *de novo* pathologic variants. People with ACH experience significant medical and functional complications over their lifespan including multiple surgeries and impaired quality of life (Horton 2007).

2.2.2. TransCon CNP

TransCon is an innovative technology platform for drug development. By attaching two branched (2×10 kDa) mPEG groups to a CNP moiety via the TransCon Linker, the CNP moiety is an essentially inactive prodrug through a shielding effect, which releases CNP-38 via auto-cleavage of the TransCon Linker in a controlled manner following first-order kinetics at physiologic pH and temperature. The CNP-38 released from TransCon CNP is identical to the unmodified carboxy terminal amino acid residues 89 through 126 of human CNP.

Refer to the current version of the investigator brochure (IB) for further details of TransCon CNP properties.

2.2.3. Nonclinical Findings

Overall, TransCon CNP has shown the expected pharmacological effects on cartilage homeostasis and bone growth in the nonclinical studies. No natriuretic, diuretic or kaliuretic properties were identified, which is supported by the literature stating that CNP's main function is the auto/paracrine regulation (Takei 1999, Suda 2002) of the vascular tone and growth, while lacking a significant natriuretic function (Pham 1997). High systemic concentrations of CNP is known to decrease BP due to its vasodilatory effect (Clavell 1993, Barr 1996, Igaki 1998, Scotland 2005a, Nakao 2017).

CV changes including increased HR, decreased BP and a small increase in HR corrected QT [QTca] interval was observed in cynomolgus monkeys at doses of ≥300 µg CNP/kg but with no associated clinical signs. The CV no observed effect level (NOEL) in cynomolgus monkeys was 100 µg CNP/kg.

No off-target (non-bone related) adverse findings were observed in the toxicity studies in healthy juvenile animals, and the no observed adverse effect level (NOAEL) for off-target effects was defined as the highest dose tested (4000 µg CNP/kg/week in rats) in juvenile animals with a normal FGFR3 pathway. The only significant adverse findings were related to the expected pharmacology of CNP on bone growth and 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.

Refer to the current version of the IB for further details of the nonclinical data.

2.2.4. Clinical Studies

To date, one Phase 1 trial (TCC-101) investigating safety and tolerability of single SC doses (25, 75, and 150 µg CNP/kg) of TransCon CNP in healthy adult participants has been completed. TransCon CNP was found to be well tolerated at all dose levels and no dose limiting toxicities were identified. No clinically significant trends were observed in the clinical laboratory parameters, vital sign assessments, ECG parameters, or physical examination findings. No serious AEs were reported, and no participant was withdrawn due to an AE. In addition, no adverse immune responses (anti-drug antibodies) were observed.

Pharmacokinetic properties of TransCon CNP supports once weekly administration with release of active CNP in a sustained manner. The CNP-38 pharmacokinetic profile following release from the prodrug was characterized by a slow rise to peak plasma concentrations with median T_{max} ranging from 45 to 66 hours post-dose. After reaching C_{max}, CNP-38 concentrations declined slowly in an apparent monophasic manner. The apparent half-life ($t_{½}$) was estimated to be approximately 120 hours (Breinholt 2022). Endogenous CNP biosynthesis did not appear to be affected by single administration of TransCon CNP.

Further four clinical studies are ongoing in the TransCon CNP clinical development program:

- TCC-NHS-01 ACHieve: A multi-center, longitudinal, observational study of children with achondroplasia
- TCC-201 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
- TCC-204 ACcomplisH China: A Phase 2, multicenter, randomized, placebo-controlled, dose escalation trial evaluating safety, efficacy, and pharmacokinetics of multiple subcutaneous doses of TransCon CNP administered once weekly in children with achondroplasia
- ASND0032: A Single Center, Open-Label, Phase 1 Trial Comparing the Pharmacokinetics and Characterizing the Safety of TransCon CNP Administered as a Single Subcutaneous Dose in Healthy Male Adult Japanese and Caucasian Subjects

Refer to the current version of the IB for further details of the clinical trials.

2.3. BENEFIT/RISK ASSESSMENT

For more detailed information about the known and expected benefits and risks and reasonably expected AEs of TransCon CNP, refer to the current version of the IB.

2.3.1. Risks

2.3.1.1. Important Identified Risks

The risk profile of TransCon CNP in children with ACH is largely unknown. There are no important identified risks to date from the preclinical studies or clinical studies as assessed by the independent DMC; 16 May 2022 for any dose of TransCon CNP. In the Phase 1 trial (TCC-101) performed in healthy adult male participants, TransCon CNP was generally well tolerated (Breinholt 2022). In the ongoing Phase 2 trial (TCC-201), TransCon CNP was administered to children with ACH between the ages of 2 and 10 years old at doses up to 100 µg CNP/kg. No new signals were identified based on the unblinded safety evaluation performed by the DMC (as of 16 May 2022).

2.3.1.2. Important Potential Risks

There were no potential risks identified from preclinical studies. The following potential risks are theoretical, based on mechanism of action of CNP and/or have been reported for approved CNP pharmaceutical products.

- Cardiovascular Changes
- Bone Overgrowth

2.3.2. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Trial Treatment(s)		
Cardiovascular Changes	Decreased blood pressure (BP), increased heart rate (HR), and prolonged QTca (<10%; not considered biologically relevant [Ando 2005]) were observed in cynomolgus monkeys at doses of ≥300 µg CNP/kg (IB, Sec. 6.5). Hypotensive effects were reported to correlate with high peak plasma CNP concentrations in healthy adults administered exogenous CNP (Igaki 1998). No correlation was observed following single doses up to 150 µg TransCon CNP/kg (TCC-101), likely due to lower C_{max}	Vital signs will be assessed at all visits to monitor for hypotension and tachycardia. Ad hoc vital signs will be recorded if symptoms of hypotension (such as hypotension such as dizziness, headache, lightheadedness, blurry vision, or loss of consciousness) arise. Additional measurements of orthostatic BP will be measured at Visit 1 (pre-dose and 1- and 2-hours post-dose), Visit 6 DB and Visit 6 OLE (1- and 2-hours post-dose).

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	and peak-to-trough ratio due to the sustained exposure. Additionally, no clinically relevant effects on the studied ECG parameters were found. No signal of symptomatic hypotension has been identified in healthy participants dosed in the Phase 1 trial (TCC-101) or in children with ACH exposed to TransCon CNP in the ongoing Phase 2 (TCC-201) trial as of 16 May 2022 after unblinded DMC review.	If a participant experiences any unforeseen clinical signs/symptoms after dose administration at home, the participant may be asked to attend an unscheduled visit at the clinic for subsequent weekly dosing and post-dose monitoring. This may also be conducted remotely with the assistance from a home health nurse. The need for additional monitoring will be determined at the discretion of the investigator. ECGs will be recorded at Visit 1 (pre-dose) and Visits 3, 4, 6 DB, 9 and 11. These assessments will be addressed by the treating physician as needed, monitored by the sponsor and reviewed by the unblinded DMC.
Bone overgrowth	Pathologic variants leading to an overproduction of CNP in people without activating mutations in FGFR3 result in skeletal overgrowth, incl. long hands and feet, scoliosis and ankle valgus deformity (Bocciardi 2007, Moncla 2007, Tassano 2013, Ko 2015). No signal of bone overgrowth has been identified in children with ACH exposed to TransCon CNP in the ongoing phase 2 (TCC-201) trial as of 16 May 2022.	Physical and skeletal examinations will be performed at all in-clinic visits and radiologic assessments will be performed at screening, Visit 1, and annually during the trial. At all other visits, 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.

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical Trial Procedures		
Blood collection	Discomfort, bleeding, mild pain, and anemia	Blood will be collected by trained medical professionals to minimize potential issues. Blood will be drawn at volumes appropriate based on the weight of the child at each visit following the European Commission recommendations for ethical consideration for clinical trials in minor (European Commission 2017).
Radiographic scans	Total exposure during the trial is expected to be approximately 3.2 mSv/participant.	Assessments will be performed at a frequency most in line with what is required by their standard of care. The type and frequency of radiographic assessments has been carefully chosen to minimize exposure to radiation for the trial participants.
Visits during COVID-19 Pandemic	Possible exposure to infections given visits in the hospital environment and current global pandemic	Participants have the option to have a home health nurse conduct a focused trial visit at the participant's home if the global COVID-19 pandemic prevents the participants' ability to attend on-site trial visits. Safety lab assessments can be done locally, and Investigational Medicinal Product (IMP) can be sent directly to the home of the participants.

2.3.2.1. Risks Related to Outbreak of COVID-19 Pandemic

The CDC has published guidance on infants and children with underlying medical conditions that may increase the risk of severe illness due to SARS-CoV-2 virus infection. As per this guidance, ACH is not listed as an underlying medical condition that poses a higher risk for children to develop serious illness if afflicted with the SARS-CoV-2 virus (see CDC 2019).

The risk of participants with ACH exposed to SARS-CoV-2 developing severe COVID-19 symptoms, either on or off treatment with TransCon CNP, is assessed as similar to that of the general population. Participants and site staff involved in this trial are expected to act according to local guidelines, recommendations, national laws, local restrictions, and hospital procedures related to COVID-19. Decisions to adjust the trial conduct will be based on the risk

assessment performed by the Sponsor. The risk assessment will, as applicable, include a risk assessment for each individual trial participant.

In case of local COVID-19 outbreaks, several mitigating actions can be applied to ensure participant's safety and data integrity: site visits can be replaced by remote contacts as phone calls or virtual meetings, safety lab and assessments can be done locally, and IMP can be sent directly to the home of the participants.

There is no contraindication to the child receiving the COVID-19 vaccine (or other vaccines) while taking TransCon CNP.

2.3.3. Potential Benefit Assessment

Based on the published studies of CNP analogues in mouse models of ACH (Lorget 2012, Wendt 2015) and nonclinical studies using TransCon CNP (Breinholt 2019), treatment with TransCon CNP may promote proportional growth of the long bones and decrease the manifestations and complications associated with dysplastic bone growth in children with ACH.

2.3.4. Overall Benefit-Risk Conclusion

ACH is a congenital skeletal dysplasia that presents as rhizomelic short stature and other complications and manifestations which result in significant impact to affected patients. Children with ACH have limited treatment options that adequately address primary and secondary manifestations of ACH. The anticipated benefit of TransCon CNP in children with ACH is to counteract the skeletal growth abnormalities caused by the FGFR3 pathologic variants. Prevention of the skeletal growth abnormalities is anticipated to have meaningful improvement of medical and functional problems associated with ACH, such as cervico-medullary compression, hydrocephalus, chronic otitis media and subsequent hearing loss, obstructive sleep apnea, spinal stenosis, short arms, limited range of motion of the joints, bowing of the legs, and chronic knee pain (Hoover-Fong 2021). As of 16 May 2022, clinical safety data from preclinical studies, the Phase 1 clinical trial (TCC-101) and the ongoing phase 2 trial (TCC-201) have not raised significant safety signals. The anticipated benefits of treatment with TransCon CNP outweigh the risks.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate efficacy of TransCon CNP on growth	AGV at Week 52
Secondary	
• To evaluate efficacy of TransCon CNP on growth	Change from baseline in height Z-score at Week 52
• To evaluate the treatment impact of TransCon CNP on spinal curvature	Change from baseline in TLK ACH-specific Z-score at Week 52
• To evaluate the treatment impact of TransCon CNP on health-related quality of life	Change from baseline in the SF-10 PHS score at Week 52 Change from baseline in the following ACEM scores at Week 52: • ACEM-PF • ACEM-DF • ACEM-OSM
Safety	
• To evaluate safety and tolerability of TransCon CNP	Incidence of TEAEs, safety assessments (safety labs, vital signs, physical and skeletal examination, 12-lead ECG, Tanner staging, bone age based on X-ray, bone-related safety events (fracture, slipped capital femoral epiphysis, avascular necrosis and osteonecrosis). Tolerability and acceptability
Pharmacokinetics and ADA	
• To evaluate pharmacokinetic properties of TransCon CNP	Plasma concentrations of Total CNP, free CNP and mPEG
• To assess potential immunogenic response to TransCon CNP	Detection and characterisation of ADA

Objectives	Endpoints
Exploratory	
CCI	

Objectives	Endpoints
CCI	

4. CLINICAL TRIAL DESIGN

4.1. OVERALL DESIGN

This is a phase 2b, multicenter, double-blind, randomized, placebo-controlled trial evaluating efficacy, safety, and pharmacokinetic properties of 100 μg/kg once weekly TransCon CNP or placebo administered SC to children with ACH aged 2 to 11 years followed by an OLE period of 52 weeks.

Approximately 80 participants will be randomized in 2:1 to either TransCon CNP or placebo.

Trial participants will be stratified by age and sex at the time of randomization as the following 3 categories:

Category 1: Aged < 5 years

Category 2: Aged ≥ 5 years and female

Category 3: Aged ≥ 5 years and male

The trial consists of the following periods:

- **Screening period:** Up to 5 weeks
- **Double-Blind Treatment Period:** 52-week, double-blind (DB), randomized, placebo-controlled treatment period evaluating 100 μg/kg/week TransCon CNP or placebo (randomization ratio 2:1)
- **Open-Label Extension Period:** 52-week open-label extension (OLE) period
- **Follow-up period:** 5-week follow-up (FU) period (following last dose administered)

4.2. SCIENTIFIC RATIONALE FOR CLINICAL TRIAL DESIGN

A randomized, double-blind, placebo-controlled design is considered a scientifically sound approach to evaluate outcomes caused by the trial treatment compared to other factors including natural progression of the disease, growth of the participants, concomitant therapy, or the effect of being in a trial by minimizing bias and thereby increase the accuracy and reliability to estimate efficacy and interpret safety results.

Participants in the trial will be followed by their primary care team to receive standard of care treatment. In addition, it is expected that all participants will benefit from participation through close contact with the trial site. There are some commercially available therapeutic options available to individuals with ACH (e.g., growth hormone and vosoritide, a CNP analogue) depending on their geographic location. These treatments are not standard of care and are prohibited in this trial.

The primary endpoint is AGV assessed at Week 52. The cardinal feature of patients with achondroplasia is short stature. AGV is considered an appropriate objective as height and length measurements are clearly defined and consistently measured.

The sample size was chosen to being able to reliably demonstrate a statistically significant and clinically relevant treatment effect in AGV (see Section 9).

4.3. JUSTIFICATION FOR DOSE

For this trial, the participants will receive TransCon CNP (100 µg CNP/kg) or placebo once weekly for a 52-week treatment period followed by an OLE period where all participants will receive TransCon CNP (100 µg CNP/kg) once weekly for 52 weeks.

Single doses up to 150 µg/kg CNP of TransCon CNP have been administered to healthy adult participants (TCC-101) and multiple doses of TransCon CNP up to 100 µg CNP/kg/week have been administered to children with ACH between the ages of 2 and 10 years in an ongoing double blinded trial (TCC-201).

4.4. END-OF-TRIAL DEFINITION

The end of the clinical trial is defined as the date of Last Participant Last Visit of the OLE period.

4.5. UNSCHEDULED VISITS

Unscheduled Visits are visits that may occur between regularly scheduled visits at the investigator's 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 Unscheduled Visit.

5. CLINICAL TRIAL POPULATION

In total, approximately 80 participants will be enrolled. The participants will be aged 2 to 11 years (inclusive).

Children who have severe ACH-related complications, significant risk factors that could affect growth, or confound trial analysis will not be considered eligible for participation (see Section 5.2).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Each criterion must be assessed during screening period and based on the laboratory results obtained from the central and/or local laboratory unless stated otherwise. Eligibility of each participant must be confirmed by the investigator prior to randomization.

5.1. INCLUSION CRITERIA

Participants are eligible to be included in the trial only if all of the following criteria apply:

1. Written, signed informed consent of the parent(s) or legal guardian(s) of the participant, and as required by the institutional review board/human research ethics committee/independent ethics committee (IRB/HREC/IEC).
2. Male or female, between 2 and 11 years of age (inclusive) at the time of Screening.
3. Clinical diagnosis of ACH with documented genetic confirmation available.
4. Able to stand without assistance.

5. Parent(s)/legal guardian(s) willing and able to administer weekly SC injections of IMP and to follow the protocol.
6. At least six months of growth and disease history from ACHieve (TCC-NHS-01) trial or comparable growth and disease history available from medical records (pending confirmation by Medical Monitor).
7. Considered eligible based on the medical history, physical examination, and the results of vital signs, ECG and clinical laboratory tests performed during the Screening period.

5.2. EXCLUSION CRITERIA

Participants are excluded from the trial if any of the following criteria apply:

1. Participation (i.e., signed informed consent) in any interventional clinical trial before within 3 months prior to screening.
2. Closed epiphysis.
3. Known or suspected hypersensitivity to the IMP or related products (trehalose, tris[hydroxymethyl]aminomethane, succinate, and mPEG).
4. Have a growth disorder or medical condition other than ACH that results in short stature or abnormal growth such as severe ACH with developmental delay and acanthosis nigricans (SADDAN), hypochondroplasia, growth hormone deficiency, Turner syndrome, pseudoachondroplasia, inflammatory bowel disease, celiac disease, hypothyroidism, hyperthyroidism, pre-diabetes, or diabetes mellitus.
5. Have received any dose of prescription medications and IMP or surgical intervention intended to affect stature, growth, or body proportionality at any time.
6. Requires, or anticipated to require, chronic (> 4 weeks) or repeated treatment (more than twice/year and >3 weeks/year) with systemic corticosteroids during participation in the trial. Chronic use of high-dose inhaled corticosteroids is not allowed.
7. Known history of presence of injury or disease of the growth plate(s), other than ACH, that affects growth potential of long bones.
8. Known history of any bone-related surgery affecting growth potential of long bones, such as:
    - Orthopedic reconstructive surgery for bone lengthening (e.g., procedures for leg bowing such as 8-plate are not exclusionary).
    - Cervicomedullary decompression surgery without anticipated need for repeat decompression during the time of the trial are allowed with minimum of 6 months of bone healing.
    - Ventriculoperitoneal (VP) shunt and laminectomy with full recovery are allowed with minimum of 6 months of bone healing.
    - Bone fracture within 6 months prior to screening (within 2 months for fracture of digits and buckle fractures).

9. Clinically significant findings at Screening, such as:
    - Expected to require surgical intervention during participation in the trial. Common surgeries, such as insertion of grommets, adenoidectomy, tonsillectomy, or myringotomy tube placement, are permitted.
    - Severe untreated sleep apnea or newly initiated sleep apnea treatment (e.g., Continuous Positive Airway Pressure [CPAP] in the previous 2 months prior to Screening.
    - Musculoskeletal disease, such as Salter-Harris fractures or clinical and/or radiographic evidence of severe hip pathology, or
    - Otherwise, are considered by the Investigator and Medical Monitor to make a participant unfit to receive trial treatment or undergo trial related procedures.
10. Have evidence at Screening that are consistent with severe cervicomedullary junction compression based on clinical and/or radiologic findings that indicate immediate surgical intervention is required.
11. Have a clinically significant finding or arrhythmia as determined by the investigator in consultation with the medical monitor that indicates abnormal cardiac function or conduction that includes, but is not exclusive to:
    - Repaired or unrepaired coarctation.
    - Moderate or greater complexity congenital heart disease including tetralogy of Fallot, Atrioventricular septal defects, truncus arteriosus, total anomalous pulmonary venous return, double outlet right ventricle, or single ventricle heart disease.
12. QTcF $\geq$ 450 msec at the Screening Visit.
13. Known history or presence of condition that impacts hemodynamic stability (such as autonomic dysfunction and orthostatic intolerance).
14. Known history or presence of the following:
    - Chronic anemia (iron deficiency anemia that is resolved or adequately treated in the Investigator's opinion is allowed).
    - Chronic renal insufficiency (GFR <60 mL/min/1.73 m^2 for >3 months).
    - Chronic or recurrent illness that can affect hydration or volume status, including conditions associated with decreased nutritional intake or increased volume loss.
15. Known history or presence of malignant disease.
16. Participant with serum 25-hydroxy-vitamin D (25OHD) levels of <30 nmol/L (<12 ng/mL) at Screening Visit will be excluded. Participants with 25OHD levels between 30-50 nmol/L (12-20 ng/mL) can be randomized provided treatment with Vitamin D supplementation is initiated.

17. 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 may present undue risk from receiving trial treatment. This could include family situations, complications or manifestations, or medications that might impact safety or be considered confounding.
18. Sexually active male and female participants and female partners of male participants of childbearing potential not using a highly effective form of contraceptive (see Section 10.4 [Appendix 4]) for the entire trial period and for 90 days after last dose of trial treatment.

5.3. 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 double-blind treatment period, have not permanently discontinued IMP administration, and have completed all assessments at Visit 6 DB.
2. Do not fulfill any of the holding/stopping trial drug conditions or symptoms (see Section 7.1.2).

5.4. LIFESTYLE CONSIDERATIONS

Not applicable for this trial.

5.5. SCREEN FAILURES

A screen failure occurs when a participant whose parent(s)/legal guardian(s) has consented to participate in the clinical trial is not subsequently assigned to trial treatment. A participant is considered enrolled in the trial when the participant receives the first dose. A minimal set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

The following screen failure information is required: age, sex, screen failure reason(s), and any serious adverse event (SAE).

Individuals who are not eligible for participation in this trial due to failure of meeting inclusion or exclusion criteria will be screen failed and may not be rescreened. However, if there is a technical issue with any lab sample or assessment including a lost sample, and the participant did not fail any inclusion or exclusion criteria, the participant can be rescreened pending approval by the Medical Monitor.

6. TRIAL TREATMENTS

Trial treatment is defined as any treatment(s) administered to a clinical trial participant-according to the clinical trial protocol. For this trial IMP is the only trial treatment.

6.1. TRIAL TREATMENTS ADMINISTERED

Table 1: Investigational Medicinal Products

Treatment Label	TransCon CNP	Placebo for TransCon CNP	Sterile Water for Injection (sWFI)
Treatment Name	TransCon CNP 3.9 mg CNP-38/vial[a]	Placebo for TransCon CNP 3.9 mg CNP-38/vial	sWFI prefilled syringe
Treatment Description	Once weekly	Once weekly	Once weekly
Type	Drug	Drug	Reconstitution agent
Dose Formulation	Powder for Injection	Powder for Injection	sWFI
Unit Dose Strength	3.9 mg CNP-38/vial	N/A	N/A
Dosage Level	100 µg CNP/kg	N/A	N/A
Route of Administration	SC injection	SC injection	SC injection
Use	Experimental	Placebo	Reconstitution

[a] The reference to CNP-38 per vial herein, refers to the mass of CNP peptide moiety present in the TransCon CNP within the vial.

The drug product formulation containing TransCon CNP is a lyophilized powder in a single-use vial, i.e., TransCon CNP 3.9 mg CNP-38/vial. Prior to use, the lyophilized powder must be reconstituted with sWFI from a prefilled syringe. After reconstitution, the concentration is 3.6 mg CNP-38/mL.

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.

All injections will be administered by the parent or legal guardian after being trained by the site staff and/or the home health nurse. For trial drug preparation and injection reactions, refer to the Instruction for Use (IFU). Some doses of IMP may be administered by two or more injections depending on the dose volume. There are a total of 8 possible injection sites: 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 eight injection sites. To minimize injection site effects, injection sites should be rotated between injection site locations (incl. left vs. right), for each injection. If multiple injections are required to give one dose, each injection should be administered at different injection areas.

Table 2: Clinical Trial Arms

Arm Title	Active	Placebo
Arm Type	Experimental	Placebo
Arm Description	100 µg/kg of active treatment (TransCon CNP) once weekly	100 µg/kg of placebo treatment (Placebo for TransCon CNP) once weekly
Associated Treatment Labels	For the DB period: TransCon CNP For the OLE period: TransCon CNP	For the DB period: Placebo for TransCon CNP For the OLE period: TransCon CNP

6.2. PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

Instructions for the preparation of trial treatments, including assembly of devices, should be provided to the parents/caregiver (e.g., reconstitution, mixing).

All IMP will be labeled according to Good Manufacturing Practice and local regulatory requirements. The labels are trial-specific, in local language and carry unique identification pack numbers.

Participants will be provided with dosing and storage instructions in the IFU and a Participant Identification Card.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all trial products received, and any discrepancies are reported and resolved before use.

Only participants enrolled in the trial may receive IMP, and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions and with access limited to the investigator and authorized site staff.

An internet-based Interactive Response Technology (IRT) is used to capture IMP inventory and accountability data, including receipt of IMP, assignment of IMP for each participant, return to the site from participants, and return to the contracted parties (or destruction on site only carried out with Sponsor's approval).

The IRT system complies with all applicable regulatory requirements for record keeping and record retention in clinical trials (21 Code of Federal Regulation [CFR] Part 11 and ICH E6 [R2] Good Clinical Practice [GCP]).

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records in the IRT).

No unused or returned IMP must be disposed until reconciliation has been performed by the monitor.

The monitor will ensure products are returned to the depot to be disposed, unless agreed otherwise in the IMP Manual. Further guidance and information for the final disposition of unused IMPs are provided in the IMP Manual.

Direct-to-participant shipments of IMP from investigational sites will be allowed in exceptional cases in which participants might not be able to attend on-site visits and risk continued access to IMP.

Accountability, Storage, and Dispensing

The investigator or authorized staff will be responsible for the administration of IMP at site in accordance with the protocol and applicable laws/regulations.

IMP 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 the Sponsor immediately if IMP has been stored outside the specified conditions on the label.

Investigator will be responsible for documenting accountability and reconciliation of IMP.

Site staff will provide each participant's parent(s)/legal guardian(s) with training on proper storage of IMP at Visit 1 and throughout the trial, as relevant. This training will also include a review of the IFU and on-site administration of the first dose of IMP by the caregiver. A copy of the IFU will be provided to the parent(s)/legal guardian(s) to take home. The parent(s)/legal guardian(s) will also have support available from home health nurses for additional training in administering injections if needed.

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

See IMP Manual and IFU for further details.

Participant Identification Card

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

- Participant number
- Participation status: that he/she is participating in a clinical trial
  - That the trial includes a treatment regimen with TransCon CNP or placebo
  - The name and phone number of the Investigator
  - Name of main Sponsor / clinical research organization (note: as required by local regulations)
- EudraCT number

The participant's parent(s)/legal guardian(s) will be instructed to always carry the card during their child's participation in the trial and asked to return the Participant Identification Card at the end-of-trial visit.

6.3. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Type of Clinical Trial	This is a double-blind, randomized, placebo-controlled trial.
Clinical trial using IRT	All participants will be centrally assigned to randomized trial treatments using an IRT. Before the clinical trial is initiated, the log-in information and directions for the IRT will be provided to relevant site staff at each site. IMP will be dispensed at the clinical trial visits as summarized in the SoA. Returned IMP must not be re-dispensed to the participants.
Blind break (IRT)	This is a double-blind clinical trial in which participants/care providers/investigators/outcomes assessors are blinded to treatment allocation during the double-blind treatment period. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' treatment allocation is warranted. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment for the participant. If a participant's treatment allocation is unblinded, the sponsor will be notified via the IRT. The date and reason that for the unblinding must be recorded by the investigator.

Treatment allocation for any participant may be unblinded if an SAE requires an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4. TRIAL TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive IMP directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

When participants are administered IMP at home by their parent/legal guardian it must be noted in the weekly diary. Compliance with IMP will be assessed at each visit by evaluation of participant diary entries, direct questioning, and accountability of returned used/unused trial products. The treatment compliance must be documented in the source documents and relevant electronic case report (eCRF) forms.

A record of the quantity of TransCon CNP/placebo (randomized period) and TransCon CNP (OLE period) dispensed to each participant must be maintained and reconciled with returned trial treatment and compliance records. Treatment start and stop dates, including dates for treatment delays will also be recorded.

Deviation(s) from the prescribed dosage regimen must be recorded in the eCRF.

6.5. DOSE MODIFICATION

Not applicable for this trial.

6.6. CONTINUED ACCESS TO TRIAL TREATMENT AFTER END OF CLINICAL TRIAL

If a trial participant completes this trial (both Randomized and OLE periods) they will be offered the opportunity to roll over to a long-term extension trial where TransCon CNP will be offered.

6.7. TREATMENT OF OVERDOSE

Overdose will be reported as a Special Situation. For further information on reporting Special Situations, see Section 10.3.4.2.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether trial treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Report as an AE in accordance with Section 8.4 and Section 10.3 [Appendix 3] and document the quantity of the excess dose as well as the duration of the overdose.
- For more information on overdose, also consult the current version of the IB.

6.8. PRIOR AND CONCOMITANT THERAPY

6.8.1. Concomitant Medication

Any medication or vaccine including over-the-counter, non-prescription or prescription medicines, recreational drugs, supplemental oxygen, vitamins, and/or herbal supplements, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication for use
- Dates of administration including start and stop dates
- Dosage information including dose, dose unit, frequency, and route of administration

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Changes in concomitant therapy must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.4

6.8.2. Vaccination

- Participants are encouraged to follow the locally recommended childhood vaccination program according to age during trial participation.
- COVID-19 vaccine is allowed during trial participation.
- If a vaccination is scheduled close to the time of randomization, it should preferably be administered during the screening period to avoid temporary overlap with TEAEs and thereby complicating causality assessment. If possible, it is recommended to allow 48-72 hours after vaccination prior to an IMP administration.

6.8.3. Prohibited Medication

Medication listed in Table 3 are prohibited medication. Prohibited medication must be not used during the trial. Doses referenced in Table 3 should be considered as a guideline and any prescribed or ongoing concomitant treatment with medication listed should be discussed with the medical monitor.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Table 3: Prohibited Medication

Type of Medication	Medication	Wash-out Period
Current use of Oral Corticosteroids	Any anticipated chronic use (defined as more than 4 weeks during participation in the trial.	14 days to accommodate corticosteroids with long half-lives (36-72 hours).
Current use of High dose inhaled corticosteroids (Daily dose above)	• Beclometasone CFC (> 400 µg) • Beclometasone HFA (> 200 µg) • Budesonide DPI (>400 µg) • Budesonide nebulized (>1000 µg) • Ciclesonide (>160 µg) • Fluticasone DPI (>400 µg) • Fluticasone HFA (>500 µg) • Mometasone (>440 µg) • Triamcinolone (>1200 µg)	From initiation of Screening
Prior use of medication intended to affect stature, growth or body proportionality	Including: Human growth hormone CNP	Any prior use

6.8.4. Concomitant Procedure

Any medical and surgical procedures including but not limited to physical therapy, speech therapy, tonsillectomy, insertion of grommets, decompression surgery or other types of procedures that the participant is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Dates of procedure or therapy including start and stop dates
- The reason for procedure conducted

Any device intended to affect stature or body proportionality is prohibited at any time during the trial.

The medical monitor should be contacted if there are questions regarding concomitant or prior procedure.

7. DISCONTINUATION OF TRIAL TREATMENT AND PARTICIPANT WITHDRAWAL

Termination of specific sites or of the clinical trial are detailed in Section 10.1 [Appendix 1].

Efforts must be made to have participants who discontinue trial treatment to continue in the trial. Parent(s)/legal guardian(s) must be educated about the continued scientific importance of their child's data, even if the trial treatment is permanently discontinued. Participants whose parent(s)/legal guardian(s) withdraw(s) consent will be considered as withdrawn from the trial.

7.1. DISCONTINUATION OF TRIAL TREATMENT

A discontinued trial participant refers to a participant who is permanently discontinued from IMP during the DB phase, but agrees to remain in the trial and complete the remaining visits until Visit 6 DB. A participant who is permanently discontinued from IMP during the OLE phase should not attend any additional trial visits and should be withdrawn from the trial.

The investigator or Medical Monitor (and, if needed, with DMC review) may temporarily or permanently discontinue the dosing of IMP to a participant at any time during the trial for safety, behavioral, or compliance reasons.

For participants who discontinue IMP for reasons related to safety, unblinding of the treatment assignment 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. Examples of conditions or symptoms that may warrant discontinuation of IMP at the discretion of the investigator or Medical Monitor include:

1. Severe fracture of long bones or growth plates regardless of causality
2. Evidence of symptomatic persistent hypotension defined as low BP for age and sex lasting over 24 hours not explained by other probable causes

3. Skeletal abnormalities typically not associated with ACH, growth or other concurrent medical conditions, such as
    - Findings from thorough skeletal exam requiring imaging or consultation with orthopedics specialist
    - Clinically relevant findings on radiologic assessments (e.g., joint abnormalities at the elbows, evidence of slipped capital femoral epiphysis)
4. A serious adverse reaction assessed as causally related to CNP by the investigator and/or the sponsor
5. QTcF value > 450 msec, or an extension > 60 msec from baseline in the absence of possible causes other than the trial treatment
6. Diagnosis of heart disease requiring pharmaceutical or surgical intervention to maintain heart function
7. Serious systemic allergic reactions related to CNP
8. Pregnancy
9. Any other situation that warrants temporarily or permanently discontinuing trial treatment at the discretion of the investigator or Medical Monitor

When a trial participant is permanently discontinued from IMP during the DB phase, ET Visit (see Section 1.3.1) should be completed as soon as possible. The participant should be encouraged to remain in the trial and attend all subsequent trial visits up to Visit 6 DB, which will be the End-of-Trial visit.

If a trial participant is permanently discontinued from IMP during the OLE phase, he/she should not continue in the trial. Visit 11 EoT should be completed as soon as possible, and site should attempt completing FU OLE Visit approximately 5 weeks after Visit 11 EoT (see Section 1.3.2).

7.1.1. Rechallenge

If trial treatment is temporarily discontinued due to safety concerns, approval by the Medical Monitor is required prior to resuming the trial treatment.

7.1.2. Stopping Criteria for Clinical Trial

Participant safety, including safety signal detection, will be continuously monitored by the Sponsor.

Stopping criteria for the clinical trial are as follows:

- Any life-threatening immunologic toxicity reactions related to CNP occurring at any time during trial treatment.
- Unexplained death or life-threatening event occurring at any time during trial treatment.

Meeting any of the stopping criteria will result in a halt in further clinical trial enrollment until all reasonable investigations into the cause of death or life-threatening event have been performed.

Further dosing of participants active on trial treatment will be determined after a benefit-risk assessment.

Single case unblinding may be performed for above reviews if necessary and *ad hoc* DMC meetings will be scheduled if needed.

7.2. PARTICIPANT WITHDRAWAL FROM THE CLINICAL TRIAL

- A participant may withdraw from the trial at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety or compliance reasons.
- If a participant is withdrawn from the trial, the site should attempt at having the participant come in for the End-of-Trial visit and, if possible, the FU visit (if participant was on IMP at the time of withdrawal). If withdrawal occurs prior to Visit 6 DB, the EoT and FU DB visits should be performed, as applicable (see Section 1.3.1). If withdrawal occurs after Visit 6 OLE, Visit 11 EoT and FU OLE visits should be performed, as applicable (see Section 1.3.2).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the trial, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

7.3. LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and the family is unable to be contacted by the clinical trial site.

The following actions must be taken if a participant fails to return to the clinic for a required clinical trial visit:

- The site must attempt to contact the participant's parent(s)/legal guardian(s) and reschedule the missed visit as soon as possible, counsel the participant's parent(s)/legal guardian(s) on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the clinical trial.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant's parent(s)/legal guardian(s) (where possible, at least three telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant's parent(s)/legal guardian(s) continue to be unreachable, the participant will be considered to have withdrawn from the clinical trial.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized. Public sources may be searched for vital status information. If vital status is determined as deceased, this

will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. CLINICAL TRIAL ASSESSMENTS AND PROCEDURES

- Clinical trial procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue trial treatment.
- Adherence to the clinical trial requirements, including those specified in the SoA, is essential and required for clinical trial conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Laboratory results that could unblind the clinical trial will not be reported to investigative sites or other blinded personnel until the clinical trial has been unblinded.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Repeat laboratory tests are permitted as long as total blood volume drawn does not exceed the allowed amount.

8.1. SCREENING PROCEDURES

8.1.1. Demographics

Demographics include date of birth, age at screening, biological sex, ethnicity, and race.

8.1.2. Baseline Data on Anthropometric Measurements and ACH-related Complications

Ideally, the participants will roll over from the observational study (ACHieve TCC-NHS-01). Prior to enrollment, participants must have a minimum of 6 months of observational period (collecting baseline data on anthropometric measurements and ACH-related complication assessments) from ACHieve (TCC-NHS-01).

For participants not from ACHieve TCC-NHS-01, a minimum of 6 months historical height/length data, which is confirmed by the medical monitor, is required to be enrolled.

8.1.3. Genetic Confirmation

If documented evidence of genetic confirmation of the pathologic variant in FGFR3 gene is unavailable, a blood sample will be collected and used to identify the most common FGFR3 variants. The test may be performed at any time after signing the consent and before Visit 1.

The central laboratory 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 per

investigator at outside laboratory as indicated. Other pathologic variants may be used as genetic confirmation of ACH, pending review of Medical Monitor (refer to Section 10.5 [Appendix 5]).

8.1.4. Medical History

The site must ask participants about and document the presence of or past medical history of conditions frequently associated with Achondroplasia including, but not limited to:

- Spinal Cord Abnormalities
  - Foramen magnum stenosis, cervical spinal stenosis, lumbar spinal stenosis, vertebral foraminal stenosis
- Spine Abnormalities
  - Scoliosis, lordosis, kyphosis, kyphoscoliosis
- Musculoskeletal Manifestations
  - Genu varum, genu valgum, tibial bowing, bone fracture, pain in joints or extremities
  - Decreased joint range of motion
- Ear Disorders
  - Acute otitis media, chronic otitis media, deafness
- Breathing-related sleep disorder
  - Adenoidal/tonsillar hypertrophy, obstructive sleep apnea, central sleep apnea, snoring, apnea hypopnea index (if available)
- Developmental Delay or Neuro Deficit
  - Gross motor, fine motor, speech delay, hypotonia, clonus, or balance issues
- Macrocephaly
  - Hydrocephalus, other
- Low Stamina

8.1.5. Historical Procedures

The site must ask participants about and document the past surgical history or procedures frequently associated with Achondroplasia manifestations including, but not limited to:

- Spinal Cord Abnormalities
  - Cervicomedullary decompression, posterior fossa decompression, spinal decompression, spinal laminectomy,
- Spine Abnormalities
  - Spinal rod placement
- Musculoskeletal Manifestations
  - 8-plate hemiepiphysiodesis surgery – date inserted, and date removed

- Ear Disorders
  - Myringotomy, tympanostomy tubes
  - Hearing aid use
- Breathing-related sleep disorder
  - Adenoidectomy or tonsillectomy, use of BiPap or CPAP machine
- Developmental Delay or Neuro Deficit
  - Physiotherapy or other therapies for developmental delay
- Macrocephaly
  - Ventriculoperitoneal shunt

8.2. EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3). Some assessments are both efficacy and safety, and these assessments will only be listed in Section 8.3.

8.2.1. Anthropometric Measurements

Anthropometric measurements, including head circumference, standing height, upper body segment length (sitting height), lower body segment length, arm span, upper leg length, lower leg length, upper arm length, lower arm length, and body weight should be assessed according to the SoAs (see Section 1.3) following the procedures described in the Anthropometric Parameter Manual (Advancing Trial Outcome Measure (ATOM) manual).

The measurements must be taken by trial staff who are responsible for anthropometry in the trial as documented on the site delegation log. All trial staff involved in anthropometry measurements must have documented training in the ATOM manual.

All measurements must be conducted by an examiner and a recorder as described in the ATOM.

A wall-mounted stadiometer must be used for standing and sitting height measurements.

Standardization/calibration of all equipment (incl. equipment supplied by Sponsor) must be performed in accordance with the ATOM manual.

Triplicate measurements must be performed and repeated for relevant assessments until all three measurements are within 0.5 cm.

Refer to the ATOM manual for detailed instructions.

8.2.2. Clinical Outcomes Assessments

Observer (parent/caregiver) reported outcome measures (ObsRO), a patient reported outcome measure (PRO) and clinician reported outcome measures (ClinRO) will be utilized in this trial. In countries where the AEM and other measures are available, all participants will be expected to complete the measures.

Note: All PROs must be completed by the parents/caregiver without assistance and prior to conducting any clinical assessments.

8.2.2.1. Achondroplasia Experience Measures

The AEMs are three disease-specific COAs that were developed and are undergoing validation by the Sponsor to assess relevant observer reported symptoms, disease impacts, and the impact on parents of having a child with ACH.

- ACEM-OSM is a parent/caregiver ObsRO with captures the observed physical symptoms in a child with ACH.

  The Caregiver Guidance document for the ACEM–OSM is intended to assist caregivers/parents in understanding and reporting on the 8 signs/symptoms of ACH in children that are included in the measure.

  To ensure caregiver/parent understanding and to train caregivers to report on the sign/symptom items in the measure accurately, please review the sign/symptom table in the Caregiver Guidance document with caregivers at the screening visit (before they complete the ACEM–OSM measure for the first time at Baseline visit). The table lists the 8 signs/symptoms included in the measure and provides a lay definition for each sign/symptom and examples of observable events or behaviors that caregivers might see or hear about their child. If needed to improve caregiver understanding about these signs and symptoms, you can expand on these definitions and examples. Please do not show the actual ACEM-OSM to the caregiver or give them a copy of the measure. After reviewing the table, please be sure to ask caregivers if they have any questions or are unclear about any of the signs/symptoms. Please give caregivers a paper copy of the Caregiver Guidance document to take with them for future reference.

- ACEM-Impact is an ObsRO measure that captures the impacts of ACH on children's functioning/daily life, school participation, emotional well-being, social well-being, and need for adaptations/adaptive devices.

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[redacted]

8.2.2.8. Phone Exit Interviews

Phone interviews after the Blinded Treatment Period, in selected English-speaking countries/sites are used to assess the participant's experience in the trial in their own words and supply a qualitative view to complement the quantitative COAs. The exit interviews will collect information from parents on the participant's evaluation of treatment received, and the participant's experience of taking part in the clinical trial, and aid in the interpretation of changes in clinical and ObsRO scores, including the ACEM-OSM and ACEM-Impact measures, to determine what constitutes meaningful change for patients with ACH.

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[redacted]

8.3. SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA. Some assessments are both efficacy and safety, and these assessments will only be listed in this section.

8.3.1. Head Circumference

Assessment described under Section 8.2.1.

8.3.2. Physical Examinations

Full and limited, symptom directed physical examinations will be performed at the designated trial visits as specified in the SoA (see Section 1.3).

8.3.2.1. Full Physical Examination

Full physical examination includes assessments of all major body systems including:

- General appearance
- HEENT (head, eyes, ears, nose, and throat)
- Neck (including thyroid)
- Lung/pulmonary
- Chest
- Cardiovascular
- Abdomen
- Back
- Genito-urinary
- Neurological
- Extremities

- Skin

Abnormal findings assessed by the investigator as clinically significant worsening from baseline must be recorded as an AE. Clinically significant baseline findings must be captured in medical history.

8.3.2.2. Limited, Symptom-Directed Physical Examination

Limited, symptom-directed physical examination as needed at the discretion of the investigator should be performed to provide appropriate medical care to the participants.

Examination of all systems are not required for limited symptom-directed physical examination and should be performed at the discretion of the investigator to verify no clinically relevant changes have occurred since the Screening Visit.

Abnormal findings assessed by the investigator as clinically significant worsening from baseline must be recorded as AE. Clinically significant baseline findings must be captured in medical history.

8.3.2.3. Skeletal Physical Examination

A thorough skeletal exam will be performed at every visit by palpating the bone structure, epiphyses and joints for tenderness and mobility and any other abnormal changes. Special attention will be paid to the back exam to assess for abnormalities of spine curvature, and 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.

Abnormal findings assessed by the investigator as clinically significant worsening from baseline must be recorded as AE. Clinically significant baseline findings must be captured in medical history. If changes are noted further evaluation will be required as clinically indicated, including imaging and/or orthopedic consultation. Such findings should be assessed for whether they qualify as AEs as defined in Section 10.3 [Appendix 3].

8.3.2.4. Injection Site Findings

All visits (excluding Screening) will include a visual inspection of injection sites independent of whether a full physical examination or a limited, symptom-directed examination is performed. At Visit 1, visual inspection of the injection site must be performed prior to injection of IMP and approximately 2 hours after injection of IMP.

Any identified injection site finding fulfilling the definition of an AE per investigator judgment will be recorded as described in Section 10.3.3.3.3 [Appendix 3]. CCI [redacted] CCI A safety report (see Section 10.3.4.2.1) must further be submitted for injection site finding AEs with a severity rating of grade 2 or higher. Severity ratings is defined in Section 10.3.2.2.1.

Parents/legal guardian should assess the injection sites after each injection performed at home and report the assessment in the diary.

8.3.3. Treatment acceptability assessment

The investigator will ask the parent/caregiver about their and their child's overall acceptance of the treatment. The assessment will be performed at the designated trial visits specified in the SoA (see Section 1.3).

8.3.4. Vital Signs

Vital signs including body temperature, BP (systolic/diastolic) and HR will be assessed at all visits.

Vital signs are assessed at Visit 1 (pre-dose and 2-hours post-dose), at Visit 3 (24-72 hours post-dose), at Visit 6 DB, and at Visit 6 OLE (2-hours post-dose). At other visits, the assessment can be done any time within the allowed visit window (see Section 1.3). At any time, should symptoms of hypotension (i.e., dizziness, lightheadedness, headache, blurry vision, loss of consciousness) occur, additional measurements of vital signs (BP, HR) should be recorded as an unscheduled visit.

Orthostatic assessments will be recorded at Visit 1 (pre-dose as well as 1- and 2-hours post-dose) and at Visit 6 DB and Visit 6 OLE (1- and 2-hours post-dose), for participants who roll over to the OLE period. Orthostatic assessments include BP and HR measurements preceded by at least 5 minutes in supine position) and again within 3 minutes of standing. Assessments will be made with a completely automated device. Manual techniques will be used only if an automated device is not available. The participant must be in a quiet setting without distractions (e.g., television, cell phones) for all vital sign assessments.

8.3.5. Electrocardiograms

Single recording 12-lead ECG will be obtained after at least 5 min of supine positioning, using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals. Recordings will be taken at Visit 1 (pre-dose), Visit 3 (24-72 hours post-dose) and Visit 4 (pre-dose). At other visits, the assessment can be done any time within the allowed visit window (see Section 1.3).

ECGs will be read centrally.

If adequate tracing is unable to be collected at the site, external ECGs may be allowed for safety monitoring.

The investigator must review the ECG tracings, document this review with signature and date. The ECG tracings must be filed with the source documents. Abnormal findings assessed by the investigator as clinically significant worsening from baseline must be recorded as AE. Clinically significant baseline findings must be captured in medical history.

8.3.6. Radiographic Assessments

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.

Abnormal findings assessed by the investigator as clinically significant worsening from baseline must be recorded as AE. Clinically significant baseline findings must be captured in medical history. Refer to the radiographic assessment manual for details of the procedures for the

radiographic assessment of bone. All endpoints related to radiographic assessments will be read centrally.

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 3.2 mSv/participant.

Double-blind Period:

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Open-Label Extension Period:

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8.3.6.1. X-ray for Bone Age and Epiphyseal Changes

X-ray imaging of the left hand and wrist will be collected to assess bone age and epiphyseal changes. Right hand and wrist may be used if a medical reason prohibits use of left hand.

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8.3.7. Clinical Safety Laboratory Tests Including Urinalysis

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. For more information on blood volume drawn at each visit and throughout the trial, please see laboratory manual.

This 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 the trial, the volume of blood to be drawn at each trial visit will be restricted based on the weight of the child (measured 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 (European Commission 2017).

See Section 10.2 [Appendix 2] for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

Blood samples for clinical laboratory tests for standard panel of blood biochemistry and hematology will be drawn will be drawn at all in-clinic visits except the FU DB and FU OLE visits. Additional blood samples for lipids, 25(OH) Vitamin D, and TSH will be drawn and urine for urinalysis will be collected at selected visits according to the SoA (see Section 1.3). Blood sample for HbA1c is drawn at Screening only.

Abnormal findings assessed by the investigator as clinically significant worsening from baseline must be recorded as AE. Clinically significant baseline findings must be captured in medical history. The laboratory results must be retained with source documents.

8.3.8. Nutrition Assessment

In the case of a participant not growing well (per judgement of the investigator), other etiologies and evaluations should be considered including a referral for a nutritional assessment with discussion with the Medical Monitor. Participant’s parent(s) or legal guardian(s) may be asked to note and document their child’s dietary intake in their trial diary to assess the effect of diet on participant growth.

8.3.9. Pregnancy Testing

At all in-clinic visits throughout the trial (incl. OLE), the Investigator should ascertain an individual’s risk for becoming pregnant or fathering a child and pregnancy prevention counseling and pregnancy testing (urinary hCG test for females of childbearing potential only) should be provided as appropriate and can be tailored per the Investigator’s judgement based on maturity and cultural norms. Refer to Section 10.4 [Appendix 4] for contraception guidance.

8.4. ADVERSE EVENTS SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of AEs, SAEs, Adverse Events of Special Interest (AESI) and Special Situation Reports (SSRs) can be found in Section 10.3 [Appendix 3].

AEs, SAEs, AESI or SSRs will be reported by the participant's parents (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator or qualified designee is responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, AESIs or SSR, see Section 10.3 [Appendix 3] and remain responsible for following up all AEs including AEs that are serious, or considered related to the trial treatment or trial procedures, or that caused the participant to discontinue the trial treatment or are AESIs or SSRs, see Section 7.

Clinical laboratory, vital sign, ECG, or physical examination abnormalities will only be reported as AEs if they are deemed clinically significant by the investigator (example, associated with signs and symptoms, require treatment, or require follow-up).

The method of recording, evaluating, and assessing causality of AEs and SAEs, special situations and the procedures for completing and transmitting SAE reports are provided in Section 10.3 [Appendix 3].

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs that occur from the signing of the ICF until the initiation of trial treatment will be collected if deemed related to a trial procedure.

All AEs, AESIs, SSRs and SAEs will be collected from the start of trial treatment until the last trial visit at the timepoints specified in the SoA (Section 1.3).

In case of treatment discontinuation, AEs and SAEs will be collected until 30 days after the last dose of trial treatment.

All SAEs, AESIs, and SSRs will be reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of awareness, as indicated in Section 10.3 [Appendix 3]. The investigator will submit any follow up SAE, AESI, or SSR data to the Sponsor within 24 hours of it being available. The time period for collecting AEs, AESIs, SAEs, and special situations information is provided in Section 10.3 [Appendix 3]

Investigators are not obligated to actively seek information on AEs or SAEs and special situations after conclusion of the clinical trial participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the clinical trial, and he/she considers the event to be reasonably related to the trial treatment or clinical trial participation, the investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

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, ear infections, sleep apnea, pain, 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
- For each reported AE, the investigator must evaluate if the AE is an ACH complication or manifestation.

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 trial visit or if an unscheduled visit must be scheduled.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All ongoing AEs (irrespective of causality)**;** and SAEs, AESIs or SSRs that are not related to the trial treatment will be followed until resolution or return to baseline status, the event is deemed stable or commensurate with ongoing disease process, the participant is lost to follow-up (as defined in Section 7.3), participant death, or until the last trial visit (whichever is earlier). If the AE has not completely resolved by last follow-up visit, the final outcome of these ongoing events will be captured as “not recovered/not resolved” or “recovering/resolving”, whichever is applicable.

All ongoing SAEs and AESIs that are related to trial treatment will be followed until resolution or return to baseline status, the event is deemed stable or commensurate with ongoing disease process, the event is otherwise explained, participant is lost to follow-up (as defined in Section 7.3), participant completed the trial, or participant death. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

Every effort should be made to follow all SAEs considered to be related to trial drug or trial related procedure until a final outcome can be reported. Medical judgement should be used by the investigator to determine if attempts should be made to collect additional information for SAEs outside of regular trial visits.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a trial treatment under clinical investigation are met.
- The Sponsor determines expectedness of the event.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it in the Investigator Site File and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of trial treatment and until 90 days after the last dose of trial treatment.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.

Any posttrial pregnancy-related SAE considered reasonably related to the trial treatment by the investigator will be reported to the Sponsor as described in Section 8.4. While the investigator is not obligated to actively seek this information in former clinical trial participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the clinical trial will discontinue trial treatment or be withdrawn from the clinical trial per decision of the Medical Monitor.

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8.5. PHARMACOKINETICS

Blood samples will be collected for pharmacokinetic assessment of TransCon CNP in accordance with the SoA (Section 1.3) and the laboratory manual. Total CNP, free CNP and mPEG concentrations will be quantified at special laboratories using validated analytical methods.

At Visit 3, blood must be drawn 24-72 hours post-dose. At Visit 4 and Visit 6 DB, blood must be drawn pre-dose (trough), and IMP administration cannot take place within 6 days prior to these visits. At other visits, blood can be drawn at any time within the allowed visit window (see Section 1.3).

Samples from Placebo participants will not be analyzed.

The actual date and time (24-hour clock time) of each sample will be recorded.

Pharmacokinetics results that unblind the trial will not be reported to investigative sites or blinded personnel until after the trial results have been reported.

For retention and use of residual pharmacokinetic samples, refer to Section 10.6 [Appendix 6].

8.6. GENETICS

Refer to Section 8.1.3 and Section 10.5 [Appendix 5].

8.7. BIOMARKERS

Blood samples will be collected to evaluate exploratory biomarkers of pharmacodynamic response to treatment with TransCon CNP [redacted].

- Samples will be collected as detailed in the SoA (Section 1.3) and the laboratory manual and analyzed at special laboratories.
- Biomarker information that unblind the trial will not be reported to investigative sites or blinded personnel.
- For retention and use of residual biomarker samples, refer to Section 10.6 [Appendix 6].

8.7.1. Pharmacogenomics

Not applicable for this trial.

8.8. IMMUNOGENICITY ASSESSMENTS

- Blood samples collected to assess antibodies against TransCon CNP will be analyzed at special laboratories.
- Blood samples will be collected as detailed in the SoA (Section 1.3) and the laboratory manual and analyzed at special laboratories.
- Antibody information that unblind the trial will not be reported to investigative sites or blinded personnel.
- Samples may be used for additional characterization of anti-drug antibody responses.
- Participants that show a treatment induced anti-TransCon CNP antibody response at the last scheduled visit, should be followed after end of treatment until antibodies can no longer be detected or have a sustained level.
- If a participant experiences a suspected anaphylactic reaction (excluding anaphylactic reactions due to confirmed exposure to an allergen known to be a trigger for an individual participant), blood should be drawn as soon as possible (ideally within 48 hours) for tryptase and total immunoglobulin E (IgE) analyses. The tryptase and IgE should be analyzed at a local laboratory. The participant should also be further evaluated (by the investigator and/or an allergist or similar specialist) to confirm/refute an anaphylactic reaction through a thorough history, with consideration given to interval testing of tryptase, total IgE, and a re-challenge with trial treatment.
- For retention and use of residual antibody samples, refer to Section 10.6 [Appendix 6].

8.9. MEDICAL RESOURCE UTILIZATION

[redacted] will be collected through a [redacted] Questionnaire that will be administered to parent/caregivers. The [redacted] questionnaire will document any healthcare provider visits, hospitalizations, emergency department visits, medical testing, and surgical procedures that the trial participants may have outside of trial visits or trial-related procedures.

8.10. WEEKLY DIARY

Parents or legal guardians are trained on the weekly diary during Visit 1 and instructed to fill in the diary after each injection for trial staff review as part of concomitant drug and non-drug therapy review, adverse event review and trial treatment compliance review. Investigator or designee will be responsible for identifying any adverse events from the diary and report them to the Sponsor.

Parents or legal guardians will be required to complete a weekly diary to capture the following:

- Trial treatment, starting at Visit 1 (dose, administration date and time, injection location, and injection site findings).
- Changes to concomitant medications and concomitant procedures.
- Changes to the participant's health or well-being, including any procedures, emergency room visits, and hospitalizations.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more detailed description of the statistical analyses described in this section. 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.

9.1. STATISTICAL HYPOTHESES

The following hypothesis corresponding to the primary efficacy endpoint are as follows:

- H_0: Difference in AGV as assessed at Week 52 between TransCon CNP treatment group and the placebo group = 0
- H_1: Difference in AGV as assessed at Week 52 between TransCon CNP treatment group and the placebo group ≠ 0

9.2. ANALYSIS SETS

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Safety Analysis Set	• All randomized participants who have received at least one dose of IMP. Participants will be analyzed according to the treatment they actually received.
Full Analysis Set	• All randomized participants who have received at least one dose of IMP and have a non-missing baseline height as well as at least one post-baseline height measurement. Participants will be included in the analyses according to the planned treatment.

In general, the full analysis set is used to analyze endpoints related to the efficacy objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety.

9.3. STATISTICAL ANALYSES

9.3.1. General Considerations

In general, analyses will be done by treatment arms and overall if applicable. 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).

9.3.2. Primary Endpoint/Estimand Analysis

For the primary efficacy endpoint, the primary analysis is Analysis of Covariance (ANCOVA) model. Baseline factors will be included in the model: treatment group, baseline status of stature, stratified randomization categories.

The definition of estimand for primary analysis is as follows:

- **Treatment Condition**: The effect of treatment with TransCon CNP versus the effect of treatment with placebo, regardless of adherence to IMP.
- **Population**: The target population comprises children with ACH and who meet the inclusion and exclusion criteria as specified in Section 5.1 and Section 5.2. The analysis population is the Full Analysis Set as defined in Section 9.2.
- **Endpoint**: AGV as assessed at week 52.
- **Remaining intercurrent events**: If a participant withdraws from the trial drug for any reason other than growth related surgical intervention but continues additional trial follow up, a treatment policy strategy will be used. If a participant withdraws from the trial and declines further follow up, a hypothetical strategy will be used. In case any participant receives surgical intervention intended to affect stature, growth, or body proportionality, the participant will be withdrawn from the trial and a hypothetical strategy will be used for cases like this.

Population-level summary: Least square mean difference between treatments (TransCon CNP and placebo) in AGV assessed at Week 52.

9.3.3. Secondary Endpoint Analysis

For the secondary efficacy endpoint as defined in Section 3, the analysis method used for the primary endpoint will be applied. Similar ANCOVA models will also be applied with corresponding baseline value as a covariate.

9.3.4. Other Endpoint Analysis

Summary statistics will be provided for other endpoints. Exploratory analysis may be performed as appropriate, and details will be provided in the SAP.

9.3.5. Safety Analyses

Analyses on safety endpoints are mainly descriptive and will include the incidence of adverse events, laboratory parameters, vital signs, radiographic findings, and 12-lead ECG. Abnormal findings of laboratory and physical examination will be listed as appropriate.

9.3.6. Pharmacokinetic and/or Pharmacodynamic Modelling

Data from this trial may be included in population pharmacokinetic and/or pharmacodynamic modelling analyses, either alone or as part of meta-analyses.

The analyses will be further detailed in a modelling analysis plan and reported separately, outside of the clinical study report (CSR).

9.4. PLANNED ANALYSIS

Planned analysis will include the following:

- DMC analysis: Summary analysis for DMC meetings is planned to monitor safety (the analysis scope and frequency will be specified in the DMC charter).
- Primary analysis: The primary analysis will be performed after all participants have completed or withdrawn from the Randomized Period and the clinical trial 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 trial and the clinical trial database has been locked.

9.4.1. Multiplicity Adjustment

The statistical comparisons for the primary efficacy endpoint and the secondary endpoints as specified in Section 3 will be carried out using a multiple testing procedure based on a graphical testing approach (Bretz 2009).

The graphical procedure is defined as follows: Initially the hypotheses (H_1 to H_7) will be tested at its local significance level α_i.

These significance levels, α_i (for $i = 1, \ldots, 7$), are initially defined to sum up to a two-sided $\alpha = 0.05$.

If a hypothesis can be rejected, its α level will be reallocated to one of the other hypotheses according to a pre-specified graph. The reallocation weights will be updated in the reduced graph and the testing steps will be repeated for the remaining, nonrejected hypotheses with the updated local significance levels. This possibly leads to further rejected null hypotheses with associated reallocation of the local α levels. The procedure is repeated until no further hypotheses can be rejected.

The graphocal testing approach implemented in this study will initially test AGV, Height Z-score, and TLK ACH-specific Z-score using a sequential strategy. Other secondary endpoints will be subsequently tested leveraging alpha splitting testing, and alpha reccling strategies.

Further details will be provided in the SAP.

9.5. SAMPLE SIZE DETERMINATION

A sample size of 52 in TransCon CNP treatment group and 26 in the placebo group will provide approximately 90% power to detect a treatment difference of AGV 1.2 cm/year at a 2-sided significance level of 0.05, assuming the SD is 1.5 cm/year.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: REGULATORY, ETHICAL, AND CLINICAL TRIAL OVERSIGHT CONSIDERATIONS

10.1.1. Regulatory and Ethical Considerations

- This clinical trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, ICF, investigator's brochure, IFU, and other relevant documents including participant-facing documents (e.g., advertisements, diary, and PROs) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the clinical trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the clinical trial design, except for changes necessary to eliminate an immediate hazard to clinical trial participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to clinical trial participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the clinical trial to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the clinical trial at the site and adherence to requirements of 21 CFR (if applicable), ICH guidelines, the IRB/IEC, European Directive 2001/20/EC for clinical trials (if applicable), European Regulation 536/2014 for clinical trials (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
  - Promptly report any suspected serious breaches to Sponsor through the contact information provided by Sponsor.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the clinical trial and for 1 year after completion of the clinical trial.

10.1.3. Informed Consent Process

- The investigator or his/her authorized designee will explain the nature of the clinical trial, including the risks and benefits, to the participant and his/her parent(s)/legally authorized representative(s) and answer all questions regarding the clinical trial. The participant should receive information in a language which is easily understood by him/her.
- Potential participants and their parent(s)/legally authorized representative(s) must be informed that their participation is voluntary. They will be required to sign and date a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or clinical trial site.
- No informed consent, whether oral or written, may include any exculpatory language through which the participant and their parent(s)/legally authorized representative(s) is made to waive or appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the Sponsor, the institution, or its agents from liability for negligence.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the clinical trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also date and sign the ICF.
- Participants must be consented/reconsented to the most current version of the ICF(s), as applicable, during their participation in the clinical trial.
- A copy of the ICF(s) must be provided to the participant's parent(s)/legally authorized representative(s).
- The participant and his/her parent(s)/legally authorized representative(s) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial.
- For retention and usage of human bio samples, refer to Section 10.6 [Appendix 6].

10.1.4. Recruitment Strategy

Participants enrolled in this trial will mainly be recruited from the ACHieve TCC-NHS-01 observational study with at least 6 months of baseline data. All clinical sites recruiting participants for this trial are already participating in the ACHieve TCC-NHS-01 study.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable must not be transferred.
- The participant's families must be informed that the participants personal trial-related data will be used by the Sponsor in accordance with local data protection law.

- The participant and family must be informed that the participant's medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and clinical trial sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Investigator must promptly report to the Sponsor any suspected data breaches relevant to the personal trial-related data the Sponsor holds about the participant and where appropriate also inform local data protection authorities.
- Investigator must promptly report to the Sponsor any participant's request to know what personal trial-related data the Sponsor holds about the participant.

10.1.6. Committees Structure

10.1.6.1. Sponsor Safety Monitoring

Participant's safety will be continuously summarized and reviewed by the Clinical Development team including the Medical Monitor, and representatives from the Global Pharmacovigilance team.

10.1.6.2. TransCon CNP Data Monitoring Committee

An independent TransCon CNP DMC has been established for this trial to monitor the safety data. The DMC will review unblinded data from both the randomized and OLE periods. The details of the frequency and format of the DMC meetings, membership, objectives, and responsibilities are described in the DMC Charter.

10.1.7. Dissemination of Clinical Trial Data

The data and information collected during this trial will be reported in a CSR in accordance with ICH E3. A signatory investigator will review and sign the CSR.

Trial information will be disclosed at clinicaltrials.gov, EudraCT and, if applicable, also on national or regional trial registries. It will be disclosed according to applicable requirements, relevant recommendations, or regulations, such as the Declaration of Helsinki (WMA 2013), the International Committee of Medical Journal Editors (ICMJE) (De Angelis 2004), the Food and Drug Administration Amendment Act (FDA 2016), European Commission Requirements (EC 2006) and in accordance with Ascendis Pharma commitment to clinical transparency. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

Disclosure of CSRs, periodic safety reports, and clinical trial summary reports after review by regulatory authorities. This includes access to CSRs from studies with negative outcomes and from terminated development programs.

The posting of company-sponsored trial information and tabular trial results on the US National Institutes of Health's website www.clinicaltrials.gov and other publicly accessible sites.

Publication planning and other activities related to nonpromotional, peer-reviewed publications, to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company. The granting of access to analyzable datasets from clinical studies through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party.

10.1.8. Data Quality Assurance

- All participant data relating to the analysis of the clinical trial will be recorded on eCRFs and printed case report form (CRF)s (i.e., SAE form) or transmitted to the Sponsor electronically. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided.
- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents, including those in electronic health records.
- Monitoring details describing strategy, including definition of clinical trial critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plans.
- The Sponsor is responsible for the data management of this clinical trial, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g. contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this clinical trial must be retained by the investigator for 25 years after clinical trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the clinical trial. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the source data agreement.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring activities to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the clinical trial is being conducted in accordance with the currently approved protocol and any other clinical trial agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Clinical Trial and Site Start and Closure

10.1.10.1. First Act of Recruitment

The first screening visit of the first patient will be defined as the clinical trial start date.

10.1.10.2. Clinical Trial/Site Termination

The Sponsor reserves the right to close the clinical trial site or terminate the clinical trial at any time for any reason at the sole discretion of the Sponsor. Clinical trial sites will be closed upon clinical trial completion. A clinical trial site is considered closed when all required documents and clinical trial supplies have been collected and a clinical trial site closure visit has been performed.

The investigator may initiate clinical trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a clinical trial site by the Sponsor or investigator may include but are not limited to:

For clinical trial termination:

- Discontinuation of further trial treatment development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the clinical trial is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the clinical trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- The results of this clinical trial may be published or presented at scientific meetings in accordance with the terms and conditions of the clinical trial agreement.

- The Sponsor will comply with the requirements for publication of clinical trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. APPENDIX 2: CLINICAL LABORATORY TESTS

- The laboratory tests detailed in Table 4, Table 5 and Table 6 will be performed by the central or other specialized laboratories.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either trial treatment administration and/or response evaluation. If the local laboratory results are used to make either a trial related decision or response evaluation, the results must be recorded.
- All laboratory tests or evaluations for safety described in this protocol will be conducted in accordance with quality standards as described in the standard operating procedures of the central or specialized laboratories. The central laboratory must provide a list of reference ranges for applicable safety analyses before the trial is initiated. The methods employed by each assay should be available on request. The laboratories may be audited by the Sponsor or by competent authorities. The details regarding laboratory sample collection and quality standards are included in the laboratory manuals.
- COVID-19 test may be performed at any time during the trial as required by local requirements or deemed necessary by the investigator or by sponsor. Laboratory results will not be transferred to the trial database, but COVID-19 infection should be registered as concomitant illness or AEs.
- The investigator must keep an overview, e.g., a log of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g., a log of laboratory samples stored at site.
- Investigators must document their review of all laboratory results for concomitant illnesses and AEs by signing and dating each laboratory report.

Table 4: Protocol-required Eligibility Laboratory Tests

Laboratory Tests	Parameters
Genetic confirmation of ACH tests	Documented results of the FGFR3 pathologic variant for ACH through a test for the G380R substitution in FGFR3, i.e., G to A transition or G to C transversion at nucleotide 1138 of FGFR3 gene
Other	25(OH) Vitamin D, TSH, HbA1c

Table 5: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	Hemoglobin Hematocrit Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential: – Leukocytes – Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
Biochemistry[a]	Alanine aminotransferase (ALT)/ glutamic-pyruvic transaminase (GPT) Albumin Alkaline phosphatase[b] (ALP) Aspartate aminotransferase (AST)/ glutamic-oxaloacetic transaminase (GOT) Bicarbonate Bilirubin (total) Bilirubin (direct) Blood urea nitrogen (BUN) Calcium (total) Chloride Creatinine Creatine phosphokinase Gamma glutamyl transferase (GGT) Highly sensitive C-reactive protein (hsCRP) Lactate dehydrogenase (LDH) Magnesium Phosphate Glucose (non-fasting) Protein (total) Potassium Sodium Uric acid
Lipid panel	Total cholesterol High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Triglycerides

Laboratory Tests	Parameters
Hormones	25(OH) Vitamin D Thyroid Stimulating Hormone (TSH)
Glucose metabolism	HbA1c[c]
Urinalysis	pH, glucose, protein, billirubin, urobillinogen, nitrite, erythrocytes, ketones, leukocyte, and bacteria by dipstick
Pregnancy test[d]	Urine human chorionic gonadotropin (hCG) pregnancy test

NOTES:
[a] All events of ALT/AST ≥5 × upper limit of normal (ULN), or ALP ≥2 × ULN, or ALT/AST ≥3 × ULN and total bilirubin ≥2 × ULN (> 35% direct bilirubin) must be reported to the sponsor in an expedited manner.
[b] If alkaline phosphatase is elevated, consider fractionating.
[c] Analyzed at screening only
[d] Applicable for females of childbearing potential only.

Table 6: Protocol-required Specialty Laboratory Tests

Laboratory Tests	Parameters
Biomarkers (blood)	Exploratory biomarkers of pharmacodynamic response to treatment
Immunogenicity assessments	Anti-drug antibodies
Pharmacokinetic assessments	Free CNP Total CNP mPEG

10.3. APPENDIX 3: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1. Definitions

10.3.1.1. Adverse Events Definition

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An Adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to that product.
- AEs not previously observed in the participant that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with ACH that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated treatments (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of trial treatment associated with medication washout, no treatment run-in, or other protocol-mandated treatment.
- 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.

10.3.1.2. Serious Adverse Events Definition

An SAE is any untoward medical occurrence that, at any dose, that meets any of the following criteria:

- 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
- 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 trial treatment.
- 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 treatment 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 (according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 10.3.2.2.1); 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 10.3.4.2 for reporting instructions).

10.3.1.3. Adverse Events of Special Interest

AESIs are a subset of events that are of scientific and potential medical concern specific to the product, for which ongoing monitoring and reported by the Investigator within 24 hours to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g. Regulatory Authorities) may also be warranted.

10.3.1.4. Special Situation Report 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
- Medication error

The Medical Monitor will review all safety information on an ongoing basis. The safety data will also be reviewed periodically by Medical Monitor/ an Independent Safety Committee (ISC)/Safety Review Board in accordance with its governing charter.

10.3.1.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction (SUSAR) is used to refer to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and/or trial investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the trial treatment. Reports of these reactions are subject to expedited submission to health authorities.

10.3.2. 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 clinical trial are collected and reported to Sponsor, in accordance with FDA CFR 312.32 (IND Safety Reports) and ICH E6.

10.3.2.1. Adverse Event Reporting Period

The Adverse Event Reporting Period is the period requiring reporting of AEs and SAEs for any participants exposed to IMP product and/or any clinical trial related procedures.

Reporting period begins from the time when the informed consent is obtained and ends 30 days following the last administration of trial treatment or clinical trial discontinuation/ termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior trial treatment.

If the eCRF system is not available, the investigator should report these events directly to the Sponsor outlined in Section 10.3.4.2.

10.3.2.2. Severity, Causality, and Outcome Assessment

10.3.2.2.1. Severity Rating

The adverse event severity is determined by the investigator. The below grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or treatment not indicated
2	Moderate; minimal, local, or non-invasive treatment indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b, c]
4	Life-threatening consequences or urgent treatment indicated[d]
5	Death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm:

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 10.3.4.2 for reporting instructions), per the definition of serious adverse event in Section 10.3.1.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 10.3.4.2 for reporting instructions), per the definition of serious adverse event in Section 10.3.1.2.

10.3.2.2.2. Causality Rating

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

Each reported AE, AESI or SAE must be described by its duration (i.e., start and end dates), seriousness criteria if applicable, suspected relationship to the [trial treatment] (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 trial treatment. 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 trial treatment or with similar treatments. And/or the AE abates or resolves upon discontinuation of the trial treatment or dose reduction and, if applicable, reappears upon re-challenge.
- **Not Related (No)** Evidence exists that the AE has an etiology other than the trial treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication). The AE has no plausible temporal relationship to trial treatment administration (e.g., cancer diagnosed 2 days after first dose of trial treatment).

Expected adverse events are those adverse events that are listed or characterized in the Reference Safety Section of the current Investigators Brochure (IB).

Unexpected adverse events are those not listed in the Reference Safety Section of the current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the current IB. For example, under this definition, hepatic necrosis would be unexpected if the IB only referred to elevated hepatic enzymes or hepatitis.

10.3.2.2.3. Outcome Assessment

Information will be elicited at all participant evaluation time points to determine outcome for all AEs at regular trial visits until AEs have either resolved, participants have returned to their baseline status, or participants are deemed stable or commensurate with ongoing disease processes or participant is lost to follow up or participant death. Additional details are provided in Section 8.4.3.

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 consequent 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).

10.3.3. Procedures for Eliciting, Recording and Reporting Adverse Events

10.3.3.1. 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?"

10.3.3.2. 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 either observed by the investigator or reported by the participant must be recorded regardless of causality.

The following attributes must be documented for each investigator reported AE:

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

Any medical history condition, signs, symptoms, and illnesses active during the Screening Period 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 trial treatment

administration will be documented as medical history unless the event is trial procedure–related, in which case it will be reported as an AE. Any new or worsening pretreatment event that occurs from the time of the first trial treatment administration until the end of the AE Reporting period 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, AESIs or SAEs. Avoid colloquialisms and abbreviation (e.g., hypertension for elevated BP that persists and requires chronic treatment and follow-up, or increased BP for elevated BP that occurs for a limited time and does not persist or require ongoing treatment).

AEs will be documented at the maximum intensity experienced.

If a previously recorded and closed/resolved AE or a condition recorded as part of medical history increases in severity or frequency, it will be recorded as a new AE.

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 e CRF. Regardless of classification as an AE or not, all overdoses should be documented, and the participant(s) monitored. Since accidental overdoses with the trial treatment 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.

10.3.3.3. Specific Instructions for Recording Adverse Events

10.3.3.3.1. Abnormal Laboratory and Vital Sign Assessments

Not every trial assessment qualifies as an adverse event. A laboratory or vital sign assessment must be reported as an AE if it is a worsening from baseline and is clinically significant. Clinical significance is defined as the following:

- Is accompanied by clinical symptoms or diagnosis, then the diagnosis is recorded event
- Requires additional monitoring or diagnostic studies
- Results in a medical treatment (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 and vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory or vital sign abnormality should be classified as an adverse event.

If a clinically significant laboratory or vital sign abnormality is a sign of a disease (e.g., alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality or vital signs is not a sign of a disease, 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 or vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

10.3.3.3.2. 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.

10.3.3.3.3. Injection Site Findings

CCI [redacted]. The reported AEs should include “injection site” in the reported term such as injection site erythema, injection site induration etc. Signs and symptoms of injection site reactions include but are not limited to pain, numbness, itching, burning, redness, induration, swelling, dimpling, macula, hematoma and bleeding. The diagnosis is at the discretion of the investigator, refer to Section 8.3.2.4.

*10.3.3.3.4. **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”.

*10.3.3.3.5. **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 clinical trial, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the clinical trial

10.3.3.3.6. ***Preexisting Medical Conditions***

A preexisting medical condition is one that is present at the start of the clinical trial. 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 clinical trial. 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”).

10.3.3.3.7. ***Pregnancy***

If a female participant becomes pregnant while receiving the trial treatment or within 90 days after the last dose of trial treatment, or if the female partner of a male clinical trial participant becomes pregnant while the clinical trial participant is receiving the trial treatment or within 90 after the last dose of trial treatment, a Pregnancy report should be completed and expeditiously submitted to Sponsor. Follow-up to obtain the outcome of the pregnancy should also occur and the outcome reported to Sponsor. 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 trial treatment should be expeditiously reported as an SAE.

10.3.3.3.8. 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.

In this clinical trial, the TransCon CNP system is a single use system and consists of a vial with Swfi syringe used for administering the drug which is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible including the product batch number and forward the information to the Sponsor immediately (refer to the IMP Manual for further details). If the medical device results in an adverse event to the clinical trial participant, the event must be reported on the AE eCRF and submitted. If the event is serious, the AE eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 10.3.4.2.

10.3.3.3.9. ***Diary Data***

The participant diary data is reviewed by the site staff to determine if diary entries reflect any AEs at applicable visits, any changes from baseline noted during a physical examination should be assessed for potential AEs. If any e-diary responses suggestive of a possible adverse event are identified during site review, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

10.3.4. Safety Reporting Requirements

10.3.4.1. Non-Serious Adverse Events Leading to Discontinuation

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

10.3.4.2. Reporting

All initial and follow-up information regarding SAEs, AESIs and Special Situations reporting must be reported by the investigator to the Sponsor or its representatives within 24 hours of discovery/awareness, 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 10.3.1.1 for seriousness criteria), severity (see Section 10.3.2.2.1), and causality (see Section 10.3.2.2.2).

Reporting must not be delayed by waiting for additional information. The minimum information required for reporting an SAE, AESIs and SSR are the AE term (diagnosis), participant, trial treatment, reporter, and the investigator's initial causality assessment. Additional information must be reported to the Sponsor or its representatives as a follow-up report. Reporting details are provided on the Safety Report Form.

10.3.4.2.1. Serious Adverse Event, Adverse event of special interest and Special Situation Reporting to Ascendis Safety

All SAEs, AESIs CCI and Special Situations (including follow-up information) must be reported using the Safety report form or the Pregnancy report form provided. A completed Safety report form /Pregnancy report form must be uploaded to the Safety Reporting Portal, within 24 hours of awareness, at:

PPD

Specific instructions regarding completion of the form and reporting details are provided on the

Safety report form. 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)
- Local IRBs/HRECs/IECs (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.

10.3.5. 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 trial treatment 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.

10.4. APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1. Definitions

Acceptable highly effective methods of contraception:

- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion (must be documented)
- combined or progestogen-only hormonal contraception associated with inhibition of ovulation
- vasectomized partner (must be documented)
- sexual abstinence (only when it is the usual and preferred lifestyle of the participant)

Other clinically acceptable methods of contraception:

- permanent sterilization (must be documented)
- hysterectomy (must be documented)
- bilateral salpingectomy (must be documented)
- bilateral oophorectomy (must be documented)

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception for this clinical trial.

10.4.2. Contraception Guidance

Females of childbearing potential must accept to use the methods of contraception described in Section 10.4.1 from the beginning of screening and 90 days after last dose of trial treatment.

For participants using oral combined hormonal contraception (i.e., containing estrogen), the dose and route must be stable for ≥6 weeks prior to screening, throughout the trial until 90 days after last dose of trial treatment.

Male participants or his female partner of childbearing potential must use a highly effective form of contraception as described in Section 10.4.1 from the beginning of screening and 90 days after last dose of trial treatment.

10.5. APPENDIX 5: GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to trial treatment, susceptibility to, and severity and progression of disease. Variable response to trial treatment may be due to genetic determinants that impact treatment drug absorption, distribution, metabolism, and excretion; mechanism of action of the treatment drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be analyzed for clinical confirmation of ACH. The results of genetic analyses will be reported in the clinical study report (CSR).
- The DNA samples will be stored in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained no longer than 15 years or other period as per local requirements.

10.6. APPENDIX 6: RETENTION AND USAGE OF HUMAN BIOSAMPLES

Additional analysis as defined in below sections will be reported separately from the CSR. Genetic analyses will not be performed on any of these blood samples.

10.6.1. Residual Pharmacokinetics and Biomarker Samples

Residual pharmacokinetics and biomarker samples may be retained to allow exploratory investigation of metabolites, pharmacodynamic, and safety biomarkers and for method development and validation purposes.

The samples may be stored until marketing authorization approval or until the research project terminates, but no longer than 15 years (or according to local regulation) from end of trial after which they will be destroyed.

10.6.2. Antibody Samples

Antibody samples may be retained for later analysis for further characterization of antibody responses towards drug, if required by health authorities, for safety reasons, or for method or assay development and validation purposes. In addition, samples may be retained to allow exploratory investigation of metabolites, pharmacodynamic, and safety biomarkers.

The samples may be stored until marketing authorization approval or until the research project terminates, but no longer than 15 years from end of trial (or according to local regulations) after which they will be destroyed.

10.6.3. Hypersensitivity Reaction Samples

In case of a systemic hypersensitivity reaction, the additional blood samples taken in relation to the reaction (see Section 8.8) may be retained to follow-up on the hypersensitivity reaction.

If deemed relevant by the sponsor, additional exploratory tests may be performed.CCI [redacted] CCI

As described in detail for antibody samples, hypersensitivity samples may be retained for a maximum of 15 years (or according to local regulation) for potential further analysis.

10.7. APPENDIX 7: ABBREVIATIONS

Abbreviation	Definition
CCI [redacted]	
ACEM-DF	Achondroplasia child experience measure - Impact Measure – Daily Living Functioning
ACEM-Impact	Achondroplasia child experience measure - Impact Measure
ACEM-OSM	Achondroplasia child experience measure - Observed Signs Measure
ACEM-PF	Achondroplasia child experience measure - Impact Measure – Physical Functioning
ACH	Achondroplasia
ADA	Anti-drug antibodies
AE	Adverse events
AESI	Adverse Event of Special Interest
CCI [redacted]	
ANCOVA	Analysis of covariance
CCI [redacted]	
BP	Blood pressure
CFC	Chlorofluorocarbon
CFR	Code of Federal Regulations
CCI [redacted]	
ClinRO	Clinician reported outcome assessment
C_{max}	Maximum concentration
CNP	C-type natriuretic peptide
COA	Clinical outcome assessment
CONSORT	Consolidated standards of reporting trials
COVID-19	Coronavirus disease 19
CRF	Case report form
CV	Cardiovascular
DB	Double-blind
DMC	Data monitoring committee
DPI	Dry powder inhalation
CCI [redacted]	
ECG	Electrocardiogram

Abbreviation	Definition
eCRF	Electronic case report form
EOT	End of trial
ET	Early termination
CCI [redacted]	
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FGFR3	Fibroblast growth factor receptor-3
CCI [redacted]	
FU	Follow-up
GCP	Good clinical practice
GFR	Glomular filtration rate
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
CCI [redacted]	
HEENT	Head, eyes, ears, nose, and throat
HFA	Hydrofluoroalkane inhalers
HR	Heart rate
HREC	Human research ethics committee
IB	Investigator brochure
ICH	International Council for Harmonisation Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFU	Instructions for use
IMP	Investigational medicinal product
IND	Investigational new drug
INN	International Nonproprietary Names
IRB	Institutional review board
IRT	Interactive response technology
mPEG	Methoxy polyethylene glycol
CCI [redacted]	
mSv	Millisievert
NOAEL	No-observed-adverse-effect level

Abbreviation	Definition
NOEL	No observed effect level
CCI	
ObsRO	Observer (parent/caregiver) reported outcome measures
OLE	Open label extension
CCI	
PRO	Patient reported outcome
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutanous
SD	Standard deviation
SE	Standard error
CCI	
SF-10 PHS	(Short Form) SF-10™ Health Survey for Children physical summary score
SUSAR	Suspected unexpected serious adverse reaction
SSR	Special situation reports
sWFI	Sterile water for injection
TLK	Thoracolumbar kyphosis
TSH	Thyroid stimulating hormone
ULN	Upper level of normal
UNS	Unscheduled visit
CCI	

10.8. APPENDIX 8: PROTOCOL AMENDMENT HISTORY

The following updates have been made to the clinical trial protocol.

Protocol Version	Sections	Change	Rationale
Version 1.0, New protocol version, 7-Oct-2022	NA	NA	NA
Global protocol Version 2.0, substantial amendment 1.0 to the clinical trial protocol	1.3.1 Schedule of activities in DB period	Removal of IMP administration training and dispensing and IFU handout.	Correction of error in the protocol.
	1.3.2 Schedule of activities in the OLE period	Removal of body weight measurement during the visit 6 OLE	Correction of error in the protocol.
		Removal of IMP administration training and IFU handout at visit 11 EOT	Correction of error in the protocol.
	2.3.2 Risk Assessment	Addition of option for additional post-dose monitoring at the discretion of the investigator	By request from health authority
	5.2 Exclusion Criteria	Addition of exclusion criterion 18, excluding sexually active female participants and female partners of male participants of childbearing potential not using a highly effective form of contraceptive	By request from health authority
	8.3.6 Radiographic Assessment	CCI [redacted]	Text worded incorrectly in this section.
Global protocol Version 3.0, substantial amendment 2.0 to the clinical trial protocol	5.2 Exclusion Criteria	Exclusion criterion 18 updated to include sexually active male participants. Duration contraceptives updated to 90 days after last dose of trial treatment.	By request from health authority
	CCI [redacted]		By request from health authority

Protocol Version	Sections	Change	Rationale
	10.3.1.3 Adverse Events of Special Interest	Adverse events of special interest added to the protocol	By request from health authority
	10.3.1.4 TransCon CNP Adverse Event of Special Interest	Definition for adverse events of special interest added to the protocol	By request from health authority
	10.4.1 Contraceptive and Barrier Guidance definitions	Contraceptive methods not considered highly effective removed from the protocol	By request from health authority
	10.4.2 Contraception Guidance	Highly effective contraceptives updated to being used until 90 days after last dose of trial treatment.	By request from health authority
Global protocol Version 4.0, substantial amendment 3.0 to the clinical trial protocol	1.1 Synopsis	CCI [redacted]	
	1.1 Synopsis		
	3 Objectives and Endpoints		
	5.2 Exclusion Criteria	Exclusion criterion 16 updated. Requirement for at least 2000 IU/day or its weekly equivalent removed.	Vitamin D supplementation is given on an individual basis.

Protocol Version	Sections	Change	Rationale
	6.7 Treatment of Overdose	Definition of an overdose update	Alignment with other TransCon CNP trials.
	6.8.2 Vaccination	Section on vaccinations broadened the cover all types of vaccinations	Update to reflect to COVID-19 is no longer considered as critical.
	CCI	Description of assessment added to the protocol.	CCI
		Description of assessment added to the protocol.	
	8.3.2.4 Injection Site Findings	Text updated	Clarification of the reporting requirements for injection site findings.
	10.3.3.3.3 Injection Site Findings	Text updated	Clarification of the reporting requirements for injection site findings.
	General	Administrative changes and correction of minor errors in the protocol	

Protocol Version	Sections	Change	Rationale
Global protocol Version 5.0, substantial amendment 4.0 to the clinical trial protocol	1.1 Synopsis	Change in TLK, ACEM-PF, ACEM-DF, ACEM-OSM and SF-10 PHS score changed to secondary endpoints. Safety and tolerability endpoint broadened to include all safety assessments. CCI [redacted]	Alignment with SAP and testing strategy. Updates per input from EMA PDCO
	1.3 Schedule of activities	Treatment acceptability assessment added CCI [redacted]	Updates per input from EMA PDCO
	3 Objectives and Endpoints	Updates according to section 1.1.	Alignment with SAP and testing strategy. Updates per input from EMA PDCO
	6.7 Treatment of Overdose	Definition of overdose updated.	Alignment across TransCon CNP trials.
	CCI [redacted]		Updates per input from EMA PDCO
	8.3.2.3 Skeletal physical examination	Hip examination description added.	Updates per input from EMA PDCO
	8.3.2.4 Injection Site Findings	CCI [redacted]	Ensure relevant reporting criteria
	8.3.3 Treatment acceptability assessment	Treatment acceptability assessment added.	Updates per input from EMA PDCO
	8.7 Biomarkers	List of biomarkers included updated.	Due to new knowledge on relevant biomarkers

Protocol Version	Sections	Change	Rationale
	9.3.2 Primary Endpoint / Estimand Analysis	Estimand for primary analysis updated.	Alignment with SAP
	9.4.1 Multiplicity Adjustment	Testing hierarchy updated to reflect addition of 5 secondary endpoints. Multiple testing procedure changed to graphical testing.	Alignment with SAP
	10.3.4.2.1 Serious Adverse Event, Adverse event of special interest and special situation reporting to Ascendis Safety	CCI [redacted]	Ensure relevant reporting criteria
	General	Administrative changes and correction of minor errors in the protocol.	

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