STATISTICAL ANALYSIS PLAN

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:	**ASND0036**
Investigational Product:	**TransCon CNP (Navepegritide)**
Application Number:	**IND 142685**
Phase:	**2b**
Sponsor:	**Ascendis Pharma Growth Disorders A/S** **Tuborg Boulevard 12** **DK-2900 Hellerup, Denmark**
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Date:	**11 March 2025**
Version Number:	**Version 3.0**

SUMMARY OF CHANGES

Version	Date	Changes Since Last Version
1.0	12 March 2024	First version of the document.
2.0	30 August 2024	Updating statistical testing hierarchy in Section 10.5.2. Updated analysis of TLK ACH-specific Z-score in Section 10.5.4. Calculation of ACEM Observable Signs Measure (ACEM-OSM) includes questions for Ear, Pain, Sleep, Stamina, Balance. Handling of body length assessment specified in Section 9.2 and Section 7.1. Handling of multiple readings of x-ray spine data. CCI [redacted]
3.0	11 Mar 2025	Updated calculation of AGV for navepegritide in OLE period and corrected typos in formulas for derivation of AGV in Section 7.8. Added details to spaghetti plot in Section 10.5.6.1. Updated calculation of EAER in section 10.6. Included missing ADA at baseline in Treatment emergent positive definition in Section 10.6.10.

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ABBREVIATIONS

Abbreviation	Definition
ACEM-DF	achondroplasia child experience measure – daily living functioning
ACEM-OSM	achondroplasia child experience measure – observable signs measure
ACEM-PF	achondroplasia child experience measure – physical functioning
ACH	achondroplasia
ADA	anti-drug antibody
AE	adverse event
AEM	achondroplasia experience measure
AESI	adverse events of special interest
AGV	annualized growth velocity
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
CCI [redacted]	
AST	aspartate aminotransferase\
BUN	blood urea nitrogen
CDC	centers for disease control and prevention
CCI [redacted]	
CI	confidence intervals
CNP	c-type natriuretic peptide
COA	clinical outcome assessment
CRF	case report form
CS	clinically significant
CSR	clinical trial report
CTCAE	common terminology criteria for adverse events
DB	double-blind
DMC	data monitoring committee
CCI [redacted]	
ECG	electrocardiogram
EOI	event of interest
FCS	full conditional specification
CCI [redacted]	

Abbreviation	Definition
HLGT	high-level group term
HLT	high-level term
IMP	investigational medicinal product
IQC	internal quality control
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
mLDFA	mechanical lateral distal femoral angle
mLDTA	mechanical lateral distal tibia angle
mMPTA	mechanical medial proximal tibia angle
MNAR	missing not at random
CCI [redacted]	
NCI	national cancer institute
NCS	non-clinically significant
OLE	open-label extension
PHS	physical summary
CCI [redacted]	
CCI [redacted]	
PK	pharmacokinetic
PT	preferred term
CCI [redacted]	
OSM	observable signs measure
QTc	QT interval corrected
QTcF	QT interval corrected with Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
CCI [redacted]	
SF-10 PHS	10-item short form health survey for children – physical summary

Abbreviation	Definition
CCI [redacted]	
SI	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
TLK	Thoracolumbar Kyphosis
VAS	visual analogue scale
Xcal	cross-calibration

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a more technical and detailed elaboration of the statistical analyses of efficacy and safety data as outlined and/or specified in the final trial protocol (version 5.0 dated 08 Mar 2024). The SAP for pharmacokinetic/pharmacodynamic and/or health economics and outcomes research data (if applicable) will be prepared separately.

2. TRIAL DESIGN

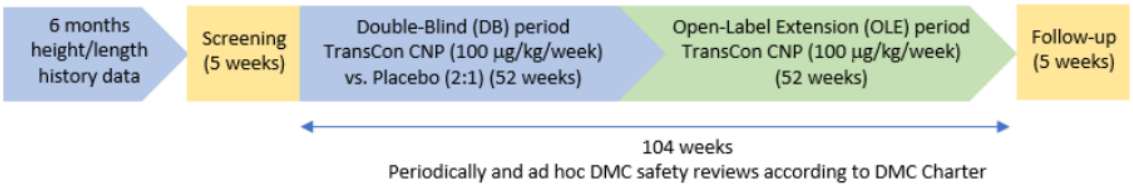
Navepegritide is an investigational long-acting prodrug of C-type natriuretic peptide (CNP), designed to provide continuous exposure of CNP at safe, therapeutic levels via, weekly subcutaneous dose. ASND0036 (ApproaCH) is a multicenter, double-blind, randomized, placebo-controlled, phase 2b trial to assess the efficacy and safety of subcutaneous doses of 100 µg/kg CNP administered once weekly for 52 weeks in children aged 2 to 11 years with genetically confirmed achondroplasia (ACH). 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 open-label extension (OLE) period where all participants will receive 100 µg CNP/kg/week.

Prior to enrollment, participants must have at least six months of growth and disease history from TCC-NHS-01 or comparable growth and disease history available from medical records, which will be confirmed by the medical monitor prior to enrollment.

The treatment period of the trial has a total duration of 104 weeks, as shown in Figure 1.

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

Figure 1: Trial Design in the double-blind and OLE Periods



The Schedule of Activities is detailed in the trial protocol Section 1.3.

2.1. BLINDING AND RANDOMIZATION METHODS

The trial will be double-blind so that neither the sponsor, participants, or site personnel involved in trial conduct will know the identity of a participant's treatment during the blinded phase.

The Investigator and site personnel will remain blinded to the randomization code during the trial. Treatment assignment for an individual participant should be unblinded by the investigator only in an emergency e.g., event concerning participant safety, and only if knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the participant. Please refer to trial protocol Section 6.3 for details about unblinding. For participants who discontinue investigational medicinal product (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. Please refer to trial protocol Section 7.1.

Eligible participants will be enrolled in the trial and sequentially assigned an identification number. A randomization schedule will be developed by an independent party to maintain blinding. In total, approximately 80 participants will be enrolled in a 2:1 randomization ratio to receive 100 µg CNP/kg/week or placebo. Trial participants will be stratified by age and sex at the time of randomization as the following 3 strata:

- Aged < 5 years
- Aged ≥ 5 years and female
- Aged ≥ 5 years and male

3. TRIAL 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 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) Observable Signs Measure (ACEM-OSM)
• 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
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)

Objectives	Endpoints
• To assess potential immunogenic response to TransCon CNP	Detection and characterisation of anti-drug antibodies (ADA)
Exploratory	

CCI

Objectives	Endpoints
CCI [redacted]	

4. SAMPLE SIZE CONSIDERATIONS

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

5. PLANNED ANALYSIS

Planned analyses will include the following:

- Data monitoring committees (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 DB Period and the clinical trial database for the DB 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.

6. DATA MONITORING COMMITTEE

An independent DMC with relevant expertise in the conduct of clinical trials will act in an advisory capacity to monitor participant safety on a routine basis throughout the trial as specified in the trial protocol Section 10.1.6.2.

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

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

7. DEFINITIONS

7.1. BASELINE

Baseline (initial baseline) is defined as the last non-missing assessment prior to or on the date of administration of the first dose of investigational medicinal product (IMP) (navepegritide or placebo).

OLE baseline is defined as the last non-missing assessment prior to the administration of the first dose of navepegritide in OLE period. If both body length and standing height are measured at the same date, the standing height measurement is used as the OLE baseline for height.

X-Ray assessments are allowed to be taken later than the scheduled visit according to the protocol. X-Ray assessments will be analyzed according to the visits for which they are reported in the CRF.

7.2. TRIAL DAY

If the date of an assessment is on or after the first dose of IMP:

trial day = date of assessment – date of the first dose of IMP + 1.

If the date of an assessment is prior to the first dose of IMP:

trial day = date of assessment – date of the first dose of IMP.

7.3. AGE

Unless otherwise specified, the age at baseline will be derived based on the first dose date of IMP: age = (first dose date – birth date + 1)/365.25. When date of birth is missing, the age recorded on case report form (CRF) will be used as baseline age.

If birth date is missing and age recorded on CRF is also missing, the birth date will be imputed to calculate (See Section 9.2.1 the algorithm to impute birth date) age.

7.4. DURATION OF EXPOSURE

Duration of exposure to IMP during Double-Blind (DB) Period or OLE Period, in weeks, is defined as in each period:

(the date of last IMP – the date of first IMP + 7)/7.

Total duration of exposure to navepegritide, in weeks, is defined as:

(the date of last dose of navepegritide – the date of first dose of navepegritide + 7)/7.

7.5. DOSE COMPLIANCE

Dose compliance (%) during DB Period or OLE Period is defined as in each period, (total number of actual doses / total number of planned doses) × 100.

CNP dose compliance (%) throughout the trial is defined as the (total number of actual CNP doses / total number of planned CNP doses) × 100.

Total number of actual doses is calculated based on dose injection records collected on CRF. In cases of multiple injections within 24 hours, it will be counted as one dose. For participants who completed the DB period, the total number of planned doses in the DB period is 52. For participants who withdraw early from treatment in the DB period, the total number of planned doses is defined as (treatment withdrawn date - date of first IMP + 7)/7. The total number of planned doses in the OLE period will be calculated following the same way.

7.6. ACTUAL DOSE

Navepegritide dose is provided in CNP equivalents, for the DB Period or OLE Period:

- Total actual dosage (µg/kg) is defined as sum of IMP dosage: (concentration (mg/mL) × volume (mL) × 1000 / weight (kg)) in the specific period.
- Average weekly actual dosage (µg/kg/week) is defined as total actual dosage / total number of actual doses in the specific period.

For CNP overall:

- Total actual CNP dosage (µg/kg) is the sum of CNP dosage: (concentration (mg/mL) × volume (mL) × 1000 / weight (kg)) throughout DB Period and OLE Period.
- Average weekly actual CNP dosage (µg/kg/week) is defined as total actual CNP dosage (µg/kg) / total number of actual CNP doses throughout DB Period and OLE Period.

In above calculations, "weight" refers to body weight measured at each scheduled on-site visit.

7.7. BASELINE ANNUALIZED GROWTH VELOCITY

Historical height measurement will be used to calculate baseline for AGV.

Historical height could be the height measurements collected from the observational trial TCC-NHS-01 (ACHieve) or medical history records for participants who are not rolled over from the TCC-NHS-01 trial.

For children 3 years or more at baseline, all available historical height measurements taken between 6 months and 18 months prior to the first dose of IMP will be considered. For children younger than 3 years at baseline, all available historical height measurements taken between 6 months and 12 months prior to the first dose of IMP will be considered. The measurement that is closest to date of 6 months prior to the first dose of IMP will be used in the following calculation of baseline AGV:

[Height (Baseline) – Height (historical measurement)] × 365.25 / [Date (Baseline) – Date (historical measurement)]

7.8. ANNUALIZED GROWTH VELOCITY

During the randomized period, the AGV at each visit will be derived based on the height at initial baseline:

[Height (Visit x) – Height (initial baseline)] × 365.25 / [Date (Visit x) – Date (initial baseline)]

During the OLE Period, the AGV at each visit will be derived depending on randomization group:

For navepegritide:

- based on the height measured 1 year prior to the visit of interest as

  [Height (Visit x) – Height (Visit "x-52")] × 365.25 / [Date (Visit x) – Date (Visit "x-52")]

For placebo:

- based on the height at OLE baseline:

[Height (Visit x) – Height (OLE baseline)] × 365.25 / [Date (Visit x) – Date (OLE Baseline)]

7.9. HEIGHT Z-SCORE

ACH-specific height Z-score is derived using age and gender specific mean and (upper or lower, depending on whether the height value is larger or smaller than its age and sex specific mean height) standard deviations from ACH population (Hoover-Fong 2021), as follows:

(Height – mean)/standard deviation.

Height Z-score assessed via the Centers for Disease Control and Prevention (CDC) 2000 (United States of America) / Kuczmarski method will also be derived as follows:

$$\frac{\left(\frac{H_i}{M}\right)^L - 1}{L \times S}$$

where H_i = height of participant i, M = median, S = generalized coefficient of variation, and L = power in the Box-Cox transformation, the *M, S, L* values are obtained from the CDC website (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm); Percentile Data Files with LMS Values. M, L, and S will be interpolated based on the next lower age category, and the next upper age category. Age at the corresponding height measurement will be used for the derivation.

8. ANALYSIS POPULATIONS

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

8.1. SCREENED POPULATION

The Screened Population will consist of all participants who underwent a screening visit and received a participant identification number.

8.2. RANDOMIZED POPULATION

The Randomized Population will consist of all enrolled participants who were randomized to a treatment group in the trial.

8.3. FULL ANALYSIS SET

The Full Analysis Set will include all randomized participants. Participants will be analyzed according to trial treatment as randomized.

8.4. SAFETY ANALYSIS SET

The Safety Analysis Set will include all randomized participants who have received at least one dose of IMP. Participants will be analyzed according to trial treatment as treated.

8.5. PHARMACOKINETIC ANALYSIS SET

The Pharmacokinetic (PK) Analysis Set includes all participants in the Safety Analysis Set who have evaluable PK data. A sample result that is below the assay limit of quantification is considered evaluable.

9. DATA SCREENING AND ACCEPTANCE

9.1. GENERAL PRINCIPLES

During trial conduct, data will be reviewed periodically. Any questionable data will be reported to the clinical data manager promptly for query and resolution.

9.2. HANDLING OF MISSING AND INCOMPLETE DATA

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

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

9.2.1. Missing Birth Dates

When calculating height Z-score at specific visits the exact age is needed and it is based on the birthdate and visit data. To impute missing birth date, the following rules will be applied:

- If day is missing, impute 15.
- If month is missing, impute June.

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

9.2.2. Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events (AE) and medications. The imputed dates are used to access treatment emergent or not for adverse events and to access if a medication is prior or concomitant medication. In listings no imputed dates will be shown. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the first dose of IMP start date month and year in this trial, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If both the day and month are unknown, then:
  - If the year matches the year of the first dose of IMP date in this trial, then impute the month of the first dose date in this trial.

  - Otherwise, assign ‘January 01’

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

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

Missing end dates and not ongoing for concomitant medications

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

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

9.2.3. Missing Date Imputation for Historical Anthropometric Measurements

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

9.2.4. Missing Causal Relationship to Investigational Product for Adverse Events

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

9.2.5. Safety Laboratory Values Below or Above Quantification Limits

Safety laboratory measurements shown as ‘<x.x’ or ‘>y.y’ wil be imputed with x.x and y.y in summaries but shown as ‘<x.x’ or ‘>y.y’ in data listings.

9.2.6. Missing Data for Endpoints

In general, missing data for endpoints will not be imputed, unless otherwise specified. Please refer to Section 10.5 for the proposed methods for dealing with missing data for efficacy endpoints.

9.3. VISIT TIME WINDOWS

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

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

Visit window assigned for assessments scheduled and the corresponding range of trial days (window) during which an actual visit may occur is defined as below:

Period	Visit	Week	Scheduled Visit Day	Window (trial days)
Randomized	Baseline	0	1	Refer to baseline definition in Section 7.1
	2	4	29	[2, 57]
	3	12	85	[58, 134]
	4	26	183	[135, 228]
	5	39	274	[229, 319]
	6	52	365	[320, trial day of first OLE dose]
OLE	7	56	393	[trial day of first OLE dose + 1, 424]
	8	64	456	[425, 501]
	9	78	547	[502, 592]
	10	91	638	[593, 683]
	11	104	729	≥ 684

For each type of assessments, only protocol-defined scheduled visits will be presented in by-visit summary.

9.4. SOFTWARE

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

10. STATISTICAL METHODS OF ANALYSES

10.1. GENERAL PRINCIPLES

Unless otherwise specified, summaries will be performed descriptively by treatment group that are assigned during DB Period. Summaries by actual treatment throughout DB Period and OLE period may be performed and will be specified in the corresponding sections below.

Continuous, quantitative (absolute values at each timepoint and change from baseline if applicable) variable summaries for protocol defined visits will include the number of participants

(n) with non-missing values, mean, standard deviation (SD), standard error (SE) of the mean, median, minimum, and maximum values. Categorical, qualitative variable summaries for protocol defined visits will include the frequency and percentage of participants in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of participants in the trial population for the treatment arm.

All statistical tests will be two-sided and tested at a statistical significance of 0.05. P-values will be rounded and displayed in three decimals. If a p-value is less than 0.001, it will be shown in tables as <0.001. Confidence intervals will be 2-sided 95% confidence intervals (CI), unless stated otherwise.

10.2. PARTICIPANT ACCOUNTABILITY

The number and percentage of participants in each of the trial populations will be summarized. Participants excluded from the analysis set will be listed. Screen-failure participants and the associated reasons for failure to randomize will be listed. The number and percentage of participants who complete the treatment periods and participants who prematurely discontinue either treatment or trial will be presented for each treatment group for the Randomized Population. The reasons for premature discontinuation from trial and/or treatment as recorded on CRF will be summarized.

10.3. PROTOCOL DEVIATIONS

Important protocol deviations will be summarized by type in each treatment group for the Randomized Population. Important protocol deviations will be listed by category, treatment, and participant ID.

10.4. INVESTIGATIONAL MEDICINAL PRODUCT ADMINISTRATION

10.4.1. Extent of Exposure

Exposure to the IMP will be summarized for the Safety Analysis Set.

The following parameters of the IMP will be summarized for DB and OLE Period, separately, and DB + OLE period for the total exposure.

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

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

10.4.2. Measurement of Treatment Compliance

Descriptive statistics for IMP compliance, as defined in Section 7.5 will be presented for the Safety Analysis Set.

10.4.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Full Analysis Set and presented by treatment group.

Demographic will be summarized as:

- Age at randomization (in years)
- Age group (< 5, 5 - < 8, ≥ 8 years)
- Sex
- Randomization strata (< 5 years, ≥ 5 years and female, and ≥ 5 years and male)
- Race
- Ethnicity
- Region (US, Europe and Rest of World (ROW))

Baseline characteristics will be summarized as:

- Height (cm)
- Height Z-score using reference data from normal population as well as ACH patients (ACH-specific), as described in Section 7.9
- Weight (kg)
- Body mass index (BMI, kg/m2)
- Baseline AGV (cm/year)
- Age at ACH diagnosis (Pre-birth, At birth, 0-6 months, 7-12 month, ≥ 12 months)
- Type of mutation
- Rollover from TCC-NHS-01 (yes / no)

For above categorical variables, unless specified, the categories specified in the CRF will be presented in the summary.

10.4.4. Prior and Concomitant Medication

Prior medication is defined as any medication started and ended before the date of the first dose of IMP (medication start date and end date prior to the first dose date).

All other medication is defined as concomitant medication.

Both prior and concomitant medications will be coded by drug name and therapeutic class using World Health Organization (WHO) Drug Dictionary and will be summarized by ATC level 2 and level 4 showing number and percentage of participants for the Safety Analysis Set. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant will be counted only once for the coded drug name or therapeutic class.

10.4.5. Medical History

Medical history will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term (PT) for the Full Analysis Set.

10.5. EFFICACY ANALYSIS

Unless otherwise specified, efficacy analyses will be conducted using Full Analysis Set.

10.5.1. General Analysis Methods

For the DB Period, an Analysis of Covariance (ANCOVA) model will be used as the primary analysis for the primary and secondary efficacy endpoints. For other specified efficacy endpoints, ANCOVA models will be performed as appropriate to determine treatment difference. Given randomization ratio of 2:1 (navepegritide vs. placebo), the ANCOVA model assuming unequal variances will be used to account for possible unequal residual variance and the group option (i.e., group = TRT01P) in the repeated statement in the SAS procedure PROC MIXED.

During the OLE Period, the efficacy endpoints and applicable change from baseline will be summarized descriptively by treatment group and overall, and in general, both initial baseline and OLE baseline will be used.

10.5.2. Multiplicity Adjustment

The null hypotheses for statistical comparisons for the primary efficacy endpoint (Section 10.5.3) and the secondary endpoints (Section 10.5.4) (in total 6 endpoints) are tested using a multiple testing procedure based on the graphical approach in Bretz 2009. Significance levels, α_i (for $i = 1, \ldots, 6$), are initially defined such that they sum to α (for $\alpha = 0.05$ two-sided). The first two hypotheses are tested sequentially where H_1 (the primary endpoint) is first tested and α is only allocated to the next hypothesis if we reject H_1.

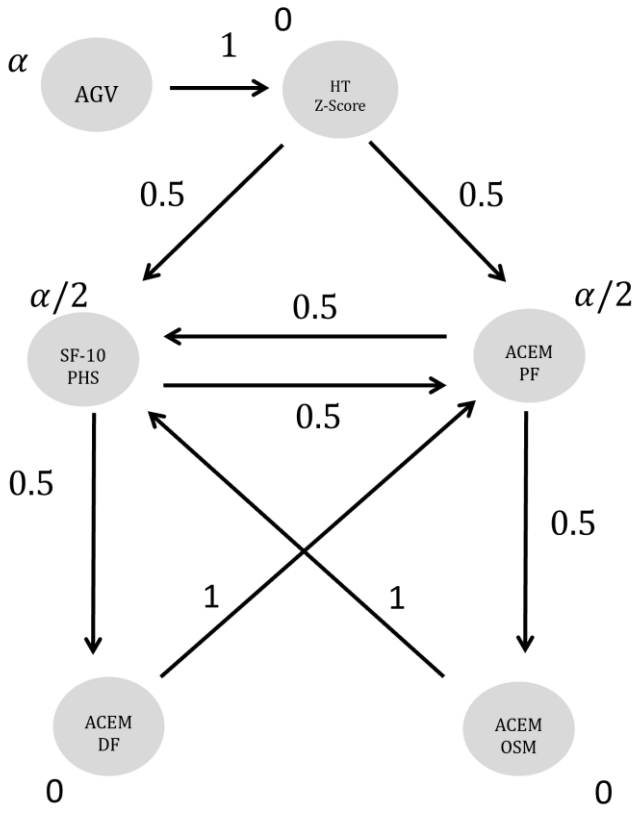
The graphical procedure is defined as follows: Test the hypotheses H_i (for $i = 1, \ldots, 6$) each at its local significance level α_i. If a hypothesis can be rejected, reallocate its α level to one of the other hypotheses according to the pre-specified rule represented by the weighted graph shown in Figure 2. Update the reallocation weights in the reduced graph and repeat the testing steps 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 reallocation of the local alpha levels is fully determined by the initial graph given below (Figure 2) and an update algorithm described in Bretz 2009.

The endpoints included in the multiple testing strategy are listed below:

- AGV at Week 52
- Change from baseline in ACH-specific height Z-score at Week 52.

- Change from baseline in SF-10 Physical Summary Score (SF-10 PHS) at Week 52 (only relevant for participants of 5 years or older at baseline)
- Change from baseline in ACEM-Physical Functioning (ACEM-PF) at Week 52
- Change from baseline in in ACEM-Daily Living Functioning (ACEM-DF) at Week 52
- Change from baseline in ACEM-OSM at Week 52

Figure 2: Testing Strategy for Primary and Secondary Endpoints



Note that based on the graph and the update algorithm the multiple testing procedure is equivalent to:

- Test AGV at α = 5%, and if significant then continue (else stop)
- If AGV is significant then test change from baseline in ACH-specific Z-score at α = 5%, if significant then continue (else stop)

If both the above tests are significant at α = 5%, the procedure will move on to the COAs as described in Figure 2 and in words below.

Test SF-10 PHS like this:

- Test SF-10 PHS at α = 2.5%

- Test SF-10 PHS at α = 3.75% if ACEM-PF is significant (at α = 2.5%)
- Test SF-10 PHS at α = 5% if ACEM-PF is significant (at α = 2.5%) and AECM-OSM is significant (at α = 1.25%)

Test ACEM-PF like this:

- Test ACEM-PF at α = 2.5%
- Test ACEM-PF at α = 3.75% if SF-10 PHS is significant (at α = 2.5%)
- Test ACEM-PF at α = 5% if SF-10 PHS is significant (at α = 2.5%) and ACEM-DF is significant (at α = 1.25%)

Test ACEM-DF like this:

- Test ACEM-DF at α = 1.25% if SF-10 PHS is significant (at α = 2.5%)
- Test ACEM-DF at α = 2.5% if SF-10 PHS is significant (at α = 2.5%) and ACEM-PF is significant (at α = 3.75%)
- Test ACEM-DF at α = 2.5% if SF-10 PHS is significant (at α = 3.75%) and ACEM-PF is significant (at α = 2.5%)
- Test ACEM-DF at α = 5% if SF-10 PHS is significant (at α = 2.5%), ACEM-PF is significant (at α = 3.75%), and ACEM-OSM is significant (at α = 2.5%)
- Test ACEM-DF at α = 5% if SF-10 PHS is significant (at α = 3.75%) and ACEM-PF is significant (at α = 2.5%), and ACEM-OSM is significant (at α = 2.5%)
- Test ACEM-DF at α = 5% if ACEM-PF is significant (at α = 2.5%), SF-10 PHS is significant (at α = 5%), and ACEM-OSM is significant (at α = 1.25%)

Test ACEM-OSM like this:

- Test ACEM-OSM at α = 1.25% if ACEM-PF is significant (at α = 2.5%)
- Test ACEM-OSM at α = 2.5% if SF-10 PHS significant (at α = 3.75%) and ACEM-PF is significant (at α = 2.5%)
- Test ACEM-OSM at α = 2.5% if SF-10 PHS significant (at α = 2.5%) and ACEM-PF is significant (at α = 3.75%)
- Test ACEM-OSM at α = 5% if SF-10 PHS is significant (at α = 3.75%), ACEM-PF is significant (at α = 2.5%), and ACEM-DF is significant (at α = 2.5%)
- Test ACEM-OSM at α = 5% if SF-10 PHS is significant (at α = 2.5%), ACEM-PF is significant (at α = 3.75%), and ACEM-DF is significant (at α = 2.5%)
- Test ACEM-OSM at α = 5% if SF-10 PHS is significant (at α = 2.5%), ACEM-PF is significant (at α = 5%), and ACEM-DF is significant (at α = 1.25%)

10.5.3. Analysis of Primary Efficacy Endpoint

The estimand supporting the primary objective is defined as follows:

- **Treatment Condition:** The effect of treatment with navepegritide 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 the Protocol. The analysis population is the Full Analysis Set as defined in Section 8.3.
- **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 (navepegritide and placebo) in AGV assessed at Week 52.

The primary analysis is an ANCOVA model with AGV at Week 52 as the response variable, treatment (navepegritide vs. placebo), baseline age, baseline height Z-score and strata as covariates. The estimated treatment difference will be presented with p-value and 95% CI and the effect within each treatment group will be presented with 95% CI. Missing AGV values at Week 52 will be imputed by a multiple imputation method as described in Section 10.5.3.1.

The model will assume unequal residual variance between treatment groups.

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

- H0: Difference in mean AGV at Week 52 between navepegritide treatment group and the placebo group = 0
- H1: Difference in mean AGV at Week 52 between navepegritide treatment group and the placebo group ≠ 0

10.5.3.1. Missing Data Imputation for Primary Analysis

Subjects with missing standing height assessment that have body length assessment will be included with their body length assessment converted to standing height assessment using the conversion: standing height (cm) = body length (cm) - 0.8 cm.

Participants with missing height data at Week 52 will have missing height measurements (cm) imputed by multiple imputation method. The multiple imputation of the missing measurements of non-retrieved dropouts will be based on known measurements from retrieved dropouts in the same treatment group, where a retrieved dropout refers to a participant who discontinued treatment before Week 52 and did have a measurement at week 52. Such method will be implemented if there are sufficient number ($n \geq 5$) retrieved dropouts in the navepegritide group. If there are insufficient number of retrieved dropouts, a copy reference imputation method will

be used where the off-treatment missing data will be imputed based on the model built from the placebo group:

Step 1: Imputation of missing data

The missing data imputation will be implemented using the SAS procedure PROC MI with the missing-not-at-random (MNAR) statement. First intermittent missing values will be imputed to monotone missing pattern using the Markov Chain Monte Carlo (MCMC) methodology. Then all the monotone missing values will be imputed using the model built from the placebo group, i.e., assuming the missing data in the treatment group will have a profile that equals the profile of the placebo group for all time points (i.e., a copy-reference imputation). The baseline age, strata, height Z-score as well as post-baseline height data at each visit will be listed in the Var statement.

Step 2: Inference

A total of 200 datasets with imputed height data will be generated and corresponding AGV will be calculated as described in Section 7.8. For each imputed dataset, the ANCOVA model specified in Section 10.5.3 will be applied and the results will be combined using the PROC MIANALYZE procedure to obtain the overall statistical inferences.

10.5.3.2. Sensitivity Analyses

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

10.5.3.2.1. Sensitivity Analysis 1

ANCOVA model with change from baseline in AGV at Week 52 as the response variable, treatment (navepegritide vs. placebo), baseline age, baseline height Z-score, strata, and baseline AGV as covariates, assuming unequal variances to account for possible unequal residual variance.

Estimated treatment difference will be presented with p-value and 95% CI and the effect within each treatment group will be presented with 95% CI.

Missing height data at Week 52 will be imputed as for primary endpoint.

10.5.3.2.2. Sensitivity Analysis 2

A two-dimensional tipping point analysis will be conducted by iteratively assigning plausible outcomes to missing height data for participants in different treatment group independently until the conclusion is reversed. The set of shift parameters, K_1 and K_2, will be selected to explore the space of possible missingness assumptions systematically and comprehensively. K_1 and K_2 are chosen such that the means are shifted to reduce the treatment different and to identify the point where the p-value is tipped to be insignificant ($P \geq 0.05$) (Little 2002, Rubin 1987).

The steps for conducting tipping point analysis using PROC MI are described below:

Step 1: The pre-specified set of shift parameters are K_1 for navepegritide group and K_2 for placebo group. K_1 is a set of shift parameters lying between -5 to 0 cm/year and K_2 is a set of

shift parameters lying between 0 to 5 cm/year by every 0.2 cm/year. Let $k_1 \in K_1$ and $k_2 \in K_2$. Start the tipping point algorithm assuming k_1= 0 and k_2=0.

Step 2: For each k_1 and k_2, impute missing height data conditional on $k_1$and k_2 using PROC MI to form 200 complete datasets and calculate AGV at Week 52.

Step 3: Given the shift parameters (k_1, k_2), conduct pre-specified statistical analysis as described in Section 10.5.3 for each of the 200 complete datasets and integrate the results across 200 datasets by using the PROC MIANALYZE procedure.

Step 4: In the event that the tipping point is not identified using the pre-specified set of shift parameters K_1 and K_2, extend K_1 to include additional shift parameters between -10 and -5 and extend K_2 to include additional shift parameters between 5 and 10. Repeat steps 2-3 utilizing the additional shift parameters until the tipping point is identified or all possible pairs have been analyzed.

10.5.4. Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints are described in Section 10.5.2 where the testing strategy is also defined. The secondary endpoints will all be analyzed and presented using the same method including imputation of missing values and same estimand as the analysis of the primary efficacy endpoint.

The following hypothesis will be tested (two-sided):

- H0: Difference in mean change from baseline in endpoint at Week 52 between navepegritide treatment group and the placebo group = 0
- H1: Difference in mean change from baseline in endpoint at week 52 between navepegritide treatment group and the placebo group ≠ 0

Change from baseline in *endpoint* at Week 52 will be analyzed as response variable using an ANCOVA model, treatment (navepegritide vs. placebo), baseline age, baseline *endpoint* and strata as covariates, assuming unequal variances to account for possible unequal residual variance. Missing ACH-specific height Z-score will be calculated from the imputed standing height data as described in above Section 10.5.3.1. Other missing secondary endpoint (except TLK) values at Week 52 will be imputed using similar approaches as described in Section 10.5.3.1.

The analysis of change from baseline in ACH-specific TLK Z-score will be performed on the following two subgroups as well as on the full analysis set:

- TLK angle at baseline ≥ 10°
- TLK angle at baseline ≥ 5°

Change from baseline in ACH-specific TLK Z-score will be analyzed in a similar model as for the other secondary endpoints but without imputation of missing data.

10.5.5. Analyses of Subgroups

Subgroup summary output for the primary and secondary efficacy endpoints in the testing strategy will be presented for the below subgroups. ANCOVA models will also be applied on each subgroup (if sample size allows) and the results will be displayed in a Forest Plot.

- Age (<5, 5 - <8, ≥ 8 years)
- Age (<5, ≥ 5 years)
- Sex (Male, Female)
- Race (White, Non-white)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- Region (US, Europe and Rest of World (ROW))

Change from baseline in ACH-specific TLK Z-score will be analyzed for the age subgroup. Analyses to further explore age subgroups will be considered using different age cuts depending on the parameter of interest.

10.5.6. Analyses of Other Efficacy Endpoints

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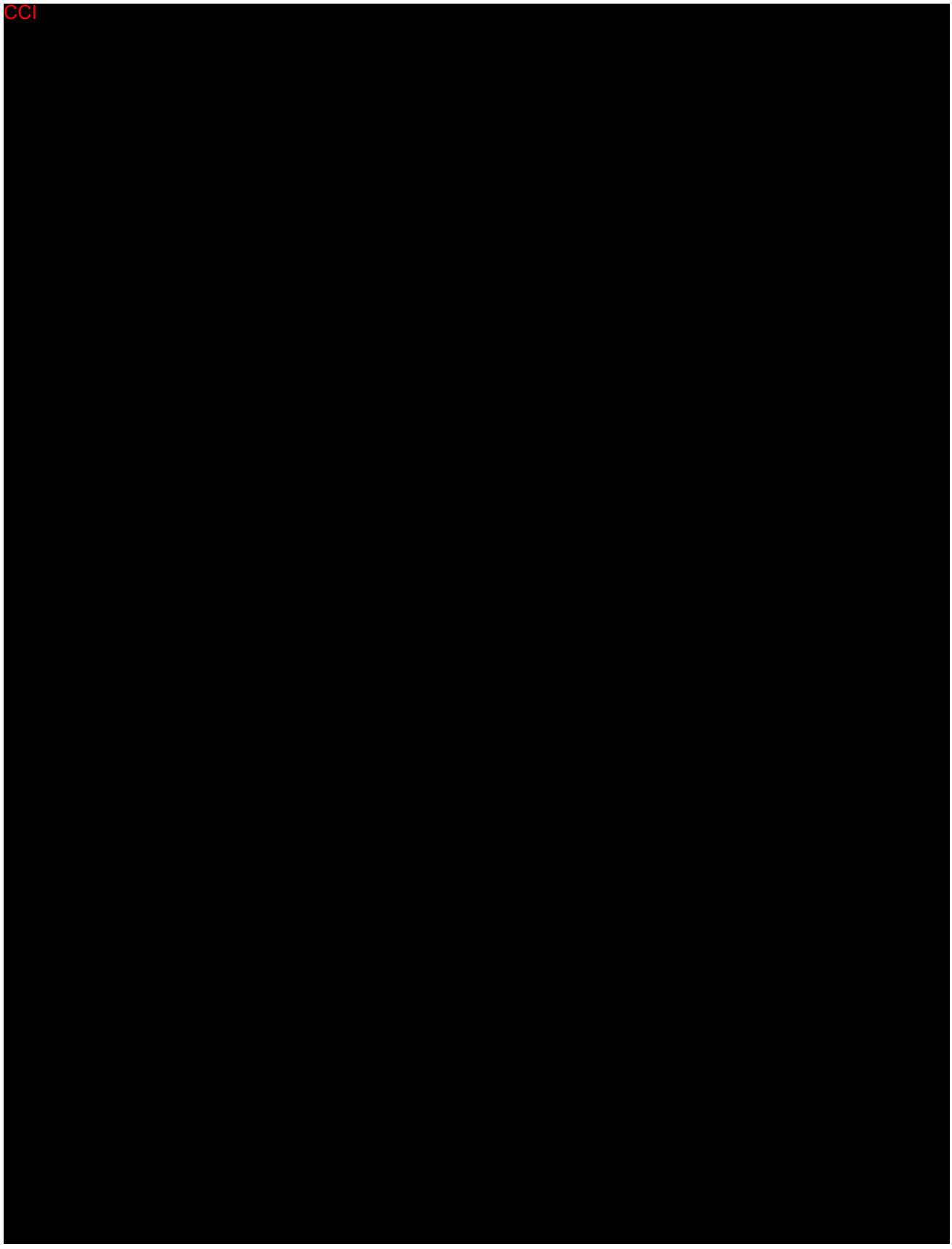
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READER and ADJUDICATION

An additional reader is to assess the sagittal spine radiographs. For each visit and each assessment, the average of assessments will be reported and will be used for the calculation of the corresponding z-score. According to the Independent Imaging Charter, an adjudication of the two readers may be warranted. In case an assessment has an adjudication reading, the two closest assessments are averaged. And in the case where one reader is the average of the other two readers, the average of all three assessments is used.

ENDPOINT Z-SCORES

As many of these parameters vary naturally during growth, published normative data from both healthy and ACH populations will be used to calculate Z-scores where possible. Ascendis Pharma will derive Z-scores for Ratio of Tibia to Femur Length using age-specific mean and standard deviations from normal children (Robinow 1982), as follows: (ratio – mean)/standard deviation. Mean and SD are calculated using appropriate interpolation of mean and SD from reference groups.

Spine:

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Selected body composition parameters such as change in %lean mass, %fat mass, visceral adipose tissue mass at Week 52 will be analyzed by an ANCOVA model with treatment (navepegritide vs. placebo), baseline age, baseline value, and strata as covariates, assuming unequal variances to account for possible unequal residual variance. Achondroplasia Experience Measures

The 3 achondroplasia experience measures (AEMs) were developed by Ascendis Pharma and The Brod Group to evaluate the impact of ACH on the functioning and well-being of patients and caregivers during the past 2 weeks. Details about AEM development and the scoring algorithm can be found in Psychometric Evaluation of the Achondroplasia Experience Measures Final Expanded Psychometric Analysis Report (dated 20 July 2023).

10.5.6.2.1. ACEM Observable Signs Measure (ACEM-OSM)

ACEM-OSM derivation includes 5 of the 8 items as shown in Figure 3. Each of the 8 ACEM-OSM items is scored using 0 = ‘never’ (best state) to 4 = ‘very often/always’ (worst state). The following 5 questions are included in the ACEM-OSM derivation: Ear problems, Pain, Sleep apnea, Low stamina, and Balance issues. The remaining 3 questions regarding Trouble breathing,

Hearing problems, and Speech issues are reported but not included in the ACEM-OSM derivation.

ACEM-OSM ranges from 0 (best) to 100 (worst) and is derived as a linear transformation of the average of the non-missing item-level scores when at least 3 of the 5item scores are non-missing. The average of the non-missing items scores is linearly transformed to a 0-to-100 scale using the following formula:

Average raw score / 4*100

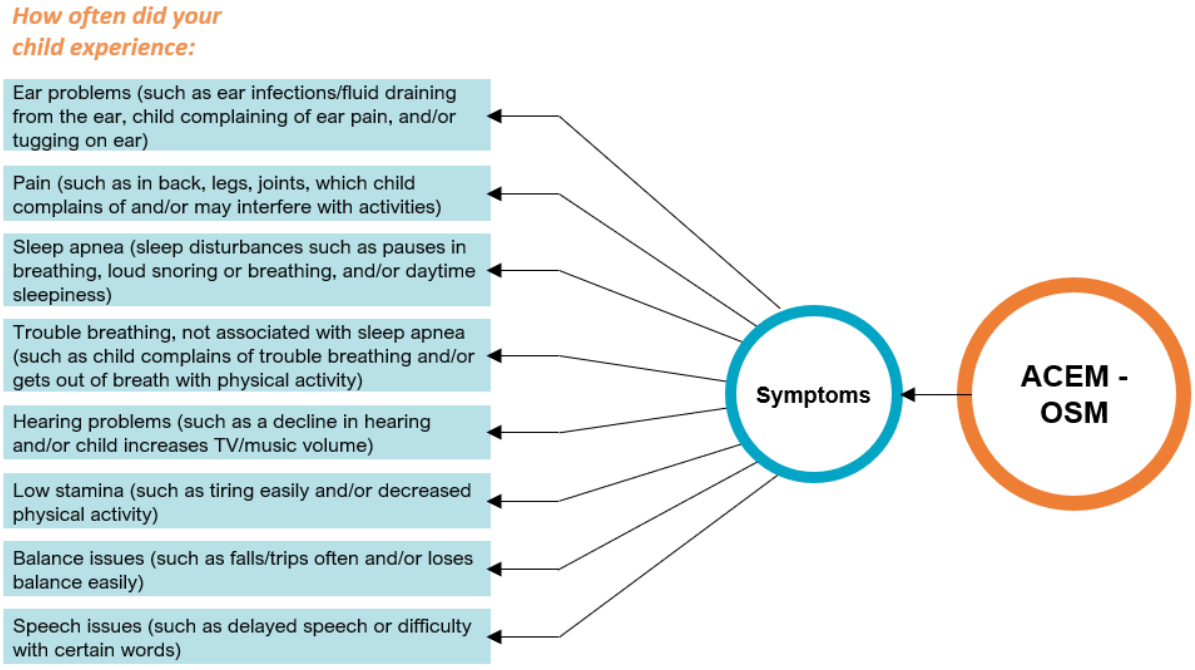
If less than 3 of the 5 ACEM-OSM item scores are available the ACEM-OSM score is not derived.

Change from baseline at Week 52 in ACEM-OSM will be analyzed by an ANCOVA model with treatment (navepegritide vs. placebo), baseline age, baseline score and strata as covariates, assuming unequal variances to account for possible unequal residual variance.

Estimated treatment difference will be presented with p-value and 95% CI and the effect within each treatment group will be presented with 95% CI.

The ACEM-OSM is part of the testing strategy defined in Section 10.5.2.

Figure 3: ACEM-OSM Conceptual Framework



10.5.6.2.2. ACEM Impact

ACEM Impact has 6 domains, including a total of 25 items as shown in Figure 3. For each domain, the score ranges from 0 (best) to 100 (worst). Each domain score is computed as the average of the non-missing item scores and then normalized to obtain the range 0 to 100. The

average is computed if at least 50% of item scores are non-missing, otherwise, the domain score is not computed.

The domain scores for ACEM Impact daily living functioning (ACEM-DF) and physical functioning (ACEM-PF) are normalized as: Average raw score / 5*100

The domain scores for ACEM Impact school, well-being, social functioning, social well-being are normalized as: Average raw score / 4*100

For each of the 6 domains the change from baseline at Week 52 will be analyzed by an ANCOVA model with treatment (navepegritide vs. placebo), baseline age, baseline score and strata as covariates, assuming unequal variances to account for possible unequal residual variance.

Estimated treatment differences will be presented with p-value and 95% CI and the effect within each treatment group will be presented with 95% CI.

The 2 domains ACEM-PF and ACEM-DF are part of the testing hierarchy defined in Section 10.5.2.

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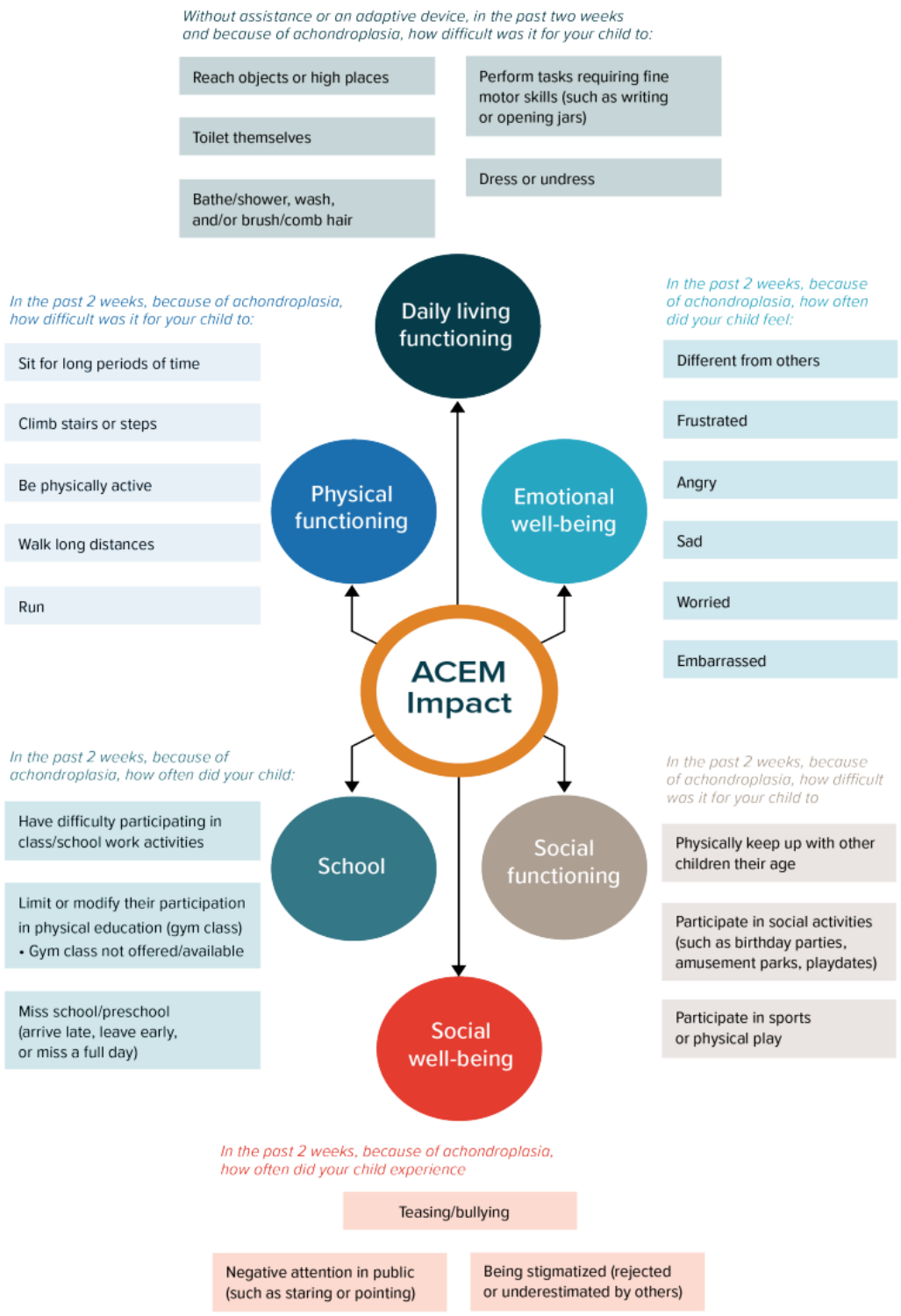
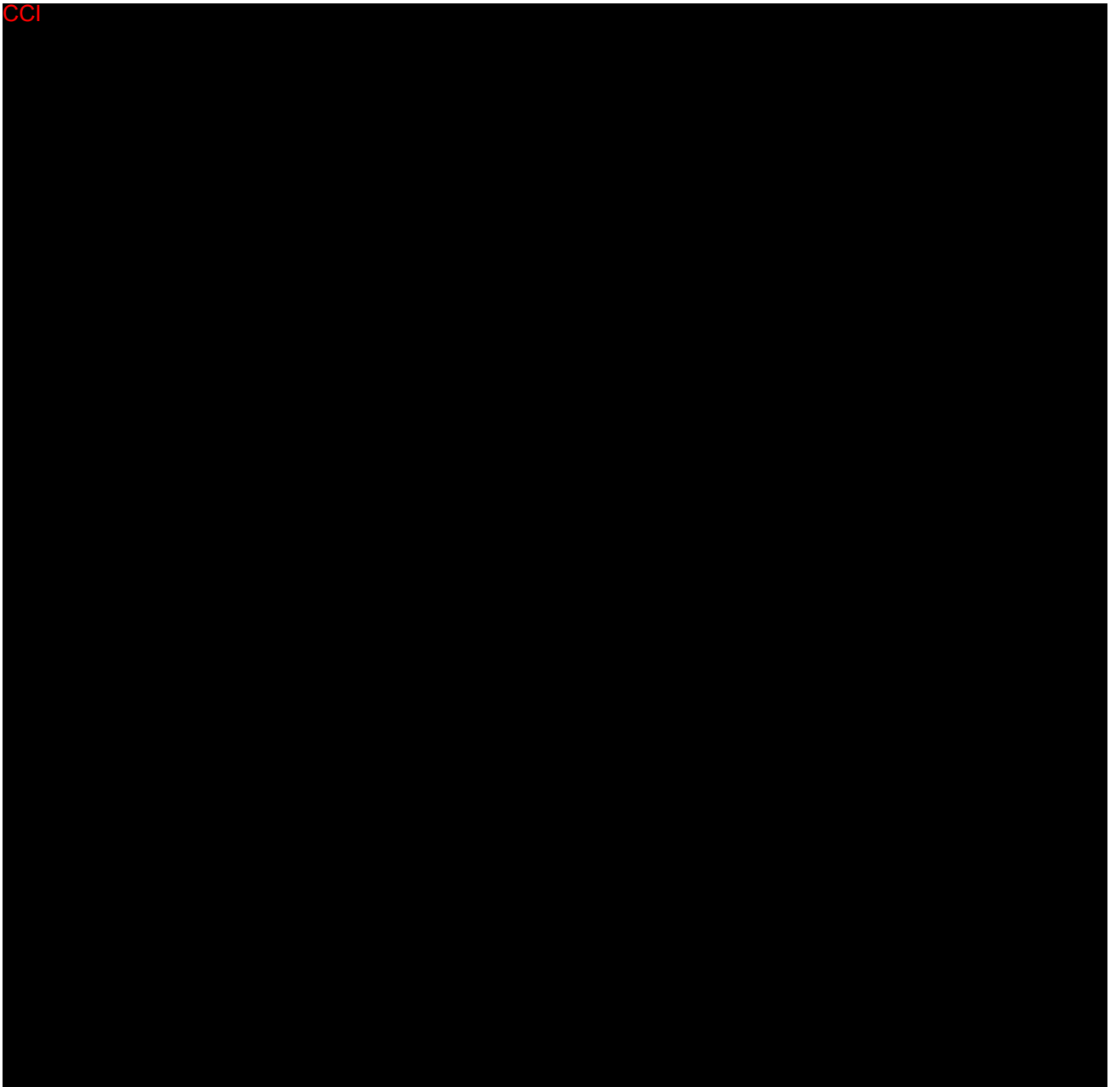
Figure 4: ACEM-Impact Conceptual Framework





10.5.6.3. Other Clinical Outcome Assessments

Observed values and change from baseline in other clinical outcome assessments as listed below will be summarized descriptively by treatment group.

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Change from baseline at Week 52 in SF-10 PHS will be analyzed by an ANCOVA model with treatment (navepegritide vs. placebo), baseline age, baseline score and strata as covariates, assuming unequal variances to account for possible unequal residual variance.

Estimated treatment difference will be presented with p-value and 95% CI and the effect within each treatment group will be presented with 95% CI.

The analysis will be done for all participants and for participants 5 years or older at baseline.

The analysis of SF-10 PHS for participants 5 years or older at baseline is part of the testing strategy defined in Section 10.5.2.

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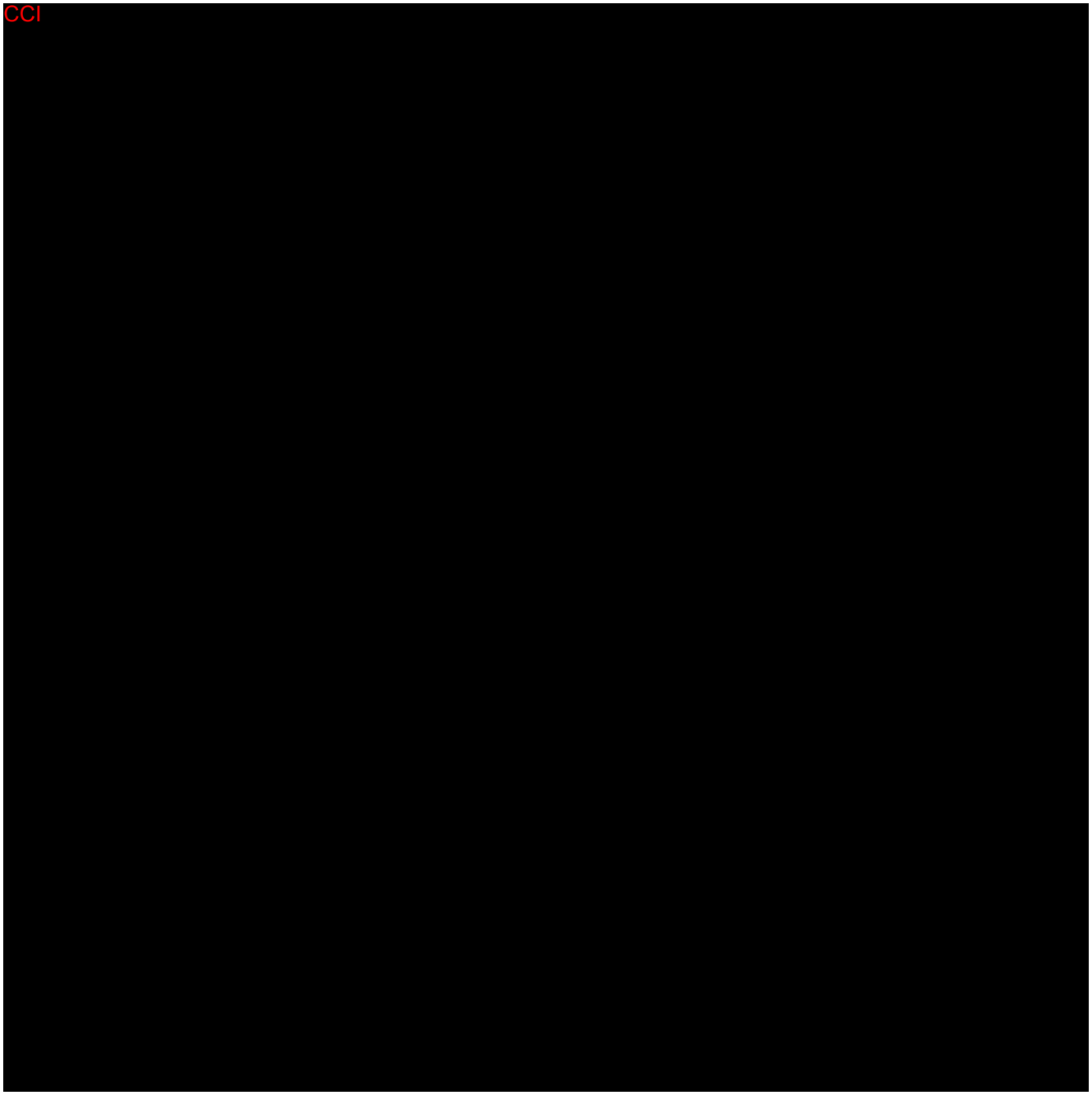

10.6. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Analysis Set for DB Period, OLE Period, and DB + OLE periods separately. For each period, exposure-adjusted event rate (EAER) in person-year may be calculated as appropriate for adverse events. The below formulas will be used:

- For exposure adjusted event rates, the individual exposure (years) will be derived as

(date of last visit attended in the period - date of first dose in the period +1)/365.25

- The EAER will be derived as

EAER (events/person year) = total number of events / sums of total exposure time (year)

The safety parameters will include adverse events (AEs) and clinical laboratory, vital signs, and ECG parameters and other safety parameters if collected. For safety endpoints, all analyses will be based on the observed data (i.e., with no imputation of missing data), except that some missing data in AEs will be imputed based on rules described in Section 9.2.

10.6.1. Adverse Events

The reporting period for adverse events starts at signing of informed consent and ends 30 days after last dose of IMP. After 30 days the investigator will only report serious adverse events that are related to IMP.

Adverse events will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA). The adverse event severity is determined by the investigator. The grading scale for the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 will be used for assessing adverse event severity.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) in the DB Period if it occurred on or after the first dose of IMP and was not present prior to the first dose in the DB Period, or it was present at the first dose but increased in severity during the DB Period.

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

An AE will be considered a TEAE in the DB + OLE period if the AE start date occurs or the AE worsen in severity on or after the first dose of navepegritide throughout the randomized and OLE periods.

An overview table of TEAEs will be presented showing participant incidence and number of events by

- CTCAE Grade
- CTCAE Grade 3 or higher
- Serious events
- Treatment-related events
- Serious treatment-related events
- Adverse event of special interest (AESI) incl. type of event
- ACH-related TEAEs
- Events leading to trial/IMP discontinuation.
- Events leading to death

Participant incidence and number of events of the following TEAEs will be tabulated by treatment group if applicable:

- TEAEs by SOC and PT
- TEAEs related to trial drug by SOC and PT
- Serious TEAEs by SOC and PT
- Serious related to trial drug TEAEs by SOC and PT
- Grade 3 or higher TEAEs by SOC and PT
- TEAEs by maximum severity
- ACH-related TEAEs by SOC and PT
- TEAEs leading to discontinuation of trial by SOC and PT
- TEAEs leading to discontinuation of treatment by SOC and PT
- Adverse event of special interest (AESI) for each type of event
- Other significant adverse events (e.g. bone related safety events)
- TEAEs with frequency of 5% or higher by SOC and PT
- Non-serious TEAEs with frequency of 5% or higher by SOC and PT
- TEAEs by PT
- Related to trial drug TEAEs by PT
- Serious TEAEs by PT

Detailed listings for all AEs, serious AEs, AEs leading to the discontinuation of study and treatment, AESIs and other significant AEs, and AEs leading to death if any will be generated. Furthermore, a listing of non-treatment emergent events will be provided if relevant.

10.6.2. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in both conventional and SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for Hematology, Biochemistry, Lipid panel, Hormones, and Glucose metabolism laboratory tests. For Urinalysis test number and percentage will be presented within each category. Refer to Protocol Section 10.2 for the laboratory parameters included in each test.

Based on creatinine values estimated glomerular filtration rate (eGFR) will be derived using the Bedside Schwartz Formula (Staples 2010):

$$[(0.413 \times \text{Height (cm)}) / \text{serum creatinine (mg/dL)}]$$

Box plots will be provided for safety parameters.

Listing with all measurements of ALT, AST, ALP, and bilirubin will be provided for participants fulfilling:

- 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)

At any timepoint.

10.6.3. Vital Signs

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

Box plots will be provided for systolic and diastolic blood pressure and heart rate.

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

All data – including temperature - will be listed.

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10.6.5. Pubertal Status

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

10.6.6. Physical Examination

Data listing for physical examination will be provided. Furthermore, a listing showing abnormal findings from physical examination will be provided.

10.6.7. Other Observations Related to Safety

Descriptive statistics for other observations related to safety (e.g. pregnancy, breastfeeding, overdose, drug abuse, misuse, medication error) will be prepared.

10.6.8. Electrocardiogram

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

Box plot for QTcF will be provided showing all scheduled visits.

The number and percentage of participants with shift from baseline to the worst post-baseline ECG interpretation by investigator will be summarized by treatment group.

Categorical analysis of QTcF results will be presented.

10.6.9. Radiographic Findings and Assessments

The below radiographic assessments will be summarized including change from baseline for at each time point and presented by treatment group:

- Bone age
- Ratio of bone age over chronological age
- Delay in bone age calculated as chronological age – bone age

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For exploratory purposes, BMD Z-score will be analyzed in ANCOVA model with treatment (navepegritide vs. placebo), baseline age, baseline value and strata as covariates, assuming unequal variances to account for possible unequal residual variance.

10.6.10. Antibody Parameters

The appropriateness of the approach taken to analyze and report anti-drug antibody data should be evaluated on a case-by-case basis (FDA 2016), following recent regulatory guidance and white papers (Shankar 2014). Statistical analysis of antibodies against drug (ADA) will include (but not be limited to) the following tabulated summaries of antibody frequencies and population percentages for 3 antibody types, namely anti-TransCon-CNP (named anti-TC-CNP), anti-CNP-38 and anti-CNP-22 binding antibodies:

- Incidence of pre-existing antibodies (positive baseline)
- Incidence of treatment induced antibodies by positive types (treatment emergent positive and treatment boosted positive) and overall
- Incidence of persistent antibodies by positive types and overall
- Incidence of transient antibodies by positive types and overall

Treatment induced ADA will include two positive types:

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

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

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

10.7. PHARMACOKINETIC CONCENTRATION DATA

Descriptive statistics will be provided for plasma concentration of Total CNP, free CNP (measured as Free CNP(89-126) also referred to as Free CNP-38) and mPEG at scheduled visits. Plasma concentration values below the limit of quantitation will be treated as zero in the descriptive statistics calculations. Missing values will be treated as if the sample was not taken. Concentration data will be tabulated in listings by analyte and visit. Summary tables will include the number of participants, number of samples with values below the limit of quantitation, mean, SD, SE, median, minimum, maximum, geometric mean, and geometric %CV. Plasma concentration data versus visit will be presented in figures.

Listing of individual plasma concentration of PK analytes will be presented.

11. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Not Applicable.

12. REFERENCES

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13. APPENDICES

13.1. SAP APPROVAL FORM

Statistical Analysis Plan
Approval Signature Form

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:	**ASND0036**

Original Statistical Analysis Plan: Version #: 3.0

Author:

_____ _____

Name, Title Date

PPD

Approved by:

_____ _____

Name, Title Date

PPD

_____ _____

Name, Title Date

PPD

Name, Title	Date
PPD	