Official Title: enliGHten: A Multicenter, Phase 3, Long-term, Open-label Trial Investigating Safety and Efficacy of TransCon hGH Administered Once-Weekly in Children with Growth Hormone Deficiency (GHD) Who Have Completed a Prior TransCon hGH Clinical Trial

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Statistical Analysis Plan

Protocol Title:	enliGHten: A Multicenter, Phase 3, Long-term, Open-label Trial Investigating Safety and Efficacy of TransCon hGH Administered Once-Weekly in Children with Growth Hormone Deficiency (GHD) Who Have Completed a Prior TransCon hGH Clinical Trial
Protocol Number:	TransCon hGH CT-301EXT
Compound:	TransCon hGH
Phase:	3
Sponsor:	Ascendis Pharma, Inc. 500 Emerson Street Palo Alto, California 94301
SAP Author:	PPD PhD FMD K&L Inc. 1300 Virginia Dr., Ste 408 Fort Washington, PA 19034 www.klserv.com
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Signature Page:

Issued by: _____ Date: _____
PPD Ph.D.
PPD Biostatistician
FMD K&L

Approved by: _____ Date: _____
PPD Ph.D.
PPD Biostatistician
Ascendis Pharma, Inc.

Approved by: _____ Date: _____
PPD Ph.D.
PPD
Ascendis Pharma, Inc.

Approved by: _____ Date: _____
PPD M.D.
PPD
Ascendis Pharma, Inc.

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List of Abbreviations

ΔHSDS	change in height standard deviation score
µg	microgram
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
AGHD	adult growth hormone deficiency
C&OS-C	Convenience & Overall Satisfaction domains of the abbreviated 9-item Treatment Satisfaction Questionnaire for Medication - Child
C&OS-P	Convenience & Overall Satisfaction domains of the abbreviated 9- item Treatment Satisfaction Questionnaire for Medication - Parent
cm	centimeter
CSDS-C	Child Sheehan Disability Scale – Child
CSDS-P	Child Sheehan Disability Scale – Parent
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
HbA1c	hemoglobin A1c
HV	height velocity
ICH	International Council on Harmonization
ICF	informed consent form
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor binding protein-3
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mPEG	methoxypolyethylene glycol
PD	pharmacodynamics
PQ-C	Preference Questionnaire – Child
PQ-P	Preference Questionnaire – Parent
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDS	standard deviation score
TQSM	Treatment Satisfaction Questionnaire for Medication
TSQM-9	Abbreviated 9-item Treatment Satisfaction Questionnaire for Medication
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 EXT (enliGHten: A Multicenter, Phase 3, Long-term, Open-label Trial Investigating Safety and Efficacy of TransCon hGH Administered Once-Weekly in Children with Growth Hormone Deficiency (GHD) Who Have Completed a Prior TransCon hGH Clinical Trial), Protocol 1.0 dated 29 August 2017.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (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. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, 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 EXT and Case Report Forms (CRFs) for Protocol TransCon hGH CT-301 EXT.

The reader of this SAP is encouraged to 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. Objectives

2.1. Primary Objective

- To assess long-term safety of weekly TransCon hGH in children with GHD previously treated in a phase 3 TransCon hGH trial

2.2. Secondary Objectives

- To assess annualized height velocity (HV) with long-term dosing of weekly TransCon hGH treatment

- To assess the proportion of subjects with IGF-1 standard deviation score (SDS) in the normal range of 0.0 to +2.0 with long-term dosing of weekly TransCon hGH treatment
- To evaluate the change in height standard deviation scores (ΔHSDS) with long-term dosing of weekly TransCon hGH treatment
- To determine the incidence of antibodies against TransCon hGH (anti-hGH and anti-PEG) with long-term dosing of weekly TransCon hGH treatment
- To assess the preference for weekly TransCon hGH or daily Genotropin
- To assess the treatment satisfaction of weekly TransCon hGH over time

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a multicenter, phase 3, long-term, open-label extension trial of weekly TransCon hGH in children with GHD who previously participated in a phase 3 TransCon hGH trial, i.e., Study CT-301 (heiGHt trial) or Study CT-302 (fliGHt trial). All subjects completing a prior phase 3 TransCon hGH trial who have not permanently discontinued trial medication, are without evidence of closed epiphyses, and meet all other entry criteria will be invited to participate. In general, the final visit of the prior trial should serve as the first visit of the extension trial.

Following informed consent, subjects will enter the extension trial and begin or continue TransCon hGH (depending on prior trial medication). To continue uninterrupted treatment with hGH, Day 1 (the first weekly dose) should occur on the day of Visit 1, or as soon as possible thereafter. To accommodate extension trial activities and scheduling of procedures, the weekly dosing and visit schedule may need to be adjusted as a subject enters the extension trial. In unusual situations, a period of up to approximately 6 weeks between the final visit of the prior trial and the first dose of the extension trial is acceptable. After Visit 1, subsequent visits will occur 5 days (±1 day) post-dose at Week 13 (±2 weeks) and then every 13 weeks (±2 weeks) ongoing. TransCon hGH will be provided in single-use glass vials and administered with syringe and needle, initially at a strength of 12.1 mg hGH/vial and subsequently at either 12.1 mg hGH/vial or 24.2 mg hGH/vial. Once available, TransCon hGH will be supplied in DCCs for administration using a TransCon hGH auto-injector in select countries.

The trial will be conducted at approximately 100 sites specialized in the management of pediatric GHD that participated in and enrolled subjects in prior TransCon hGH trials.

Based on the subject's prior study info, he/she will be classified into one of the following treatment groups in this extension study:

(1) Parent Study CT-302;
(2) Parent Study CT-301 -TransCon hGH;
(3) Parent Study CT-301 - Genotropin;

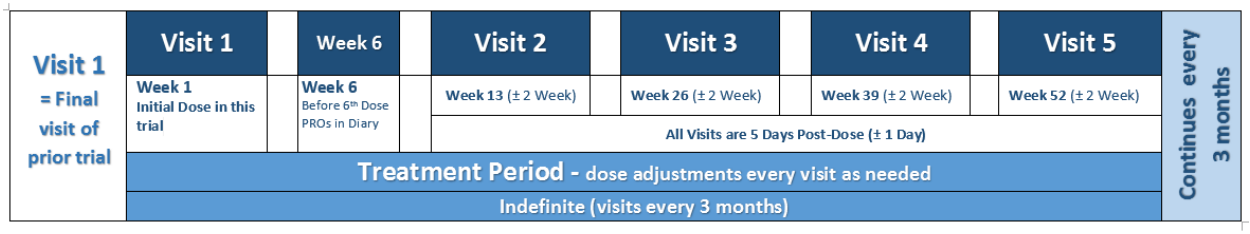
The trial consists of:

1) Visit 1 – the first visit of this extension trial

2) Treatment Period – ongoing treatment until either a) the product is approved and commercially available, b) alternative arrangements have been made for continued subject access to hGH treatment, or c) treatment for pediatric growth hormone deficiency is no longer considered appropriate

The total duration of participation for each subject in the trial will therefore depend on the conditions listed above in the Treatment Period, and may be different in different countries and regions.

Figure 1: Overall Trial Design



Note Week 6 is not a clinical visit. For subjects who were treated with Genotropin in the TransCon hGH CT-301 trial, patient-reported outcome questionnaires within the subject diary will be completed immediately prior to the 6th study drug administration (Week 6).

3.2. Sample Size

This trial is intended to assess long-term safety and efficacy in support of market approval. All subjects who have completed a prior phase 3 TransCon hGH trial, have not permanently discontinued study drug, and meet eligibility criteria will be invited to participate. The sample size is determined by the prior trial sizes. Up to approximately 400 (male and female) children are expected for this study.

Table 1 Schedule of Events

	VISIT 1[1]	VISIT 2	VISIT 3	VISIT 4	VISIT 5/CV/ETV[2]
	Week 1	**Week 13**	**Week 26**	**Week 39**	**Week 52**
	Day 1	**(± 2 weeks)**	**(± 2 weeks)**	**(± 2 weeks)**	**(± 2 weeks)**
	Morning	**5d ± 1d Post-Dose, Morning**	**5d ± 1d Post-Dose, Morning**	**5d ± 1d Post-Dose, Morning**	**5d ± 1d Post-Dose, Morning**
Informed consent	x				
Interval history, medications and health status	x				
review[3]					
Vital signs measurements[4]	x	x	x	x	x
Height[5] & weight	x	x	x	x	x
Physical examination	x	x	x	x	x
Pubertal status assessment	x	x	x	x	x
Blood sample collection – A[6]	x	x	x	x	x
Blood sample collection – B[7]	x		x		x
Bone age x-ray[8]	x				x
Study drug preparation/administration training	x				
Training on auto-injector[9]	(x)	(x)	(x)	(x)	(x)
Subject diary training	x	x			
C&OS-P[11]	X[10]	x			
CSDS-P[11]	X[10]	x			
CSDS-C[11,12]	X[10]	x			
PQ-P[11]		x			
PQ-C[11,12]		x			
Study drug dose adjustment[13]	x	x	x	x	x
Local tolerability assessment[14]	x	x	x	x	x
Study drug & subject diary dispensing	x	x	x	x	x
Study drug compliance[15]		x	x	x	x
Concomitant medications		x	x	x	x
Adverse events[16]		x	x	x	x

1 Visit 1 of this extension trial should be the same day as the final visit of the prior trial, and the first dose should occur as soon as possible. A period of up to approximately 6 weeks between the final visit of the prior trial and first dose (Day 1) of the extension trial is acceptable. Visit 1 assessments should be performed unless they were performed for the final visit of the prior trial. In the unusual event there is a gap of 4 to approximately 6 weeks, then all Visit 1 assessments should be repeated for Day 1 except physical exam, blood collection and bone age x-ray.
2 After Visit 5, visits continue every 3 months (See Section 10.2.2.3 and Section 10.2.2.4). A Completion Visit (CV)/Early Termination Visit (ETV) should be performed for all subjects either completing the trial as described in Section 10.1, or terminating trial participation prematurely. The visit should include all procedures listed for Visit 5, as applicable.
3 Interval history, medications and health status: disease states diagnosed since the initiation of the prior trial (eg, new onset migraines) are medical history; Medical history from the prior trial will be carried forward into this trial's database; Ongoing AEs from the prior trial will be followed until resolution or stabilization; Review of subject diary from the prior trial; Current therapies.
4 Vital sign measurements include heart rate, blood pressure, respiratory rate and body temperature, which should be performed after the subject has rested for at least 5 minutes.
5 Height should be measured at each visit at approximately the same time of day, preferably by the same auxologist.
6 Blood sample collection – A includes IGF-1, IGFBP-3, antibodies against hGH and PEG, and for females of child-bearing potential hCG. If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers
7 Blood sample collection – B includes mPEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Fasting not required.
8 Bone age x-ray may not be required at Visit 1 if there is documentation of a bone age x-ray performed within the past 52 weeks. However, if subject's prior documented bone age was > 12.0 years, and it was performed greater than 9 months prior to Visit 1, a bone age x-ray should be performed within approximately 4 weeks of Visit 1. Bone age x-ray may also be performed at any time, if clinically indicated.
9 Once the auto-injector is available, transition to the auto-injector will occur in select countries at the next regularly scheduled trial visit when thorough training on preparation and administration will occur.
10 At Visit 1, the C&OS-P, CSDS-P, and CSDS-C should be completed for all subjects.
11 For subjects who were treated with Genotropin in the prior TransCon hGH CT-301 trial, C&OS-P, CSDS-P, CSDS-C, PQ-P, and PQ-C will be completed (as applicable) within the subject diary immediately prior to the 6th dose of study drug, and in clinic at Visit 2, prior to review of the subject diary, AEs, and concomitant medications.
For subjects transitioning to the auto-injector, C&OS-P, CSDS-P, and CSDS-C will be completed (as applicable) within the subject diary immediately prior to the 6th dose after transition to the TransCon hGH auto-injector, and again in clinic at the following scheduled visit, prior to review of the subject diary, AEs, and concomitant medications.
12 CSDS-C and PQ-C should only be completed by subjects ≥ 9 years old at the time of Visit 1, and/or at the transition to the TransCon hGH auto-injector, as applicable.
13 Dose adjustments at visits are based on subject weight at visits. However, dose adjustments may occur between visits per Section 9.6.
14 Local tolerability assessment at the injection site to be performed at time of injection, and by the trial staff at visits.
15 Study drug compliance includes review of subject diary and returned study drug.
16 AE review includes review of subject diary and physical examination of injection sites. AEs that are considered mild and not related to study drug will not be reported on the AE CRF.

3.3. Study Endpoints

3.3.1. Safety Endpoints

The safety endpoints as measured throughout the long-term dosing of weekly TransCon hGH treatment include the following:

- Incidence of AEs
- Incidence of antibodies against hGH, including neutralizing antibodies
- Incidence of antibodies against PEG
- Incidence of IGF-1 SDS > 2.0, > 3.0 with confirmation
- Parameters of HbA1c and lipids
- Hormone levels, including thyroid status and morning cortisol
- All other hematology and chemistry parameters
- Vital sign measurements

3.3.2. Efficacy Endpoints

The efficacy endpoints of long-term weekly TransCon hGH treatment include the following:

- Annualized HV
- Δ HSDS
- Proportion of subjects with IGF-1 SDS of 0 to +2.0. Additionally, cut points of -2.0 to +2.0 and -1.0 to +2.0 will be assessed.
- IGF-1 SDS
- IGFBP-3 SDS

3.3.3. Pharmacodynamic Endpoints

- Serum IGF-1 SDS at 5 days ±1day post-dose

3.3.4. Other Endpoints

- Preference for weekly TransCon hGH or daily Genotropin treatment
- Satisfaction with weekly TransCon hGH

4. Analysis and Reporting

4.1. Interim Analysis

This is an open label study. Interim analysis can be done at sponsor's discretion to support regulatory submission or product planning. 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 an efficacy perspective.

4.2. Final Analysis

All final, planned analyses identified 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 database.

5. General Statistical Considerations

All analysis will be performed based on full analysis set and summaries will be presented overall and for subjects rolling over from Study CT-301 and Study CT-302 TransCon hGH group and Genotropin group separately. Descriptive summaries will be provided where appropriate for each of the primary and secondary variables.

Continuous, quantitative (absolute values at each time point 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), 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.

All data collected on eCRF will be presented in listings.

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

5.1. Baseline Data

Two baselines are defined. One is referred to as parent study baseline and the other one is extension study baseline.

Parent study baseline is defined as the last non-missing assessment collected before the first study treatment in the parent study. Extension study baseline is defined as the last non-missing assessment collected before the first study treatment in the extension study. Some of the information does not change and are only collected in parent studies, i.e., race, gender, and parent heights. In those cases, parent baseline data will be carried into extension study to serve as the baseline values.

For majority endpoints, including height, IGF-1 and etc., the extension study baseline values will be utilized for the analysis except for antibodies. For antibodies, the status before the first dose of TransCon will be considered as the baseline.

For annualized height, the rolling baseline will be used to calculate the annualized height velocity to make sure there is one-year gap in the calculation. In other words, from the 15-month (65 weeks) visit onwards, the baseline value used for each successive HV calculation was the patient's height at the visit 52 weeks previously, e.g. height at 13 week served as the baseline value to determine HV at the 65 week ('moving 52 weeks HV basis')." If height at visit 52 weeks previously is missing then most recent height prior to the visit will be used.

5.2. Handling of Missing Data

In general, the observed data will be presented in listings. Imputed data will be used for summary analysis.

For determination of treatment-emergent adverse event (TEAE), 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 on or after the first dose in the study (worst case approach).

The following rules are used for TEAE determination where the AE has a missing start date.

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 of study day.

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 end of study month 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 of study year 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.

5.3. Visit Window

The final visit of the parent trial should serve as the first visit (Visit 1) of the extension trial and data collected in the parent trial before the first study treatment will serve as baseline data for the extension trial. After Visit 1, subsequent visits will occur 5 days (±1 day) post-dose at Week 13 (±2 weeks) and then every 13 weeks (±2 weeks) ongoing.

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 closest target study day for each scheduled assessment according to Table 2. 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 visit in the same window, the visit closer to the target assessment day will be used. If more than one visit has the equal distance to the target day then the later one will be used, if more than one visit 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 2. Analysis Window

VISIT	Week	Target Study Day	Study Day Window
Visit 1	Week 1	1	<=1
Visit 2	Week 13	90	2, 135
Visit 3	Week 26	181	136, 226
Visit 4	Week 39	272	227, 317
Visit 5	Week 52	363	318, 408
Visit 6	Week 65	454	409, 499
Visit 7	Week 78	545	500, 590
Visit 8	Week 91	636	591, 681
Visit 9	Week 104	727	682, 772
Visit x	Every 13 Weeks 13(x-1)	7*13*(x-1)-1 if x>1	Floor (7*13* (x-1.5)), Floor (7*13* (x-0.5))-1

5.4. Derived and Computed Variables

Table 3 provides the rules for derived and computed variables which have been initially identified as important for the analysis of the safety or efficacy 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.

The birth date for each subject is collected on the eCRF. To be consistent with all the other TransCon hGH studies, the 15th day of the reported month is used to calculate the age and related scores. In such case, all the height SDS for the subjects will be calculated using 15th as the birth day. The HSDS reported in the eCRF will not be used as it is based on the actual birth date reported by the subject. FMD K&L will utilize the published SAS macro to calculate the height SDS and no independent QC is required for published SAS macro.

Table 3. Parameter Definition

Parameter	Definition
Annualized Height Velocity at visit x (HV) cm/year	((Height (Visit x) - Height (Visit 1))* 365) / (Date (Visit x) - Date (Visit 1)) From the 15-month (65 weeks) visit onwards, the baseline value used for each successive HV calculation was the patient's height at the visit 52 weeks previously, e.g. height at 13 week served as the baseline value to determine HV at the 65 week ('moving 52 weeks HV basis')." If height at visit 52 weeks previously is missing then most recent height prior to the visit will be used.
Height Deviation Standardized Score (HSDS)	Height SDS will be derived using CDC 2000 (United States of America). A standard SAS program is published at: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm
Change from baseline	The value of each variable at each post-baseline time point minus the baseline score.
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.
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
Total Duration of Treatment (day)	Last treatment date of the extension study – first treatment date of the extension study +7
Total Duration of Treatment (week)	Round (Total Duration of Treatment in days /7) to the nearest integer

Treatment Compliance	Total number of dose taken in the extension study/Total duration of treatment (week) in the extension study

5.5. Analysis Population

The Full Analysis Set includes all subjects who signed inform consent for this study and received at least one dose of study drug during the trial. The efficacy and safety analysis will be performed based on full analysis set.

6. Subject Disposition

6.1. Disposition

The number of subjects who are enrolled for the trial, i.e., the subjects who signed inform consent, the number of subjects who received any doses and the number of subjects who complete the trial will be presented. The frequency and percentage of subjects who withdraw or discontinue from the trial, and the reason for withdrawal or discontinuation, will also be summarized.

The summaries will be presented in a table and subject disposition data will be presented in a listing.

6.2. Protocol Deviations

A list of major protocol deviations that could significantly affect study assessments will be identified by Clinical and the Medical Experts based on the pre-specified criteria. A data review meeting will be held to determine this list. This list will be finalized prior to database lock. A listing will be produced for protocol deviation.

7. Demographics and Other Characteristics

7.1. Demographics and Disease Characteristics

Descriptive summaries of the parent study baseline and extension study baseline will be summarized for the full analysis set.

- Extension Study Baseline Demographics and Disease Characteristics:

  o Age (years) at Visit 1
  o Age category (<3 years, ≥3 to <6 years, [≥6 to <11 years for girls, ≥ 6 to <12 years for boys] and [≥11 years for girls, ≥12 years for boys])
  o Gender
  o Race
  o Ethnicity
  o Region (North America, Europe, and Oceania)
  o Absolute height (cm)
  o Height SDS
  o Weight (kg)
  o Body mass index (BMI) (kg/m^2)
  o Pubertal status (Tanner stage)
  o Mother's height (cm)
  o Father's height (cm)
  o Average-parental height SDS
  o IGF-1
  o IGF-1 SDS
  o IGFBP-3
  o Prior use of hGH therapy (Daily GH or TransCon, Dose and duration)
  o Bone Age
  o Peak stimulated GH (levels <=5 ng/mL, >5 ng/mL) at diagnosis

7.2. Medical History

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

7.3. Prior and Concomitant Medications

All medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version March 2018 or later). The frequency and percentage of all prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification and preferred term. Listings of all medications will also be provided.

7.3.1. Prior Medication

Prior medication is defined as any medication started before the date of the first dose of investigational product in this extension study, where the medication start date is prior to the date of the first dose date in this extension study.

If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed to be a prior medication if it cannot be definitely shown that it started on or after the first dose of the investigational product. Missing dates will not be replaced.

7.3.2. Concomitant Medication

Concomitant medication is defined as medication taken on or after the date of the first dose of investigational product in this extension study, where the medication end date is on or after first dose date in this extension study (or ongoing)]

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.

Permitted Concomitant Medications

- Replacement therapy for other non-GH pituitary deficiencies. As hGH may enhance the transformation of hydrocortisone to cortisone, the investigator may increase the dose of hydrocortisone replacement therapy if needed (eg, for anticipated stress).
- 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

- Weight-reducing drugs or appetite suppressants, unless used for management of ADHD
- hGH therapies other than TransCon hGH

Use of prohibited concomitant medications will be summarized and listed.

8. Safety Analysis

The safety endpoints (Section 3.3.1) are measured throughout the long term TransCon hGH treatment. These safety variables will be summarized in tables and all safety evaluations will also be listed.

8.1. Adverse Events

AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including

abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to that product. An AE can arise with any use (e.g., in combination with another drug), route of administration, formulation, or dose, including an overdose.

An AE is considered treatment emergent, i.e., Treatment Emergent Adverse Event (TEAE), is any AE that was first occurred or worsened after the first dose in this extension study and before the end of study. If the AE has any missing start date, the rules stated in Section 5.2 will be applied to determine if it is treatment-emergent.

A serious AE (SAE) is SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

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. In addition, related TEAE, non-related TEAE, TEAE leading to study drug discontinuation, and serious TEAE, by SOC, the preferred term and TEAE by preferred term will be also summarized. Especially, related includes definite, probable and possible relationship. Not-related includes unlikely/remote and unrelated/not related.

Each subject will be counted only once within each preferred term. If a subject experience 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.

Data listing of AEs, TEAE leading to study drug discontinuation, serious TEAE will also be provided.

8.2. Antibodies

The appropriateness of the approach taken to analyze and report anti-drug antibody data should be evaluated on a case-by-case basis [1], following recent regulatory guidance and a white paper [2]. Statistical analysis of antibodies against drug (ADA) will include (but not be limited to) the following tabulated summaries of antibody frequencies and percentages:

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 by positive types and overall
6. Incidence of persistent anti-hGH neutralizing antibodies by positive types and overall
7. Incidence of transient anti-hGH neutralizing antibodies by positive types and overall
8. Incidence of treatment induced anti-PEG antibodies by positive types and overall

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

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.

The baseline antibody status is the status before the first dose of TransCon hGH. Therefore, for subjects from Study CT-302 and Study CT-301 TransCon hGH group, the baseline is the parent study baseline. But for subjects from Study CT-301 Genotropin group, the baseline is the extension study baseline.

In order to derive transient ADA and persistent ADA, all the data from baseline till the end of extension study will be used. In other words, for subjects from Study CT-302 and Study CT-301 TransCon hGH group, the data from parent study will be combined together with extension study data to get transient and persistent ADA status. For subjects from Study CT-301 Genotropin group, only the data from extension study will be used.

8.3. IGF-1 SDS

A descriptive table including the number and percentages of subjects by visit will be presented where:

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

Listings of IGF-1 and IGF-1 SDS for subjects with abnormally high IGF-1 SDS will be generated.

8.4. Clinical Laboratory Evaluations

Descriptive summaries of actual (absolute) values and changes from extension study baseline values if applicable will be presented in the tables for the following by visit for the full analysis set:

- Chemistry: 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.
- Lipid Metabolism: Total cholesterol, triglycerides, HDL and LDL

Laboratory values will also 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.

8.5. Vital Signs

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

A data listing of vital signs will also be provided.

8.6. Exposure and Compliance

Summary tables for extension study will be presented for the following variables:

- Total duration of treatment
- Total number of actual doses

- Total actual dosage (mg)
- Compliance rate

The dosage (mg) is the product of the dose volume (mL) and dose concentration (mg/mL) reported in the eCRF. When there are three or more consecutive doses with more than 15% difference between actual dose and expected dose (0.24mg/kg/week), it will be considered as a dose reduction/increase. The frequency and percentages of subjects for dose not changed, dose increased or decreased will also be summarized by visit and overall.

The compliance rate will be calculated based on the rules in Section 5.4. Compliance rate will be summarized using the following categorization; <80%, ≥80%, ≥90%, ≥95% and 100%.

Listings will be presented for all exposure information.

8.7. Other Assessments

Other safety assessments include weight, pubertal status, fundoscopy and bone age.

Weight and pubertal status are measured at each visit. Summary tables will be produced for these assessments by visit.

Fundoscopy is measured during the end of study. A listing will be presented for fundoscopy at each visit.

Bone age and delay in bone age are measured annually. Summary of the change from baseline will be presented in tables. Listing will also be provided. for bone age and delay in bone age.

9. Efficacy Analyses

9.1. Annualized HV

Annualized height velocity is calculated based on the rules stated in Section 5.4. Summary tables and listings for HV absolute values at each timepoint by each group and overall will be generated.

9.2. ΔHSDS

Height Standard Deviation Score is derived based on the rules stated in Section 5.4. Summary tables for absolute values and change from baseline at each timepoint by each group and overall will be generated. The listings will also be presented.

9.3. IGF-1 SDS and IGFBP-3 SDS

A descriptive table including the frequency and percentages of subjects at each visit by each group and overall will be presented where:

- IGF-1 SDS < - 2.0
- 0 <= IGF-1 SDS <= 2.0
- -2.0 <= IGF-1 SDS < =2.0
- -1.0 <= IGF-1 SDS <= 2.0
- IGF-1 SDS > 2.0
- IGF-1 SDS > 3.0

The absolute values and change from baseline at each visit of the IGF-1, IGFBP-3, IGF-1 SDS and IGFBP-3 SDS will be presented with descriptive statistics. Listings will be generated for these outcomes.

9.4. Subgroup Analysis

Efficacy variables including annualized HV, HSDS and IGF-1 SDS, demographic and baseline characteristics and TEAE may also be summarized based on the following subgroups.

- Age (< 3 years, >=3 to <6 years. [>= 6 to <11 years for girls, >=6 to <12 years for boys] and [>=11 years for girls, >=12 years for boys])
- Gender
- Asian vs Non-Asian
- Tanner Stage
- US vs. Non-US

For US sites, subjects will be switched from syringe to auto-injector during the study. The following analysis will be repeated for US subjects for auto-injection:

- Exposure/compliance
- TEAEs
- Local Tolerability
- Anti-body (only the positive vs negative)
- Device related PROs

10. Pharmacodynamics Analyses

The Pharmacodynamic (PD) endpoint, Serum IGF-1 SDS will be collected at 5 days ±1 day post-dose. Listings will be generated for PD endpoints.

11. Patient-Reported Outcomes

All Patient-Reported Outcomes used in this trial have been assessed for understanding by GHD patients and their parents/legal guardians/caregivers as intended by the Sponsor in a prior Cognitive Debriefing study per the Guidance for Industry. Questionnaire are administered during the study. The following endpoints are also collected:

- Preference for TransCon hGH or commercially available daily hGH treatment
- Satisfaction with daily hGH and weekly TransCon hGH over time

11.1. Preference Questionnaire

The Preference Questionnaire should only be completed for subjects who were treated with daily Genotropin in the prior TransCon hGH CT-301 trial. The parent/legal guardian/caregiver will complete the PQ-P, while the subject, if ≥ 9 years old at Visit 1, will complete the PQ-C.

The frequency and percentages will be summarized for each question for PQ-P and PQ-C in tables. Listings will also be provided for PQ-P and PQ-C.

11.2. Child Sheehan Disability Scale

The CSDS is an adaptation of the Sheehan Disability Scale to assess impairment related to childhood anxiety on children and their parents. This measure is being adapted in this trial to assess impairment related to treatment burden on children and their parents/legal guardians/caregivers.

At Visit 1 for all subjects, the parent/legal guardian/caregiver will complete the CSDS-P, while the subject, if ≥ 9 years old, will complete the CSDS-C.

Summary score will be the sum of each question score at each visit. It will be calculated based on child and parent separately.

Each question for CSDS-P and CSDS-C at each time point will be summarized. Listings will also be provided for CSDS-P and CSDS-C.

11.3. Convenience & Overall Satisfaction Domains of the Treatment Satisfaction Questionnaire for Medication

At Visit 1, the Convenience and Overall Satisfaction (C&OS) of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) is administered to all subjects.

Only the parent/legal guardian/caregiver will complete the C&OS of the TSQM-9, thus it has been identified for this trial as the C&OS – Parent (C&OS-P).

The study C&OS-P contains two sections including convenience section (item 1-3) and global satisfaction section (item 4-6) on the questionnaires. In order to derive a summary score, the following rules are used.

The convenience score will be set as follows:

(1) 100*(sum(item 1 to 3) - 3)/18, if all the items are presented;
(2) 100*(sum(two items) - 2)/12, if one item is missing,
(3) Missing if more than one item is missing;

The global satisfaction score will be set as follows:

(1) 100*(sum(item 4 to 6) - 3)/14, if all the items are presented;
(2) 100*(sum(two items) - 2)/10 if item 4 or 5 is missing
(3) 100*(sum(item 4 and 5) - 2)/8 if item 6 is missing
(4) Missing if more than one more item is missing

Each question for C&OS -P, and the summary score, i.e., convenience score and global satisfaction score, will be summarized at each time point by each group and overall. Listings will also be provided for C&OS -P as well.

11.4. Device Usability Questionnaire

The Device Usability Questionnaire will be administered during this trial to assess GH Auto-Injector comfort, ease-of-use, and safety from the point of view of the caregivers and subjects.

The questionnaire consists of eight statements that the subject or is asked to rank on a scale indicating level of agreement. The statements relate to the level of comfort, ease-of-use, and safety.

Descriptive analysis will be conducted for each question. Listing will also be provided.

12. References

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