Official Title: A multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability, and efficacy of TransCon hGH administered once a week versus standard daily hGH replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency (GHD)

NCT Number: NCT02781727

Document Date: SAP: 19 February 2019

[redacted]

Statistical Analysis Plan

Protocol Title:	A multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability, and efficacy of TransCon hGH administered once a week versus standard daily hGH replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency (GHD)
Protocol Number:	TransCon hGH CT-301
Compound:	TransCon hGH
Phase:	3
Sponsor:	Ascendis Pharma Endocrinology Division A/S Tuborg Boulevard 5, DK-2900 Hellerup, Denmark
SAP Author:	[redacted]
SAP Version:	5.0
SAP Date:	19 February 2019

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DOCUMENT HISTORY

Version	Date	Author	Description
1	13-Sep-2017	[redacted]	First final version
2	23-Oct-2017	[redacted]	Cross references/ hyperlinks added, missing references added
3	22-Jan-2019	[redacted]	All the updates in Version 3.0 are further clarifications, rather than changes, in the intended analyses documented in Version 2.0. The updates are finalized by the Ascendis medical and statistical team blinded to study randomization before database lock and unblinding. • Added detailed criteria to define Per Protocol Population in section 5 • Updated description of data imputation in section 6.1.2 • Added description of mapping post-baseline unscheduled visits and end of study visit in section 6.1.3 • Updated the language in calculations of height SDS and height velocity SDS, and added derivations of age, total duration of treatment (day), total number of planned doses, total actual dosage (mg), and height velocity at baseline in section 6.2 • Updated the language of major protocol deviations in section 7.2 • Updated the language of prior medication definition in section 7.3 • Updated the language in section 8.2 to include height velocity SDS analysis and added description of how Visit 3 will be incorporated for the analyses of IGF-1 /IGF-1 SDS/ IGFBP-3/ IGFBP-3 SDS for the PK/PD population • Updated the language of subgroup analysis and etiology, and extent of GHD subgroup definition in section 8.5, which is also included in detail as Appendix 1 • Updated the language of lab analysis in section 9.2 • Included details for anti-body analysis in section 9.3 • Updated the language of exposure and compliance definitions in section 9.11

4.0	13-Feb-2019	[redacted]	All the updates in Version 4.0 are to address FDA's comments received on 25 Jan 2019 • Updated the language of ITT definition in Section 5 • Removed LOCF imputation for numeric and categorical variables, and added non-responder imputation for categorical variables in Section 6.1.2 • Clarified the primary analysis for the primary endpoint is the MMRM model after retrieved dropout imputation in Section 8.1 • Removed testing of IGF-1 as part of hypothesis testing in Section 8.2 • Updated the language in Section 8.3 regarding how to calculate average IGF-1 SDS at Week 52 • Removed testing of IGF-1 in the multiplicity control section in Section 8.6
5.0	19-Feb-2019	[redacted]	All the updates in Version 5.0 are to address FDA's comments received on 19 Feb 2019 • Removed retrieved dropout imputation in Section 6.1.2. There are only two subjects have discontinued early during the study. There is no retrieved dropout in the study to form the basis for imputation for the two subjects. • Updated the language of primary analysis method using multiple imputation with ANCOVA, instead of MMRM, in Section 6.1.2 and Section 8.1.

SIGNATURE PAGE AND APPROVALS

[redacted]

Date

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20 Feb 2019
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ABBREVIATIONS

Abbreviation	Definition or Description
ADHD	Attention deficit hyperactivity disorder
AE	Adverse Event
ALT	Alanine-Aminotransferase
AST	Aspartate-Aminotransferase
ATC	Anatomical Therapeutic Chemical
BA	Bone Age
BMI	Body Mass Index
CA	Chronological Age
cm	Centimeter
C_{max}	Maximum Value of Concentration
CRF	Case Report Form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
fT3	Free Triiodothyronine
fT4	Free Thyroxin
GGT	Gamma-Glutamyl Transferase
GH	Growth Hormone
GHD	Growth Hormone Deficiency
HbA1c	Hemoglobin A1c
HDL	High-Density Lipoprotein
hGH	Human Growth Hormone
HR	Heart Rate
HT	Height
HV	Height Velocity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGF-1	Insulin-Like Growth Factor 1
IGFBP-3	Insulin-Like Growth Factor Binding Protein 3
ITT	Intent-to-treat
ISC	Independent Safety Monitoring Committee
ISRs	Injection Site Reactions
kg	Kilogram
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
m^2	Square Meter
mL	Milliliter
µg	Microgram
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo

MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor/Expert
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Imaging
ng	Nanogram
PD	Pharmacodynamic
PEG	Polyethylene Glycol
PK	Pharmacokinetic
PP	Per Protocol
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDS	Standard Deviation Score
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TSH	Thyroid-Stimulating Hormone
WHO	World Health Organization

1. Overview

This Statistical Analysis Plan (SAP) describes and supplements the planned analysis and reporting for Ascendis Pharma Endocrinology Division A/S protocol TransCon hGH CT-301 (A multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability, and efficacy of TransCon hGH administered once a week versus standard daily hGH replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency (GHD)), Final Version 1.0 dated 4 August 2016, and Amendment 1 dated 12 Sept 2017.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administartion (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3], for statistical practice.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

Clinical Research Protocol TransCon hGH CT-301, and Case Report Forms (CRFs) for Protocol TransCon hGH CT-301.

ICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

2. Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to evaluate and compare the annualized height velocity of prepubertal children with growth failure due to GHD treated with weekly TransCon hGH to that of a commercially available daily hGH formulation at 52 weeks.

2.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the safety of weekly TransCon hGH administered over 52 weeks compared to daily hGH
- To evaluate and compare the annualized height velocity over 52 weeks of weekly TransCon hGH to daily hGH
- To evaluate and compare the change in height standard deviation score (SDS) over 52 weeks of weekly TransCon hGH to daily hGH
- To evaluate the change in serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) and the change in IGF-1 SDS and IGFBP-3 SDS; and the normalization of IGF-1 SDS over 52 weeks of weekly TransCon hGH or daily hGH
- To describe the PK/PD profile of TransCon hGH, hGH, IGF-1, IGF-1 SDS, IGFBP-3, IGFBP-3 SDS and Polyethylene Glycol (PEG) administered as a weekly injection (PK/PD subset; TransCon hGH cohort only)
- To compare the C_{max} for hGH of TransCon hGH to the anticipated C_{max} of daily hGH
- To determine the incidence of anti-hGH antibodies for both treatments, and treatment emergent anti-PEG antibodies for TransCon hGH over 52 weeks

2.2 Efficacy, Safety, and PK/PD Endpoints (Target Variables)

2.2.1 Efficacy Variables

The primary efficacy variable (endpoint) is:

Annualized HV at 52 weeks for weekly TransCon hGH and daily hGH treatment groups

The secondary efficacy variables (endpoints) are:

- Annualized HV for the TransCon hGH and the daily hGH treatment group over 52 weeks
- Change in height (HT) SDS over 52 weeks for the TransCon hGH and the daily hGH treatment group
- Serum IGF-1 and IGFBP-3 levels and IGF-1 SDS and IGFBP-3 SDS; and the normalization of IGF-1 SDS over 52 weeks for the TransCon hGH and the daily hGH treatment group

2.2.2 Safety Variables

The primary safety variables (endpoints) are:

- Incidence of AEs
- Local tolerability (assessed by the subject, the parents/legal guardians and the investigator)
- Incidence of anti-hGH antibodies including neutralizing antibodies as needed (both cohorts) and incidence of treatment-emergent anti-PEG antibody formation (in TransCon hGH subjects)

- IGF-1 levels and IGF-1 SDS
- Parameters of glucose metabolism (fasting glucose and insulin level, Hemoglobin A1c (HbA1c)) and lipid parameters
- Hormone levels: thyroid status and morning cortisol
- All other hematology and biochemistry blood parameters
- Electrocardiograms (ECG)
- Results of the physical examinations, vital sign measurements
- Bone age (BA) at 52 weeks

2.2.3 Pharmacokinetic/Pharmacodynamic Variable(s)

The pharmacokinetic (PK) variables (endpoints) are:

Subset of at least 8 TransCon hGH treated subjects after 13 weeks of treatment:

- PK profile of TransCon hGH over 1 week
- PK profile of hGH over 1 week
- PK profile of PEG over 1 week
- C_{max} for hGH of TransCon hGH

The pharmacodynamic (PD) variables (endpoints) are:

- PD profile of IGF-1 and IGFBP-3 over 1 week
- PD profile of IGF-1 SDS and IGFBP-3 SDS over 1 week

3. Overall Study Design and Plan

This is a phase 3, randomized, open-label, active-controlled trial of TransCon hGH as compared to standard daily growth hormone, over 52 weeks (Figure 1). The trial will be conducted at approximately 100 sites in approximately 20 countries in North America, Europe, Middle East and North Africa, and Oceania. All centers will be specialized treatment centers in the management of pediatric GHD.

The trial consists of:

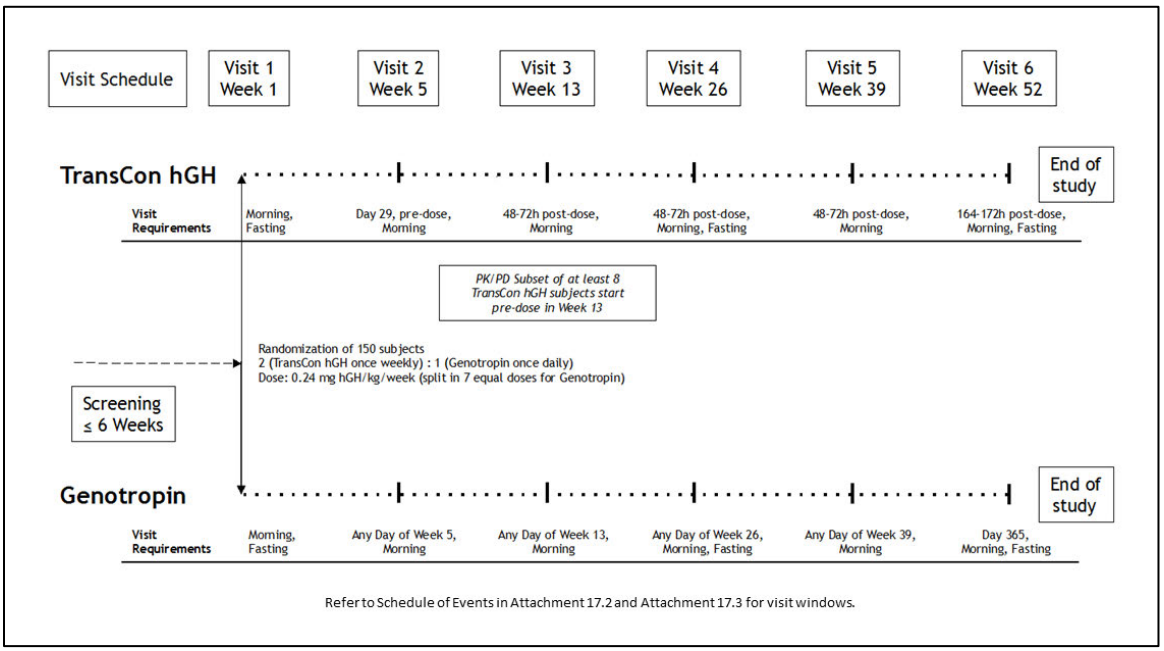
- Screening period - up to 6 weeks (plus approximately 2 weeks between randomization and V1)
- Treatment period - 52 weeks of dosing

The total duration of participation for each subject in the trial will therefore be up to about 60 weeks.

PK/PD profiling and electrocardiogram (ECG) screening bracketing presumed C_{max} of TransCon hGH, hGH, IGF-1, and PEG will be established in a subset of at least 8 TransCon hGH treated subjects (PK/PD subset).

All subjects who successfully complete the 52-week randomized trial will be invited to participate in an extension trial after the treatment period of this 52-week trial has ended. This extension period is to assess long-term safety and efficacy. Subjects on Genotropin treatment (Cohort 2) will be switched over to TransCon hGH treatment for this extension trial.

Figure 1



3.1 Measures Taken to Minimize Bias

Once all results determining the eligibility of the subject are available and reviewed by the Medical Monitor/Expert (MM), the subject will be centrally allocated to 1 of 2 cohorts: either TransCon hGH or Genotropin, in a 2:1 ratio, and allocated to strata using the minimization rule according to their age (≤6 and >6 years), peak growth hormone (GH) levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender. For the stratum peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), the stratum will be allocated based on the highest GH value of the 2 stimulation tests. The subject will be assigned a unique randomization number along with the cohort allocation. The trial auxologists will be trained and kept blinded to treatment allocation as far as possible at each site.

All efforts will be made to keep missing data to a minimum, including the following:

1. Investigators will be trained about the importance of retention
2. Investigators will be instructed to encourage complete follow-up for all subjects, including any subjects who might discontinue either weekly TransCon hGH or daily Genotropin therapy
3. The Informed Consent Form (ICF) and Assent Form will include a statement educating subjects and parents/legal guardians about the scientific importance of their data even if the subject discontinues study treatment early
4. Special efforts will be made to provide assistance to subjects/families who might discontinue due to travel or cost barriers, such as offers of transportation to the clinic
5. Most visits have visit windows to allow flexibility of clinic attendance (see Sections 10.1.2.1 and 10.1.2.2 of protocol)
6. Every effort will be made to contact subjects/legal guardians or other family members in order to maintain contact with the clinic

This is an open-label trial. Due to different dose frequencies and dosing techniques, it is not deemed suitable to employ blinding methods between TransCon hGH and Genotropin treatment assignment. However, attempts will be made to keep the the Sponsor staff (especially the MM) blinded to treatment. Any necessary unblinding to the Sponsor staff for safety purposes will be documented before database lock.

Subjects will be identified by a Subject Number (allocated at Screening), consisting of 3 digits to indicate the site and 2 digits specific for the subject.

3.2 Sample Size and Subject Population

This is a pivotal clinical trial intended to support market approval.

Based on the Phase 2 trial (Protocol ACP-001_CT-004) and similar growth hormone studies published in the literature, and assuming a SD of 3.5 cm/year with a non-inferiority margin of 2.0 cm, a sample size of 147 subjects in the ITT population will be needed to show non-inferiority of TransCon hGH treatment compared to daily hGH with a power of 90%. This sample size calculation is based on a 2:1 randomization and a 1-sided alpha level of 0.025.

A sample size of 150 subjects randomized has been chosen to account for slight imbalances in the randomization due to stratification of randomization. For 150 enrolled subjects, approximately 450 subjects may need to be screened in the trial.

Approximately 150 prepubertal, hGH-treatment naïve children (males and females) with GHD will be included. Subjects will be allocated to 1 of 2 treatment groups in a 2:1 ratio:

- Two thirds of the 150 subjects (approximately 100 subjects) will receive TransCon hGH treatment to obtain an expected 90 per protocol subjects in this cohort
- One third of the 150 subjects (approximately 50 subjects) will receive Genotropin treatment to obtain an expected 45 per protocol subjects in this cohort

4. Analysis and Reporting

4.1 Interim Analysis

No interim analysis is planned. An independent safety monitoring committee (ISC) will be established to monitor subject safety. Data used for ISC meetings will be handled according to the ICH E9 guidelines and therefore will not affect the study design and conduct from the efficacy perspective.

4.2 Final Analysis

All final, planned analyses identified in the protocol and in this SAP will be performed after the last subject has completed the last study visit and end of study assessments, and all relevant study data have been processed and integrated into the analysis data base. Any results from unplanned analyses (post-hoc) will be clearly identified in the text of the CSR.

5. Analysis Populations

The following analysis populations are planned:

Safety Analysis Population: The safety analysis population will include all randomized subjects who have received at least 1 dose of active treatment.

Intention-To-Treat Population (ITT): The Intent-to-Treat population will include all randomized subjects who have received at least one dose of active treatment

Pharmacokinetic/Pharmacodynamic Population (PK/PD): The PK/PD Population includes all subjects in the Safety Population who have PK/PD assessments. The PK/PD profile subset comprise a subset of subjects pre-identified as the PK/PD subset from the TransCon hGH cohort who attended Visit 3 as planned, and from whom blood samples were taken at time points predose, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 168 hours postdose. All subjects in the safety analysis population with additional PK/PD samples will be included in additional PK/PD analyses.

Per Protocol Population (PP): The basis of PP population is the ITT population who have relevant data evaluable for the primary efficacy endpoint of annualized HV at 52 weeks. Specifically, subjects were excluded from the PP population if they:

- Had a diagnosis known to impact growth (exclusion criteria 4, 5, 6, 10, 12, 13)
- Took the wrong treatment (eg. randomized to TransCon hGH cohort but took Genotropin in error)
- Missed or overdosed on at least 5 doses of TransCon hGH, or 35 doses of Genotropin
- Used prohibited concomitant medications at trial entry (exclusion criteria 15, 16)
- Failed to have a height measurement at the Week 52 visit

Given that the primary objective of the study is based on testing for non-inferiority, the primary efficacy analyses will be performed on both ITT and PP populations. The primary analysis population is the ITT population. The ITT population will be analyzed on the basis of the intention to treat a subject, i.e. the planned treatment regimen. The PP subset will be analyzed on the basis on the actual treatment given.

The safety analyses will be based on the Safety Analysis Population.

6. General Issues for Statistical Analysis

6.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by treatment groups.

In general, baseline and safety tables will be completed for the safety population unless otherwise specified. Efficacy tables will be presented for the ITT population and will be also completed for the PP population.

PK/PD tables will be produced for the PK/PD population, and the PK/PD profile subset.

The Analysis populations will be used according to Table 1.

Table 1: Analyses populations

Analyses	Safety Analysis Population	ITT Population	Per Protocol Population	PK/PD Population/ Profile Subset
Baseline Assessments (including inclusion/exclusion criteria and eligibility, prior therapies)	X	X	X	
Compliance and Exposure	X			
Safety (including concomitant therapies)	X			
Pharmacokinetics/ Pharmacodynamics				X
Efficacy		X	X	

Continuous, quantitative (absolute values at each timepoint and change from baseline if applicable) variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation (SD), standard error (SE) of the mean, median, minimum, and maximum, unless otherwise specified.

Categorical, qualitative, variable summaries will include the frequency and percentage of subjects who are in the particular category. In general the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the cohorts, unless otherwise specified. Where appropriate, the presentation of results will include shift tables, plots or confidence intervals.

All analysis will be performed using SAS® Software version 9.4 or later.

All PK/PD parameter estimations will be performed using Phoenix WinNonlin® version 6.4 or later.

6.1.1 Baseline Data

Baseline is defined as data collected at Visit 1. If data are missing at Visit 1, then data from screening will be used as baseline instead.

6.1.2 Handling of Missing Data

Missing height velocity will be imputed by a multiple imputation method as the primary analysis for subjects who prematurely discontinued for the primary endpoint:

Subjects with missing primary endpoint will have height value imputed using a multiple imputation model that contains the following variables: gender, baseline age, peak GH levels (log-transformed) at stimulation test, baseline height SDS – average SDS of parental height, and height values at post-baseline visits. The multiple imputation will be stratified by treatment ([4-5]), which is detailed in Section 8.1.

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

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

6.1.2.1 Step I: Imputation of Missing Data

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

The following pseudo SAS code and seed (301) will be used:

```
**********************************************************************
* Note:                                                               *
*       AAGE = Baseline age                                           *
*       PEAKGHLG = Peak GH levels (log-transformed) at stimulation test *
*      TRT01P = Treatment group: Genotropin, TransCon hGH             *
*      DMPHTSDS = Baseline height SDS – average SDS of parental height *
*      SEXN = Gender: 1 – Male; 0 - Female                            *
**********************************************************************
proc sort data=indsn;
   by TRT01P SUBJID;
run;


proc mi data=indsn seed = 301 nimpute = 100 out=imputed;
    mcmc chain=single initial=em (maxiter=1000) niter=1000 nbiter=1000;
    by TRT01P;
    var AAGE PEAKGHLG DMPHTSDS SEXN week5 week13 week26 week39 week52;
run;
```

6.1.2.2 Step II: Inference

For each of the 100 imputed datasets, height velocity will be recalculated based on the multiply imputed height values. The primary efficacy analysis will then compare the annualized height veolicty at Week 52 between TransCon hGH and Genotropin groups in the ITT population. The data will be analyzed using an analysis of covariance (ANCOVA) model with treatment and gender as factors, baseline age, baseline peak GH levels (log transformed) at stimulation test, and baseline height SDS - average SDS of parental height as covariates.

The sample SAS code for the ANCOVA model can be found below:

```
**********************************************************************
* Note:                                                              *
*       AAGE = Baseline age                                          *
*       PEAKGHLG = Peak GH levels (log-transformed) at stimulation test *
*      DMPHTSDS = Baseline height SDS – average SDS of parental height *
*       _IMPUTATION_ = Iteration number in the multiple imputation   *
*       TRT01P = Treatment group: Genotropin, TransCon hGH           *
*       SEX = Gender                                                 *
**********************************************************************
ods output lsmeans=lsm diffs=diff;
proc mixed data = ADEFF;
    by _imputation_;
    class TRT01P(ref='Genotropin') AVISIT SEX;
    model AVAL= AAGE PEAKGHLG DMPHTSDS TRT01P SEX/solution cl;
    lsmeans TRT01P/e diff cl;
    where AVISIT='Week 52' and PARAMCD='HGHTVEL' and ANL01FL='Y' and ITTFL='Y';
run;
```

The estimates from the 100 fitted models for each of the 100 imputed datasets will be combined to provide an overall estimate of the least square mean with a corresponding confidence interval for each treatment group and an overall estimate of the difference in least square means between the two treatment groups and a p-value ([6]). The following pseudo SAS code will be used:

```
proc sort data=lsm;
  by trt01p;
run;
```

```
ods output ParameterEstimates=miest_lsm;
proc mianalyze data=lsm;
  by trt01p;
  modeleffects estimate;
  stderr stderr;
run;

ods output ParameterEstimates=miest_diff;
proc mianalyze data=diff;
    modeleffects estimate;
    stderr stderr;
run;
```

The primary analysis model with ANCOVA will be repeated in the PP population. Because the PP population excludes subjects who have missing data at Week 52, the multiple imputation method described above will not be used for the PP analysis.

For categorical variables, the worse case (non-responder) imputation will be applied to impute missing data for ITT analysis.

If growth hormone stimulation data is missing at diagnosis, for example due to structural abnormalities leading to hypopituitarism, a value of 2 ng/mL will be used by convention.

For subjects missing height data for one of the two parents, the average parental height SDS will be estimated based on the non-missing parental height SDS. For subjects with no parental height data, the population median parental height SDS from all subjects with parental height data will be imputed.

6.1.3 Visit Windows

Table 2: Bioanalytical Samples visit windows from Visits 1 to 6

	Time Relative to Dosing, by Visits (Hours)					
Visit	**1**	**2**	**3**	**4**	**5**	**6**
TransCon hGH	predose, morning	predose, morning	48-72h, morning	48-72h, morning	48-72h, morning	164-172h, morning
Week	1	5	13 (+2)	26 (±1)	39 (±1)	52 (+1)
Day	1	29	87-88	178-179	269-270	365
Genotropin	predose, 2h, morning	morning	morning	morning	morning	morning
Week	1	5	13 (+2)	26 (±1)	39 (±1)	52 (+1)
Day	1	29-35	85-91	176-182	267-273	365

Abbreviation: hGH=human Growth Hormone

TransCon hGH Cohort (Cohort 1)

- Visits 1 and 2 will be performed on the day of the 1st and 5th dosing (Days 1 and 29), respectively.
- Visits 3, 4 and 5 will be performed 48-72 hours after the 13th, 26th and 39th dose, respectively.
- Visit 6 will be performed 7 days after the last dose (Day 365).

All attempts should be made to adhere to the planned visit schedule as specified per Table 2. However, in case the subject is not able to attend Visits 3, 4, 5 and 6 during Week 13, 26, 39 or 52, respectively, these visits can be performed with a + 2 week window for Visit 3, meaning either Week 14 or 15, if Week 13 is not achievable; and a ± 1 week window for Visits 4, and 5, meaning either Week 25 or 27, if Week 26 is not achievable or Week 38 or 40, if Week 39 is not achievable; and a + 1 week visit window for Visit 6, meaning Week 53, if Week 52 is not achievable.

Genotropin Cohort (Cohort 2)

- At Visit 1, subjects will be dosed in the morning at the clinic.
- All subjects in the Genotropin cohort will attend Visit 1 fasting with administration of the dose at the investigational site and predose sampling and will have an additional postdose sampling for hGH at 2 hours.
- Visits 2, 3, 4 and 5 will be performed on any day during Weeks 5, 13, 26 and 39, respectively. Preferably, all clinic visits will be in the morning for consistency of auxology measurements. Visit 4 needs to be conducted in the morning hours, since the subject is requested to be fasting. Visit 6 will be performed 1 day after the last dosing (Day 365) in the morning hours, since the subject is requested to be fasting.

All attempts should be made to adhere to the planned visit schedule as specified per Table 2. However, in case the subject is not able to attend Visit 3, 4, 5 and 6 during Week 13, 26, 39, or 52, respectively, these visits can be performed with a + 2 week window for Visit 3, meaning either Week 14 or Week 15, if Week 13 is not achievable; and a ± 1 week visit window for Visits 4 and 5, meaning either Week 25 or 27, if Week 26 is not achievable or Week 38 or 40, if Week 39 is not achievable; and a + 1 week visit window for Visit 6, meaning Week 53, if Week 52 is not achievable.

Post-baseline unscheduled visit (occurred after the date of initiation of the first dose) or end of study visit (early termination visit) will be mapped to the post-baseline scheduled visit with the closet target study day for each scheduled assessment per Table 3. If the unscheduled visit is in the middle of two scheduled visits, map it to the later one. After mapping, if there are more than one visits in the same window, the visit closer to the target assessment day will be used. If more than one visits have the equal distance to the target day then the later one will be used, if more than one visits on the same day, use the time or the sequence number to select the later record. For listings and shift tables, all data points will be included.

Table 3: Analysis Window to Map Unscheduled and Early Termination Visits

VISIT	Week	Target Study Day	Study Day Window
Visit 1	Week 1	1	<=1
Visit 2	Week 5	29	2-58
Visit 3	Week 13 (± 2 Week)	88	59-133
Visit 4	Week 26 (± 1 Week)	179	134-224
Visit 5	Week 39 (± 1 Week)	270	225-317
Visit 6	Week 52 (+ 1 Week)	365	>=318

6.2 Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analysis of the safety, efficacy or PK/PD as appropriate. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files.

Parameter	Description of Parameter
Date of Birth	Day of 15 is used to impute the day for all birth date
Age (Years)	(Date of Measurement – Date of Birth)/365.25
Age (Months)	((Date of Measurement – Date of Birth)/365.25) * 12
C_{max}	The maximum serum concentration observed.
Annualized Height Velocity at visit x (HV) cm/year	[(HT(Visit x) - HT (Visit 1)]* 365)/[(Date (Visit x) - Date (Visit 1)]
Change from baseline over 52 weeks	The value of each variable at each post-baseline timepoint minus the baseline score. The change from baseline will be calculated for: • change in height (HT) SDS • change in serum IGF-1 • change in serum IGFBP-3 • change in IGF-1 SDS • change in IGFBP-3 SDS
Normalized serum IGF-1 SDS	Proportion of subjects with IGF-1 Standard Deviation Score (SDS) of 0 to +2.0. Also derive for -2.0 to +2.0, -1.0 to +2.0.

Parameter	Description of Parameter
Total duration of treatment (day)	TransCon hGH Last dose date – first dose date + 7 Genotropin Last dose date – first dose date + 1
Total number of planned doses	TransCon hGH Round (Last dose date – first dose date + 7)/7 to the nearest integer Genotropin Last dose date – first dose date + 1
Total Actual Dosage (mg)	TransCon hGH Sum Concentration (mg/mL) x volume (mL) over all injections Genotropin Sum dose (mg) over all injections
Parents' Height SDS	((Parents Height/M)^L)-1)/(L x S) Where M=median , S= generalized coefficient of variation, and L= power in the Box-Cox transformation, the M, S, L values are obtained from the CDC website; Percentile Data Files with LMS Values
Region	• Australia and New Zealand will be mapped to 'Oceania' • Belarus, Bulgaria, France, Georgia, Germany, Greece, Italy, Poland, Romania, Russia and Ukraine will be mapped to 'Europe' • Canada and United States of America will be mapped to 'North America' • Egypt and Jordon will be mapped to 'Middle East and North Africa' • Turkey and Armenia will be mapped to 'Asia'
Height Velocity at Baseline	Calculated based on the height measurement pre-dose, with the measurement closest to the time of one year before baseline if we have multiple height measurements before baseline. If the there are two measurements with equal distance to one year prior to baseline, we use the one closer to baseline of the two to calculate baseline height velocity

Parameter	Description of Parameter
Height SDS	Height expressed in Standard Deviation Score (SDS) is derived using CDC 2000 (United States of America)/Kuczmarski method as ((Height/M)^L)-1)/(L x S). Where M=median , S= generalized coefficient of variation, and L= power in the Box-Cox transformation, the M, S, L values are obtained from the CDC website; Percentile Data Files with LMS Values. M, L, and S need to be interpolated based on the next lower age category, and the next upper age category.
Height Velocity SDS	The Height Velocity expressed in SDS is derived as follows. HV SDS = (Observed HV – Reference HV) / Reference HV SD. Mean age at the two visits where HV is calculated will be used to determine reference HV and HV SD. Mean HV and SD HV are defined by age categories between male and female as in the Tanner's publication [7a, 7b]. Reference HV and HV SD are interpolated based on the lower age category and the next upper age category and mean age

The following variables are automatically calculated in the eCRF. However, the reference methods for calculation are reported in the following table for completeness of information.

Parameter	Description of Parameter
Birth Weight SDS	The Birth Weight Standard Deviation Score is calculated in the eCRF using the method described in [8]

7. STUDY SUBJECTS AND DEMOGRAPHICS

7.1 Disposition of Subjects and Withdrawals

The number of subjects included in each analysis set (Safety, ITT, and PP) will be presented by treatment group and overall. The number and percentage of subjects in the Safety population, who completed the study treatment period, who discontinued the study prior to the end of treatment and the reason for discontinuation, along with the number who completed the Follow-up Visit will be presented for each treatment group and overall.

7.2 Protocol Violations and Deviations

A list of major protocol deviations that could significantly affect study assessments will be identified. The incidence of major protocol deviations will be presented by treatment group for all randomized subjects if appropriate.

7.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for all enrolled subjects in the study population by treatment groups.

Descriptive summaries of demographic and other baseline conditions for each analysis set (ITT and PP) will include:

- Demographics:
  - Age (years)
  - Age category (≤6 years, >6 years)
  - Gender (male, female)
  - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Region (North America, Europe, Middle East and North Africa, and Oceania)
  - Absolute height (cm)
  - Weight (kg)
  - Body mass index (BMI) (kg/m^2)
  - Mother's height (cm)
  - Father's height (cm)
  - Mid-Parental Height (MPH) SDS
- Medical History (including pre-study height velocity)
- Anti-transglutaminase antibodies
- Results of GH stimulation tests: insulin tolerance test (with cortisol response to hypoglycemia), arginine test, clonidine test, glucagon test (with or without propranolol, with cortisol response), L-dopa test
- Peak GH levels in stimulation tests (≤5 ng/mL, >5 ng/mL)
- IGF-1 SDS
- Bone age
- Assessment of adrenal and thyroid status
- Results of karotype testing
- Results of Brain and Sellar Magnetic Resonance Imaging (MRI)
- Prior Medications

Prior medication: Note that all medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version WHODrug-DDE-B2-201603). The frequency and percentage of all prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) class 2 and ATC class 4 if applicable for all safety population by treatment group.

Prior medication is defined as any medications which have a start date prior to the date of the first administration of the study drug.

Note that medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0). Incidences of findings in medical history will be summarized by system organ class (SOC) and preferred term by treatment group.

8. Efficacy Analysis

It may be necessary to complete additional exploratory analyses after the planned analyses are completed. Full details of additional analyses will be presented in the CSR.

All statistical tests except non-inferiority tests will be based on a 2-sided test at the significance level of 0.05 and 95% confidence intervals, unless otherwise specified. Non-inferiority tests will be based on a one-sided significance level of 0.025.

8.1 Primary Efficacy Variable Analysis

The absolute values and mean change from baseline at each timepoint of the annualized height velocity will be presented by treatment group with descriptive statistics.

The primary endpoint, annualized height velocity at week 52, will be compared between TransCon hGH treatment and daily hGH treatment, by a non-inferiority comparison with a non-inferiority margin of 2.0 cm/year, followed by a test of superiority if non-inferiority is established.

As the primary analysis, an ANCOVA model will be used to analyze annualized height velocity at week 52, after potential multiple imputation as described in Section 6.1.2. The annualized height velocity at week 52 will be included in the model as a response variable. The model will include baseline age, peak GH levels (log transformed) at stimulation test, baseline height SDS – average SDS of parental height as covariates, treatment and gender as factors. The estimates from the 100 fitted models for each of the 100 imputed datasets will be combined to provide an overall estimate of the between treatment group difference with a corresponding confidence interval and a p-value.

For the primary efficacy analysis, a 2-sided 95% confidence interval will be calculated for the difference in least square means between the 2 treatment groups [TransCon hGH treatment minus daily hGH] at Week 52. If the lower confidence bound is >-2.0 cm, non-inferiority is demonstrated in terms of effectiveness. If the lower confidence bound is >0, superiority is established.

Treatment-by-covariate interaction will be examined as appropriate as part of the analysis model examination.

Hight velocity at other post-baseline visits will be analyzed similarly using the same ANCOVA model as described above for the primary efficacy analysis. The same ANCOVA model described above will also be used to analyze observed cases as a sensitivity analysis of the primary analysis.

8.2 Secondary Efficacy Variable Analysis

The absolute values and mean change from baseline at each timepoint of other secondary efficacy endpoints will be presented by treatment group with descriptive statistics. Height velcocity SDS will also be summarized. Mixed model for repeated measurement (MMRM) models will be used for the following continuous secondary efficacy endpoints. Missing data will not be imputed before conducting the MMRM model. The MMRM model for height velocity will include baseline age, peak GH levels (log transformed) at stimulation test, baseline height SDS – average SDS of parental height, as covariates, gender as a fixed factor, and subject as a random effect. The MMRM model for all all the following continues variables will include treatment, timepoint, and treatment by timepoint interaction.

- height velocity
- change in height SDS
- serum IGF-1 levels
- serum IGFBP-3 levels
- IGF-1 SDS
- IGFBP-3 SDS

The MMRM model for change in height SDS, IGF-1, IGFBP-3, IGF-1 SDS and IGFBP-3 SDS will include baseline age, peak GH (log transformed), baseline (of the corresponding variable) as covariates, and gender as a factor.

For the patients who are in PK/PD population, the average values from hour 48 and hour 72 at Visit 3 (Week 13) will be considered as the Visit 3 value for IGF-1, IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS, and used in the analyses for Visit 3.

Two sided 95% confidence intervals will be calculated for the difference in least square means between the 2 treatment groups. Change from baseline will be summarized when appropriate as supportive analyses.

The rate of subjects achieving normalization of serum IGF-1 SDS will be calculated by treatment group and visit defined as SDS scores of 0 to 2.0. Additionally, cut points of -2.0 to +2.0 and -1.0 to +2.0 will be assessed. The following IGF-1 SDS variables will be derived:

- Average IGF-1 SDS at visits 3, 4, and 5
- Proportion of subjects achieving normalization of IGF-1 SDS of 0 to 2.0 based on the average IGF-1 SDS at visits 3, 4, and 5

The rates of subjects achieving IGF-1 SDS 0-2.0 will be analyzed by logistic regression adjusting for baseline age and baseline IGF-1 SDS. In case of model convergence issues caused by sparse cells, Fisher's exact test will be carried out instead.

8.3 Average IGF-1 SDS at Week 52 based on population PK/PD modeling

Due to differences in the PD profiles of the two treatment groups, the analysis of superiority in IGF-1 SDS described in Section 8.2 will be supported by the analysis of average IGF-1 SDS starting from Visit 3 (Week 13) to end of study. The average IGF-1 SDS at Week 52 group will be calculated based on the following steps:

1. A non-linear mixed model by treatment will be conducted for IGF-1 concentration data, based on rich sampling data from the Phase 2 study in growth hormone deficient pediatrics (Ascendis Pharma study no. ACP-001 CT-004), and from the rich sampling in the PK/PD population in this study, and from all sampling data at steady state (visits 3-6) from the rest of the subjects in this study.
2. The non-linear mixed model of IGF-1 concentration will be fitted to describe relationship of dose, time since dosing to IGF-1 concentration. The most simple compartment model which can sufficiently explain IGF-1 kinetics will be selected and goodness of fit will be assessed based on standard model diagnostics.
3. The weekly IGF-1 AUC (0-168 hours after dosing) will be calculated for each individual subject based on the non-linear mixed model established from Step 2.
4. The weekly average IGF-1 concentration for each subject is calculated as:
   Weekly average IGF-1 concentration = Weekly IGF-1 AUC (from Step 3)/168.
5. The average IGF-1 SDS at Week 52 is determined based on the weekly average IGF-1 concentration in Step 4 for each individual subject.

The average IGF-1 SDS at Week 52 will be analyzed by an analysis of covariance (ANCOVA) model with the same model covariate selection as described for the MMRM model in Section 8.2. The proportion of subjects achieving average IGF-1 SDS within 0-2.0 will be analyzed with the same logistic regression model as described in Section 8.2.

8.4 Other Efficacy Variable Analysis

All efficacy endpoints will be summarized descriptively by treatment group. Additional descriptive summaries may be added by treatment group and randomization stratum, separately for all 3 randomization strata.

Figures will be created to display the time course of continuous efficacy endpoints by treatment group.

8.5 Subgroup Analysis

Efficacy variables will be summarized by age (<6 years and ≥ 6 years), gender, the baseline GH-stimulation strata (≤5 ng/mL and >5 ng/mL), etiology and extent of GHD (isolated idiopathic vs isolated organic (determined by abnormal MRI) vs multiple pituitary hormone deficiencies) (Appendix 1).

The Etiology and extent of GHD subgroup definition:

Isolated idiopathic GHD: Subjects without deficiencies of other pituitary axes, and without a history of brain irradiation, and with either a normal MRI assessment or an abnormal MRI that is irrelevant to pituitary gland deficiency based on review of the MRI report text by a medical monitor.

Isolated organic GHD: Subjects without deficiencies of other pituitary axes, and with either a history of brain irradiation, or with an abnormal MRI that is relevant to pituitary hormone deficiency based on review of the MRI report by a medical monitor.

GHD associated with multiple pituitary hormone deficiencies: Subjects with deficiencies of multiple pituitary axes regardless of MRI results.

Abnormal MRI results are considered as relevant to pituitary hormone difficiency if the MRI report states any small or absent pituitary gland or pituitary stalk, or stalk interruption, or ectopic pituitary. The determination of brain irradiation history and the MRI abnormality relevance to pituitary hormone deficiency will be determined by sponsor medical monitor review and will be recorded and captured in the CDISC database.

8.6 Multiplicity Analysis/Procedure

The familywise type-1 error of the study is controlled at 2-sided alpha = 0.05. Non-inferiority for AHV will be tested first, based on the primary analysis (method as described in Section 8.1). If successful, then the superiority for AHV will be tested next.

9. Safety and Tolerability Analysis

The analysis of safety assessments will include summaries of the following categories of safety and tolerability data collected for each subject and will use the safety analysis set:

Adverse Events

- Adverse Events (AEs), treatment-emergent AEs (TEAEs), and serious adverse events (SAEs)
- AEs leading to withdrawal
- Any deaths

Clinical Laboratory Investigations (Biochemistry, Hematology, Hormone Levels, Glucose Metabolism, Lipid Metabolism, Antibodies)

Vital Signs (blood pressure, heart rate, respiratory rate, body temperature)

Electrocardiograms (ECG)

Physical Examinations

Concommitant Medications

Study Drug Exposure

9.1 Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA (Version 19.0).

TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). Missing dates and times will not be replaced.

The following are used for guidance for programmers.

- If the start time of an AE is missing, but the start date is complete, an AE will only be excluded from treatment-emergent AEs if the start day is before day of first treatment or the start day is after end day of the treatment-emergent period.
- If the start time and day are missing but the start month is complete, an AE will only be excluded from treatment emergent AEs if the start month is before month of first treatment or the start month is after end month of treatment-emergent period or if the stop date/time is before the start of first treatment.
- If the start day and months are missing but the start year is complete, an AE will only be excluded from treatment-emergent AEs if the start year is before year of first treatment or if the start year is after end year of treatment-emergent period or if the stop date/time is before the start of first treatment.

If the start date is completely missing, an AE will not be excluded from treatment-emergent AEs unless the stop date/time is before the start of first treatment.

All AEs will be summarized in a table whose rows give the number of subjects for each of the following:

- All TEAEs
- SAEs
- Drug-related TEAEs
- TEAEs leading to discontinuation of study drug

Summaries of incidence rates (frequencies and percentages) of individual TEAEs by MedDRA SOC and preferred term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum intensity, and TEAEs by strongest relationship to study drug.

Each subject will be counted only once within each preferred term. If a subject experiences more than one TEAE within a preferred term only the TEAE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity.

No inferential statistical tests will be performed.

In the AE data listings, all AEs will be displayed.

9.1.1 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term, will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages) of SAEs by treatment group, SOC, and preferred term will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF.

9.2 Clinical Laboratory Evaluations

Descriptive summaries of actual (absolute) values and changes from baseline values if applicable will be presented for the following by treatment and visit in both original and standard units for the Safety Population using central laboratories data:

- Biochemistry: sodium, potassium, calcium, phosphate, chloride, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), albumin, total protein, creatinine, urea nitrogen, uric acid, serum iron and transferrin
- Hematology: hemoglobin, leukocytes, differential blood count of leukocytes, platelet count
- Hormone Levels: thyroid status (TSH, fT4, and fT3 levels) and morning cortisol
- Glucose Metabolism: HbA1c, and fasting insulin and glucose, HbA1c.
- Lipid Metabolism: Total cholesterol, triglycerides, HDL and LDL

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will be presented in a data listing. For each laboratory parameter, if applicable, shifts in assessments of abnormality from baseline to each post-baseline visit will be presented (shift tables) for data from central laboratories.

Data listings of laboratory will also be provided, displaying details of each laboratory test captured on the CRF for central and local laboratories separately.

9.3 Antibodies

The appropriateness of the approach taken to analyze and report anti-drug antibody data should be evaluated on a case-by-case basis [9], following recent regulatory guidances and white papers [10]. 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 each cohort):

1. Incidence of pre-existing anti-hGH binding antibodies (positive Baseline)
2. Incidence of treatment induced anti-hGH binding antibodies by positive types (treatment emergent positive and treatment boosted positive) and overall
3. Incidence of persistent anti-hGH binding antibodies by positive types and overall
4. Incidence of transient anti-hGH binding antibodies by positive types and overall
5. Incidence of treatment induced anti-hGH neutralizing antibodies[1] by positive types and overall
6. Incidence of persistent anti-hGH neutralizing antibodies by positive types and ovearll
7. Incidence of transient anti-hGH neutralizing antibodies by positive types and overall
8. Incidence of pre-existing anti-PEG antibodies (positive Baseline)
9. Incidence of treatment induced anti-PEG binding antibodies by positive types and overall
10. Incidence of persistent anti-PEG antibodies by positive types and overall
11. Incidence of transient anti-PEG antibodies by positive types and overall

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

In addition, treatment induced anti-hGH binding, anti-hGH neutralizing antibodies, and anti-PEG antibodies will also be summarized by visit and positive types and overall.

Treatment induced ADA will include two positive types:

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

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

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

9.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and Respiratory Rate (RR). These summaries will be presented by treatment, visit, and assessment time for the Safety Population.

A data listing of vital signs will also be provided, displaying details of each vital sign test captured on the CRF.

9.5 ECGs

Descriptive summaries will be presented for ECG measures of PR interval, RR interval, QRS interval, QT interval, and HR. These summaries will be presented by treatment group and visit.

The number and percentage of subjects with normal and abnormal ECG results (as per Appendix 2) will be summarized for the Safety Population by treatment group. For each ECG measure, if applicable, shifts in assessments of abnormality from baseline to each post-baseline visit will be presented (shift tables).

A data listing of ECG will also be provided, displaying details of each ECG measure captured on the CRF.

9.6 IGF-1

The number and percentage of subjects will be presented where:

- IGF-1 SDS > 2.0
- IGF-1 SDS > 3.0

for at least 2 consecutive assessments.

Incidence of subjects with abnormally high IGF-1 SDS will be presented

9.7 Bone Age

The change in bone age, the ratio of bone age over chronological age, and the ratio of bone age advancement over chronological age advancement will be calculated. Subjects with too much bone age advancement will be reviewed for potential safety implications.

9.8 Injection site reactions (ISRs)

The number and percentage of subjects will be presented for ISRs and ISRs resulting in discontinuation.

9.9 Further Safety Evaluations

Results of physical examination will be summarized by treatment group, body system, and visit.

A data listing of physical examinations will also be provided, displaying details of each physical examination captured on the CRF.

Local tolerability will be summarized based on the investigator's and subject/parents/legal guardians assessment of pain, erythema, bruising, itching, and swelling.

A data listing of investigator's and subject/parents/legal guardian assessment will also be provided.

9.10 Concomitant Medication

Concomitant medications will be analyzed in the same way as prior medications.

Permitted Concomitant Medications

- Replacement therapy for pituitary deficiencies of other axes. As growth hormone may enhance the transformation of hydrocortisone to cortisone, the investigator may increase the dose of hydrocortisone replacement therapy if needed (eg, for anticipated stress).
- Glucocorticoid therapy for indications other than adrenal replacement (eg, asthma) may be administered in a dose equivalent to inhaled budesonide of not more than 400 µg/d for

a maximum of approximately 1 month during 1 calendar year (approximate equivalent doses: fluticasone: 264 µg/d; beclomethasone: 504 µg/d; flunisolide 1,000 µg/d; triamcinolone: 1,000 µg/d; mometasone: 211 µg/d; ciclesonide 264 µg/d).
- Treatment for diabetes
- Over-the-counter vitamins, minerals or other dietary supplements only if their use is agreed to by the investigator.

Prohibited Concomitant Medications
- Estrogen
- Anabolic steroids; systemic corticosteroids other than in the doses indicated above
- Weight-reducing drugs or appetite suppressants other than for the treatment of ADHD

A concomitant medication is defined as any medication other than the investigational or reference product that is administered from the first day of study drug administration up until the end of the trial. The frequency and percentage of all concomitant medications will be summarized by ATC class 2 and ATC class 4 if applicable for all safety subjects in the study population by treatment group, unless otherwise specified.

If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed to be concomitant if it cannot be definitely shown that it was not administered during the treatment period. Missing dates will not be replaced.

Thus, the following approach will be taken for exclusion from concomitant medications because of discontinuation before start of treatment:

If the stop day is missing but the month is complete, then the medication will be excluded from concomitant medications only if the stop month is before the month of treatment start.

If the stop day and month are missing but the year is complete, then the medication will be excluded from concomitant medications only if the stop year is before the year of treatment start.

If the stop date is completely missing, then the medication will not be excluded.

9.11 Exposure and Compliance

For each subject, the individual extent of exposure will be calculated in terms of:
- Total duration of treatment
- Total number of planned doses
- Total number of actual doses
- Actual Total dosage (mg)

These variables will be listed by subject, sorted by treatment group and subject number. Summary statistics per treatment group will be tabulated overall.

For the TransCon hGH group, subjects whose weekly actual dosage (mg/kg/wk) differ from the planned weekly dosage of 0.24 mg/kg/wk will be identified and followed for potential explanation.

Study drug compliance will be calculated as:

Total number of doses taken /total number of planned doses

Compliance will be summarized using the following categorization; <80%, ≥80%, ≥90%, ≥95% and ≥100%

Exposure and compliance will be listed by subject and presented for the safety population set by means of summary statistics by treatment group.

10. Changes from Planned Analysis

No changes from planned analysis.

11. Other Planned Analyses

11.1 Pharmacokinetic and Pharmacodynamic Analyses

11.1.1 Safety Population Exposure Data, PK analytes

Blood samples will be processed to serum for quantitation of hGH, TransCon hGH (ie, TransCon PEG40 hGH) and PEG (measured as total methoxypolyethylene glycol, 40 KDa [mPEG40]), at Screening and Visit 1 through Visit 6. The samples will be analyzed according to Table 4 below.

Table 4: Blood Sampling Process

Cohort 1	**Analyte**	**Screening**	**Visit 1 Week 1**	**Visit 2 Week 5**	**Visit 3 Week 13**	**Visit 4 Week 26**	**Visit 5 Week 39**	**Visit 6 Week 52**
(TransCon hGH)		**-**	**Predose**	**Predose**	**48-72h post dose**	**48-72h post dose**	**48-72h post dose**	**168h post dose**
	hGH	x	x	x	x	x	x	x
	TransCon hGH	-	x	x	x	x	x	x
	PEG	x	x	x	x	x	x	x
Cohort 2		**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
(Genotropin)		**-**	**Predose, 2h**	**Morning**	**Morning**	**Morning**	**Morning**	**Morning**
	hGH	x	x	x	x	x	x	x
	PEG	x	x[1]	-	-	-	-	-

[1]Predose only

The lower limits of quantitation (LLOQ) for each of the PK analytes are as follows:

- hGH: 2.00 ng/mL
- TransCon hGH: 20.0 ng hGH/mL
- Total PEG: 300 ng/mL

Serum concentration values below the limit of quantification (BLQ) will be set to zero when calculating summary statistics. Serum concentration data will be listed and summarized by nominal visit/timepoint for each Treatment and analyte using descriptive statistics. For serum concentration listings, three significant figures will be reported as in the original serum concentration raw data.

Arithmetic mean and individual serum concentration data versus visit will be presented in figures.

Accumulation ratios will be calculated for TransCon hGH, PEG and hGH, where possible and as data permit.

11.1.2 PK/PD-subset Sample Concentration Data, PK analytes

Blood samples for PK assessment in TransCon hGH Cohort 1 PK/PD Population will be collected at Visit 3 (Week 13) at following time points: Predose (defined as time zero), 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 hours post dose.
Below are the time windows by design for PK sample collection:

- Cohort 1: Predose (-0.5 hour): within ± 30 minutes
- Cohort 1: 8 to 48 hours post-dose: ±1 hour
- Cohort 1: 72 to 168 hours post-dose: ± 3 hours

All concentrations will be included in the PK analysis using actual times post-dose.
Blood samples will be processed to serum for quantitation of hGH, TransCon hGH and PEG.
Arithmetic mean serum concentration versus nominal time profiles will be presented in figures on both linear and semi-logarithmic scales for the PK/PD subset. Individual serum concentration versus actual time profiles will be presented in figures on both linear and semi-logarithmic scales.

11.1.2.1 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated for the following analytes:

- hGH
- TransCon PEG40 hGH
- mPEG40

The individual serum concentration versus actual time data for all analytes will be used to derive the PK parameters using non-compartmental analysis, as deemed appropriate, using Phoenix WinNonlin (Version 6.4 or higher).

The following serum PK parameters will be estimated for each analyte. Other parameters may be calculated if deemed necessary and as data permit.

Parameter	Description
C_{max}	Maximum observed serum concentration
C_{max}/dose	Maximum observed serum concentration divided by dose
T_{max}	Time to reach maximum observed serum concentration
T_{last}	Time of the last quantifiable concentration
AUC_{0-t}	Area under the serum concentration-time curve from time 0 to the last quantifiable concentration calculated by the linear trapezoidal rule: $AUC_{0-t} = \sum_{i=1}^{n} \frac{(C_i + C_{i-1})}{2}(t_i - t_{i-1})$, where C_i and C_{i-1} is the serum or plasma concentration at t_i and t_{i-1}, respectively, and t_i-t_{i-1} is the time interval.
AUC_{0-168}	Area under the serum concentration-time curve from time 0 to 168 hours
AUC/dose	Area under the serum concentration-time curve divided by dose
k_{el}	Terminal phase rate constant, calculated using linear regression on the terminal portion of the ln-concentration versus time curve. At least 3 time points (excluding C_{max}) and adjusted $r^2 \geq 0.80$ are required to calculate and retain k_{el} and its associated parameters.
$t_{1/2}$	Terminal elimination half-life, calculated as $t_{1/2} = \ln(2)/ k_{el}$
r^2	Correlation coefficient (goodness of fit statistic) associated with the estimation of k_{el}
Vz/F	Apparent volume of distribution, calculated as Vz = Dose / k_{el} x AUC_{0-inf}
CL/F	Apparent Clearance, calculated as Cl = Dose/ AUC_{0-inf}

For serum concentration data, all values below the limit of quantification (BLQ) will be set to 0 for summary statistics and graphs. For the calculation of the PK parameters, serum concentrations that are BLQ will be set to 0 before T_{max}, with the exception of a BLQ value occurring between measurable concentrations, in which case it will be set to missing. All values that are BLQ will be set to missing after T_{max}.

Actual sampling times will be used to calculate the PK parameters. The individual PK parameters for hGH, TransCon PEG40 hGH and mPEG40 will be presented in a data table. Pharmacokinetic parameters will be summarized using descriptive statistics (number of subjects, arithmetic mean, 95% CI of arithmetic mean, geometric mean, arithmetic SD, arithmetic CV, geo

CV, median, minimum, and maximum). For T_{max} and T_{last}, only the range and the median will be reported. For the display of PK parameters in tables, the PK parameters and descriptive statistics will be presented with 3 significant figures.

11.1.3 PK/PD-subset Sample Concentration Data, PD analytes

Blood samples for PD assessment in TransCon hGH Cohort 1 PK/PD Population will be collected at Visit 3 (Week 13) at following time points: Predose (defined as time zero), 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 hours post dose.

Below are the time windows by design for PD sample collection:

- Predose (-0.5 hour): within ± 30 minutes
- 8 to 48 hours post-dose: ±1 hour
- 72 to 168 hours post-dose: ± 3 hours

The individual serum concentration versus actual time data will be used to derive the PD parameters.

Blood samples will be processed to serum for quantification of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3). The lower limit of quantitation (LLOQ) for each of the PD analytes are as follows:

- IGF-1: 20.0 ng/mL
- IGFBP-3 150.0 ng/mL
- SD-scores for IGF-1 and IGFBP-3 will be calculated by Laboratorium für Klinische Forschung GmbH, Germany, based on absolute serum concentration data applying published IGF-1 and IGFBP-3 age and gender-specific Standard Deviation Score (SDS) reference ranges[11,12]. If a sample concentration is below the LLOQ, the concentration will be set to the LLOQ for calculation of SD-score.

The calculation of the SDS will be performed using the following formula[13]:

$$SD - Score = \frac{\left({}^{[serum\ conc]}/_{M}\right)^{L} - 1}{S * L}$$

[serum conc]: IGF-1/ IGFBP-3 serum concentration in ng/mL

M = Median reference value age- and gender specific[11],[12]

L = Lambda (Skewness) [11],[12]

S = Sigma (Standard Deviation) [11],[12]

Individual baseline adjusted IGF-1 and IGFBP-3 concentrations will be calculated as follows:

$$C_{baseline-corrected,t} = C_{measured,t} - C_{predose},$$

where $C_{baseline\text{-}corrected,\ t}$ is the baseline adjusted concentration at a given time point; $C_{measured,t}$ is the measured concentration in the sample at a given time point and $C_{pre\text{-}dose}$ is the baseline at predose Visit 1.

Baseline corrected SD-score will be calculated as follows:

$$SDS_{baseline-corrected,t} = SDS_t - SDS_{predose},$$

where $SDS_{baseline\text{-}corrected,\ t}$ is the baseline corrected concentration at a given time point; SDS_t is the calculated SDS based on the reference range for the given sample and $SDS_{predose}$ is the baseline value at predose (Visit 1).

All serum concentration values BLQ will be set to lower limit of quantification when calculating summary statistics; baseline-corrected values which are negative will be reported as negative values.

Absolute and baseline-corrected serum concentration data will be listed and summarized by time point for using descriptive statistics (number of subjects, arithmetic mean, arithmetic SD, arithmetic CV, median, minimum, and maximum, and geometric mean and geo CV, if applicable). Concentrations/ SD-scores will be reported in the same format as the original serum concentration (1-decimal place) and SD-score (2-decimal places) raw data. Descriptive statistics will be reported to 3 significant figures.

IGF-1 and IGFBP-3 arithmetic mean serum concentration (absolute and baseline-corrected) and IGF-1 and IGFBP-3 SD-score (absolute and baseline-corrected) versus nominal time profiles will be presented in figures on both linear and semi-logarithmic (if applicable) scales. IGF-1 and IGFBP-3 individual serum concentration data (absolute and baseline-corrected) and IGF-1 and IGFBP-3 SD-score (absolute and baseline-corrected) versus actual time profiles will be presented in figures on linear scale.

11.1.3.1 Pharmacodynamic Parameters

All parameters will be calculated using Phoenix WinNonlin (Version 6.4 or higher). The PD parameters for IGF-1, IGFBP-3 and IGF-1, IGFBP-3 SDS* (absolute and baseline-corrected) to be calculated include, but are not limited to, the following:

Parameter	Description
$AUEC_{0-168}$	Area under the efficacy curve, AUEC from time 0 to 168 hours after dosing
E_{max}	Maximum observed response
TE_{max}	Time to achieve maximum observed response

*Note: Only E_{max} and TE_{max} will be reported for IGF-1 SDS and IGFBP-3 SDS.

Actual collection times post-dose will be utilized in the calculations of the PD parameters.

For the calculation of PD parameters all serum concentrations that are BLQ will be set to lower limit of quantification. Baseline-corrected concentrations which are negative will also be included in the calculation. No concentration estimates will be imputed for missing sample values. Any sample with a missing value will be treated as if the sample had not been scheduled for collection and will be ignored when calculating mean concentrations or PD parameters.

Calculation of AUEC for baseline-corrected IGF-1 and IGFBP-3 will include negative peak areas if occurring, i.e. the net area will be reported.

The absolute and baseline-corrected PD parameters of IGF-1, IGF-1 SDS and IGFBP-3 will be summarized for each treatment using descriptive statistics (number of subjects, arithmetic mean, 95% CI of arithmetic mean, arithmetic SD, arithmetic CV, median, minimum, maximum, and geometric mean and geo CV, if applicable). For the display of PD parameters in tables and listings, the PD parameters and descriptive statistics will be presented with 3 significant figures.

12. References

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13. Tables, Listings, and Figures

13.1 Planned Table Descriptions

The following are planned summary tables for protocol TransCon hGH CT-301. Tables will be numbered according to the nomenclature used to support the clinical study report (CSR) when the Premier Research CSR template is used. However, the table numbering structure can be modified per the sponsor's request to meet compatibility with the sponsor's CSR template.

13.1 Demographic Data Summary Tables and Figures (To include demographics, baseline characteristics, disposition and exposure tables: Number as 14.1.1,)

Table 14.1.1	All Subjects	Study Populations
Table 14.1.2.1	All Subjects	Screen Failures
Table 14.1.2.2	All Randomized Subjetcs	Subject Disposition
Table 14.1.3.1	ITT/PP	Demographics and Baseline Data
Table 14.1.3.2	ITT/PP	Birth Data
Table 14.1.4.1	ITT/PP	Medical History by SOC and Preferred Term
Table 14.1.4.2	ITT/PP	Other Pituitary Hormone Deficiencies
Table 14.1.5	ITT/PP	Results of Sellar MRI
Table 14.1.6	SAFETY	Prior Medications
Table 14.1.7	ITT	Summary of Protocol Deviations

13.2 EFFICACY DATA

Table 14.2.1.1	ITT/PP	Annualised height velocity by Visit: Observed Case, summary statistics
Table 14.2.1.2	ITT/PP	Annualised height velocity by Visit and Subgroup: Observed Case
Table 14.2.1.3	ITT/PP	Annualised height velocity by Visit: MMRM analysis, Observed Case
Table 14.2.1.6	ITT/PP	Annualised height velocity by Visit: Impute Missing Height Velocity after Droput, summary statistics
Table 14.2.1.7	ITT	Annualised height velocity at by Visit: Sensitivity analysis MMRM analysis, Impute Missing Height Velocity after Droput
Table 14.2.1.8	ITT/PP	Annualised height velocity by Visit: ANCOVA Analysis, Observed Case
Table 14.2.2.1	ITT	Height SDS by Visit: summary statistics
Table 14.2.2.2	ITT	Height SDS by Visit and Subgroup: summary statistics
Table 14.2.2.3	ITT	Change from baseline in Height SDS by visit: MMRM analysis
Table 14.2.2.4	ITT	Height Velocity SDS by Visit: summary statistics
Table 14.2.2.5	ITT	Height Velocity SDS by Visit and Subgroup: summary statisticsTable 14.2.3.1 ITT Serum IGF-1 by Visit: summary statistics
Table 14.2.3.2	ITT	Serum IGF-1 by Visit and Subgroup: summary statistics
Table 14.2.3.3	ITT	Serum IGF-1 SDS by Visit: summary statistics
Table 14.2.3.4	ITT	Serum IGF-1 SDS by Visit and Subgroup: summary statistics
Table 14.2.3.5	ITT	Serum IGF-1 by visit: MMRM analysis
Table 14.2.3.6	ITT	Serum IGF-1 SDS by visit: MMRM analysis
Table 14.2.3.7	ITT	Normalisation of IGF-1 SDS by visit
Table 14.2.3.9	ITT	Average IGF-1 SDS at Weeks 13, 26, and 39

Table 14.2.3.10 ITT Proportion of Subjects Achieving Normalization of IGF-1 SDS within 0 to 2.0 Based on Average IGF-1 SDS at Weeks 13, 26, and 39

Table 14.2.3.11 ITT Average IGF-1 SDS at Weeks 13, 26, and 39 (Based on the Non-Linear Mixed Model TransCon hGH, Average for Genotropin): ANCOVA Analysis

Table 14.2.3.12 ITT Average IGF-1 SDS at Weeks 13, 26, and 39 within 0-2.0 (Based on the Non-Linear Mixed Model TransCon hGH, Average for Genotropin): Logistic Regression Analysis

Table 14.2.4.1 ITT Serum IGFBP-3 by Visit: summary statistics

Table 14.2.4.2 ITT Serum IGFBP-3 by Visit and Subgroup: summary statistic

Table 14.2.4.3 ITT Serum IGFBP-3 SDS by Visit: summary statistics

Table 14.2.4.4 ITT Serum IGFBP-3 SDS by Visit and Subgroup: summary statistics

Table 14.2.4.5 ITT Serum IGFBP-3 by visit: MMRM analysis

Table 14.2.4.6 ITT Serum IGFBP-3 SDS by visit: MMRM analysis

13.3 SAFETY DATA

14.3.1 Displays of Adverse Events

Table 14.3.1.1 SAFETY Summary of Adverse Events

Table 14.3.1.2 SAFETY Treatment Emergent Adverse Events: Incidences by Preferred Term

Table 14.3.1.3 SAFETY Treatment Emergent Adverse Events: Incidences by System Organ Class and Preferred Term

Table 14.3.1.4 SAFETY Treatment Emergent Adverse Events by Strongest Relationship (CRF Categories) to Study Drug: Incidences by System Organ Class and Preferred Term

Table 14.3.1.5 SAFETY Treatment Emergent Adverse Events by Maximum Severity of Event: Incidences by System Organ Class and Preferred Term

Table 14.3.1.6 SAFETY Treatment Emergent Adverse Events leading to Withdrawal of Study Drug: Incidences by System Organ Class and Preferred Term

14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2.1 SAFETY Serious Adverse Events: Incidences by System Organ Class and Preferred Term

Table 14.3.2.2 SAFETY Summary of Related Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug: Incidences by System Organ Class and Preferred Term

Table 14.3.2.3 SAFETY Summary of Unrelated Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug: Incidences by System Organ Class and Preferred Term

14.3.3 Laboratory Data Summary Tables

Table 14.3.3.1.1 SAFETY Summary of Central Laboratory Data - Hematology by Visit (Conventional Units)

Table 14.3.3.1.2 SAFETY Summary of Central Laboratory Data - Hematology by Visit (SI Units)

Table 14.3.3.2 SAFETY Central Laboratory Data - Hematology: Assessments (SI Units) by Visit

Table 14.3.3.3 SAFETY Central Laboratory Data - Hematology: Shift in Assessments Compared to Baseline (SI Units)

Table 14.3.3.4.1 SAFETY Summary of Central Laboratory Data - Biochemistry by Visit (Conventional Units)

Table 14.3.3.4.2 SAFETY Summary of Central Laboratory Data - Biochemistry by Visit (SI Units)

Table 14.3.3.5 SAFETY Central Laboratory Data - Biochemistry: Assessments by (SI Units) Visit

Table 14.3.3.6 SAFETY Central Laboratory Data - Biochemistry: Shift in Assessments Compared to Baseline (SI Units)

Table 14.3.3.7.1 SAFETY Summary of Central Laboratory Data – Glucose Metabolism by Visit (Conventional Units)

Table 14.3.3.7.2 SAFETY Summary of Central Laboratory Data - Glucose Metabolism by Visit (SI Units)

Table 14.3.3.8 SAFETY Central Laboratory Data - Glucose Metabolism: Assessments (SI Units) by Visit

Table 14.3.3.9 SAFETY Central Laboratory Data - Glucose Metabolism: Shift in Assessments Compared to Baseline (SI Units)

Table 14.3.3.10.1 SAFETY Summary of Central Laboratory Data – Lipid Metabolism by Visit (Conventional Units)

Table 14.3.3.10.2 SAFETY Summary of Central Laboratory Data - Lipid Metabolism by Visit (SI Units)

Table 14.3.3.11 SAFETY Central Laboratory Data - Lipid Metabolism: Assessments (SI Units) by Visit

Table 14.3.3.12 SAFETY Central Laboratory Data - Lipid Metabolism: Shift in Assessments Compared to Baseline (SI Units)

Table 14.3.3.13.1 SAFETY Summary of Central Laboratory Data – Hormone Status by Visit (Conventional Units)

Table 14.3.3.13.2 SAFETY Summary of Central Laboratory Data - Hormone Status by Visit (SI Units)

Table 14.3.3.14 SAFETY Central Laboratory Data - Hormone Status: Assessments (SI Units) by Visit

Table 14.3.3.15 SAFETY Central Laboratory Data - Hormone Status: Shift in Assessments Compared to Baseline (SI Units)

Table 14.3.3.16.1 SAFETY Summary of Antibodies

Table 14.3.3.16.2 SAFETY Summary of Antibodies by visit

14.3.4 Other Safety Data Summary Tables

Table 14.3.4.1 SAFETY Summary of Vital Signs by Visit

Table 14.3.4.2 SAFETY Summary of Electrocardiogramm (ECG) Assessment by Visit

Table 14.3.4.3 SAFETY Summary of Electrocardiogramm (ECG) Data by Visit

Table 14.3.4.4 SAFETY Electrocardiogramm (ECG) Data: Shift in Assessments Compared to Baseline

Table 14.3.4.5 SAFETY Summary of Bone Age

Table 14.3.4.6 SAFETY Physical Examination Results by Body System and Visit

Table 14.3.4.7 SAFETY Pubertal Status: Summary Assessment by Sex and Visit

Table 14.3.4.8.1 SAFETY Local Tolerability from Site by Visit: Summary of Subjects with Injection Related Events

Table 14.3.4.8.2 SAFETY Local Tolerability from Site by Visit and Severity: Summary of Subjects with Injection Related Events

Table 14.3.4.8.3 SAFETY Local Tolerability from Site by Maximum Severity and Symptom for Overall Study: Summary of Subjects with Injection Related Events

Table 14.3.4.8.4.1 SAFETY Local Tolerability from Patient Diary by Week - TransCon hGH: Summary of Subjects with Injection Related Events

Table 14.3.4.8.4.2 SAFETY Local Tolerability from Patient Diary by Day - Genotropin: Summary of Subjects with Injection Related Events

Table 14.3.4.8.5.1 SAFETY Local Tolerability from Patient Diary by Week and Severity - TransCon hGH: Summary of Subjects with Injection Related Events

Table 14.3.4.8.5.2 SAFETY Local Tolerability from Patient Diary by Day and Severity - Genotropin: Summary of Subjects with Injection Related Events

Table 14.3.4.8.6 SAFETY Local Tolerability from Patient Diary by Maximum Severity and Symptom for Overall Study: Summary of Subjects with Injection Related Events

Table 14.3.4.8.7 SAFETY Exposure Adjusted Local Tolerability from Patient Diary for Overall Study

Table 14.3.4.8.8 SAFETY Exposure Adjusted Local Tolerability from Patient Diary by Severity for Overall Study

Table 14.3.4.9 SAFETY Concomitant Medication: Incidences by ATC Level 2 and 4

Table 14.3.4.10.1 SAFETY Exposure to Study Treatment and Compliance

Table 14.3.4.10.2.1 SAFETY Exposure to Study Treatment by Week – TransCon hGH

Table 14.3.4.10.2.2 SAFETY Exposure to Study Treatment by Day – Genotropin

Table 14.3.4.10.3 SAFETY Summary of Dose Timings

Table 14.3.4.10.4 SAFETY Weight-based Planned Dosage (mg/dose) by Visit

Table 14.3.4.11 SAFETY Serum concentration by Visit and PK analytes

Table 14.3.4.12 PK Serum Concentration by Time Point and PK analytes at Visit: Individual data including Summary Statistics

Table 14.3.4.13 PK PK Analysis at Visit 3: Individual PK Parameters including Summary Statistics

Table 14.3.4.14.1 PD Serum Concentration / SDS by PD analyte and Time Point at Visit 3: Individual Data Including Summary Statistics (Absolute)

Table 14.3.4.14.2 PD Serum Concentration / SDS by PD analyte and Time Point at Visit 3: Individual Data Including Summary Statistics (Baseline-Corrected)

Table 14.3.4.15.1 PD PD Analysis at Visit 3; Individual PD Parameters Including Summary Statistics (Absolute)

Table 14.3.4.15.2 PD PD Analysis at Visit 3; Individual PD Parameters Including Summary Statistics (Baseline-Corrected)

13.4 FIGURES

Figure 1 ITT Annualized HV (LS Mean ± SE) at Visit 6 (Week 52) for weekly TransCon hGH and daily hGH treatment groups

Figure 2 ITT Distribution of Annualized HV at Week 52 for weekly TransCon hGH and daily hGH treatment groups

Figure 3 ITT Annualized HV (Mean ± SE) over 52 weeks for the TransCon hGH and the daily hGH treatment groups

Figure 4 ITT Distribution of Annualized HV over 52 weeks for weekly TransCon hGH and daily hGH treatment groups

Figure 5 ITT Delta Height SDS (LS Mean ± SE) at Week 52 for weekly TransCon hGH and daily hGH treatment groups

Figure 6 ITT Distribution of delta height SDS at Week 52 for weekly TransCon hGH and daily hGH treatment groups

Figure 7 ITT Delta Height SDS (Mean ± SE) over 52 weeks for the TransCon hGH and the daily hGH treatment groups

Figure 8 ITT Distribution of delta Height SDS over 52 weeks for weekly TransCon hGH and daily hGH treatment groups

Figure 9 ITT Height SDS (Mean ± SE) over 52 weeks for weekly TransCon hGH and daily hGH treatment groups

Figure 10 ITT Distribution of Height SDS over 52 weeks for weekly TransCon hGH and daily hGH treatment groups

Figure 11 ITT Distribution of Height Velocity SDS over 52 weeks for weekly TransCon hGH and daily hGH treatment groups

Figure 12 ITT Serum IGF-1 SDS (LS Mean ± SE) over 52 weeks for weekly TransCon hGH and daily hGH treatment groups

Figure 13 ITT Distribution of IGF-1 SDS over 52 weeks for weekly TransCon hGH and daily hGH treatment groups

Figure 14 ITT Proportion of patients with normalized serum IGF-1 (0 – (+2.0) SDS) based on the average IGF-1 SDS at steady states for the TransCon hGH and the daily hGH treatment groups

Figure 15 ITT Proportion of patients with normalized serum IGF-1 (0 – (+2.0) SDS) over 52 weeks for the TransCon hGH and the daily hGH treatment groups

Figure 52.1 SAFETY Shift in Glucose Levels (mmol/L) from baseline to Week 5 for the TransCon hGH and the daily hGH treatment groups

Figure 52.2 SAFETY Shift in Glucose Levels (mmol/L) from baseline to Week 26 for the TransCon hGH and the daily hGH treatment groups

Figure 52.3 SAFETY Shift in Glucose Levels (mmol/L) from baseline to Week 52 for the TransCon hGH and the daily hGH treatment groups

Figure 53.1 SAFETY Shift in FT4 Levels (ng/dL) from baseline to Week 13 for the TransCon hGH and the daily hGH treatment groups

Figure 53.2 SAFETY Shift in FT4 Levels (ng/dL) from baseline to Week 26 for the TransCon hGH and the daily hGH treatment groups

Figure 53.3 SAFETY Shift in FT4 Levels (ng/dL) from baseline to Week 52 for the TransCon hGH and the daily hGH treatment groups

Figure 54.1 SAFETY Shift in Cortisol Levels (ug/dL) from baseline to Week 13 for the TransCon hGH and the daily hGH treatment groups

Figure 54.2 SAFETY Shift in Cortisol Levels (ug/dL) from baseline to Week 26 for the TransCon hGH and the daily hGH treatment groups

Figure 54.3 SAFETY Shift in Cortisol Levels (ug/dL) from baseline to Week 52 for the TransCon hGH and the daily hGH treatment groups

Figure 55.1 SAFETY Shift in FT4 Levels (pmol/L) from baseline to Week 13 for the TransCon hGH and the daily hGH treatment groups

Figure 55.2 SAFETY Shift in FT4 Levels (pmol/L) from baseline to Week 26 for the TransCon hGH and the daily hGH treatment groups

Figure 55.3 SAFETY Shift in FT4 Levels (pmol/L) from baseline to Week 52 for the TransCon hGH and the daily hGH treatment groups

Figure 56.1 SAFETY Shift in Cortisol Levels (nmol/L) from baseline to Week 13 for the TransCon hGH and the daily hGH treatment groups

Figure 56.2 SAFETY Shift in Cortisol Levels (nmol/L) from baseline to Week 26 for the TransCon hGH and the daily hGH treatment groups

Figure 56.3 SAFETY Shift in Cortisol Levels (nmol/L) from baseline to Week 52 for the TransCon hGH and the daily hGH treatment groups

13.5 Planned Listing Descriptions

The following are planned data and subject data listings for protocol TransCon hGH CT-301. Data listings will be numbered according to the nomenclature used to support the CSR when the Premier Research CSR template is used. However, the listing numbering structure can be modified per the sponsor's request to meet compatibility with the sponsor's CSR template.

16.2.x

16.2 Subject Data Listings

16.2.1 Subject Discontinuations/Completions

Data Listing 16.2.1.1 Study Populations

Data Listing 16.2.1.2 Subject Disposition and Study Completion

16.2.2 Protocol Deviations

Data Listing 16.2.2.1 Inclusion Criteria

Data Listing 16.2.2.2 Exclusion Criteria

Data Listing 16.2.2.3 Protocol Deviations

16.2.3 Subjects Excluded from the Efficacy Analyses

Data Listing 16.2.3 Subjects Excluded from Efficacy Analysis

16.2.4 Demographic Data and Other Baseline Characteristics

Data Listing 16.2.4.1 Demographic and Baseline Information

Data Listing 16.2.4.2 Medical History

Data Listing 16.2.4.3 Physical Examination

Data Listing 16.2.4.4 Prior Medications

Data Listing 16.2.4.5 Baseline Characteristics: Antibodies and Karotype Testing

Data Listing 16.2.4.6.1 Baseline Characteristics: GH Simulation Tests (1)

Data Listing 16.2.4.6.2 Baseline Characteristics: GH Simulation Tests (2)

Data Listing 16.2.4.7 Baseline Characteristics: Sellar MRI

Data Listing 16.2.4.8.1 Baseline Characteristics: ACTH Stimulation Tests – Local Lab

Data Listing 16.2.4.8.2 Baseline Characteristics: ACTH Stimulation Tests – Central Lab

Data Listing 16.2.4.9 Baseline Characteristics: Other Pituitary Hormone Deficiencies

16.2.5 Compliance and/or Drug Concentration Data

Data Listing 16.2.5.1 Study Drug Accountability/Administration

16.2.6 Individual Efficacy Response Data

Data Listing 16.2.6.1 Efficacy Parameter Results: Height Velocity & Height SDS

Data Listing 16.2.6.2 Secondary Efficacy Results: Serum IGF-1 (Absolute and Baseline Corrected) and IGF-1 SDS (Absolute and Baseline Corrected)

Data Listing 16.2.6.3 Secondary Efficacy Results: Serum IGFBP-3 (Absolute and Baseline Corrected) and IGFBP-3 SDS (Absolute and Baseline Corrected)

16.2.7 Adverse Event Listings (by Subject)

Data Listing 16.2.7.1 Adverse Events

Data Listing 16.2.7.2 Related Adverse Events

Data Listing 16.2.7.3 Severe Adverse Events

Data Listing 16.2.7.3 Adverse Events Leading to Deaths

Data Listing 16.2.7.4 Serious Adverse Events

Data Listing 16.2.7.5 Adverse Events Leading to Study Drug Discontinuation

16.2.8 Laboratory Values (by Subject)

Data Listing 16.2.8.1.1 Hematology Central Laboratory Evaluations

Data Listing 16.2.8.1.2 Hematology Local Laboratory EvaluationsData Listing 16.2.8.2.1 Biochemistry Central Laboratory Evaluations

Data Listing 16.2.8.2.2 Biochemistry Local Laboratory Evaluations

Data Listing 16.2.8.3.1 Glucose Metabolism Central Laboratory Evaluations

Data Listing 16.2.8.3.2 Glucose Metabolism Local Laboratory Evaluations

Data Listing 16.2.8.4.1 Lipid Metabolism Central Laboratory Evaluations

Data Listing 16.2.8.4.2 Lipid Metabolism Local Laboratory Evaluations

Data Listing 16.2.8.5 Hormone Status Local Laboratory Evaluations

Data Listing 16.2.8.6.1 Antibodibodies Evaluation

Data Listing 16.2.8.6.2 Antibodibodies Status Over the Whole Study

Data Listing 16.2.8.7 Oral Glucose Tolerance Test (Local Laboratory)

16.2.9 Other Clinical Observations and Measurements (by Subject)

Data Listing 16.2.9.1 Prohibited Concomitant Medications

Data Listing 16.2.9.2.1 Vital Signs

Data Listing 16.2.9.2.2 Vital Signs: PK/PD subset Visit 3

Data Listing 16.2.9.3 Local Tolerability

Data Listing 16.2.9.4.1 Electrocardiogram - Qualitative Results

Data Listing 16.2.9.4.2 Electrocardiogram - Qualitative Results: PK/PD subset Visit 3

Data Listing 16.2.9.4.3 Electrocardiogram - Quantitative Results

Data Listing 16.2.9.4.4 Electrocardiogram - Quantitative Results: PK/PD subset Visit 3

Data Listing 16.2.9.5 Bone Age

Data Listing 16.2.9.6.1 Pubertal Status - Male

Data Listing 16.2.9.6.2 Pubertal Status – Female

Data Listing 16.2.9.7 Individual Serum Concentrations of PK analytes [hGH, TransCon PEG40 hGH, mPEG] by Treatment

Data Listing 16.2.9.8 PK Results TransCon PK/PD subset Visit 3

Data Listing 16.2.9.9 PD Results TransCon PK/PD subset Visit 3

Data Listing 16.2.9.10 Fundoscopy

Data Listing 16.2.9.11 Prior and Concomitant Non-Pharmalogical Treatments

Data Listing 16.2.9.12.1	Patient Diary (1) - Genotropin
Data Listing 16.2.9.12.2	Patient Diary (2) - Genotropin
Data Listing 16.2.9.12.3	Patient Diary (1) - TransCon hGH
Data Listing 16.2.9.12.4	Patient Diary (2) - TransCon hGH
Data Listing 16.2.9.12.5	Treatment Compliance

14. TABLES SHELLS

Table shells will be included in a separate document.

APPENDIX 1: ETIOLOGY AND EXTENT OF GHD: DETERMINATION OF EACH SUBJECT'S GROUP ASSIGNMENT

Isolated idiopathic

- No other pituitary axis hormone deficiencies other than growth hormone deficiency.
- MRI without a midline finding that would suggest an organic cause of growth hormone deficiency. Subjects with incidental MRI findings (e.g. parietal lobe encephalomalacia) that are not thought to contribute to growth hormone deficiency are included here.

Isolated organic

- No other pituitary axis hormone deficiencies other than growth hormone deficiency.
- MRI with a midline finding that is likely the cause of the growth hormone deficiency (i.e. pituitary aplasia/hypoplasia/small; ectopic posterior pituitary; absent or interrupted stalk; empty sella; septo-optic dysplasia; Rathke's cleft cyst). Pineal cysts do not qualify as likely to cause growth hormone deficiency. The rationale for including Rathke's cleft cysts is: approximately 50% of pediatric Rathke's cleft cysts are associated with pituitary dysfunction; and these subjects have a higher pre-test probability of the Rathke's cleft cyst contributing to the GHD since they already have a pituitary dysfunction. Surgical management of Rathke's cleft cysts do not tend to reverse GHD. We recognize Rathke's cleft cysts can also be incidental findings without associated pituitary dysfunction.[†]
    - And/or a history of midline brain surgery and/or irradiation that is likely the cause of the growth hormone deficiency.

Multiple pituitary hormone deficiencies

- Has at least one other pituitary hormone axis deficiency (i.e. TSH, ACTH, gonadotropin, ADH) other than growth hormone deficiency.
- Subjects are included here regardless of MRI findings (or absence of findings) as most with MPHD are likely to have a relevant MRI finding and/or history of brain surgery and/or irradiation.

Data to support the above was extracted from:

- Pituitary hormone deficiencies form in EDC
    - Subjects who had evidence of biochemical central hypothyroidism (low free T4 and inappropriately low TSH) at baseline and were subsequently started on levothyroxine replacement during the trial are grouped as "multiple pituitary hormone deficiencies" just as subjects who had evidence of central hypothyroidism and were already on levothyroxine replacement at baseline. (This pertains to subjects 59001, 58001, 38001, 59501.)
- Past medical history form in EDC—to ascertain history of brain surgery and/or irradiation.
- MRI form in EDC (investigator's assessment of MRI read and reported locally)

[†]SS Erdeve et. al. J Pediatr Endocr Met 2011; 24:867-875.

A Jahangiri et. al. Neurosurg Focus 2001; 31:E3.

HH Lim et. al. Korean J Pediatr 2010; 53:759-765.

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APPENDIX 2: ECG – NORMAL RANGES

For use on Pediatric Studies:
BMS uses global superimposed median beat as our preferred measurement methodology for pediatric studies. The Normal Range values below are based on this methodology.

Interval	Normal	Abnormal ECG, Not Clinically Significant	Abnormal ECG, Potentially Clinically Significant
HR			
2 to < 6 years	80-140 bpm	60-79 bpm, or 141-180 bpm	< 60 bpm or >180 bpm
6 to < 12 years	60-120 bpm	50-59 bpm, or 121-150 bpm	< 50 bpm or >150 bpm
12 to < 18 years	50-100 bpm	40-49 bpm, or 101-150 bpm	< 40 bpm or >150 bpm
PR			
2 to < 6 years	90-150 ms	Short if <90 ms, otherwise first degree AV block if 151-170 ms	> 170 ms
6 to < 12 years	100-170 ms	Short if <100 ms, otherwise first degree AV block if 171-190 ms	> 190 ms
12 to < 18 years	110-180 ms	Short if <110 ms, otherwise first degree AV block if 181-220 ms	> 220 ms
QRS			
2 to < 6 years	≤ 90 ms with no QRS disturbance	91-100 ms with no QRS disturbance or IVCD or any QRS disturbance (except Left Posterior Fascicular Block) with a QRS ≤ 100 ms	IVCD or any QRS conduction disturbance with a QRS > 100 ms
6 to < 12 years	≤ 100 ms with no QRS disturbance	101-110 ms with no QRS disturbance or IVCD or any QRS disturbance (except Left Posterior Fascicular Block) with QRS ≤ 110 ms	IVCD or any QRS conduction disturbance with a QRS > 110 ms
12 to < 18 years	≤ 110 ms with no QRS disturbance	111-120 ms with no QRS disturbance or IVCD or any QRS disturbance (except Left Posterior Fascicular Block) with a QRS ≤ 120 ms	IVCD or any QRS conduction disturbance with a QRS > 120 ms
QTcF			
0 to < 12 years	Males and Females: 320-450 ms	451-480 ms	QTcF > 480 ms
12 to < 18 years	Male: 320-450 ms	451-500 ms	QTcF > 500 ms
12 to < 18 years	Female: 320-470 ms	471-500 ms	QTcF > 500 ms
			All ages (male/female): Short QTcF < 320 ms
		All ages: Increase of QTcF (30 - 60 ms)*	All ages: Increase of QTcF (> 60 ms)*