Official Title: fliGHt: A Multicenter, Phase 3, Open-Label, 26-Week Trial Investigating the Safety, Tolerability and Efficacy of TransCon hGH Administered Once Weekly in Children with Growth Hormone Deficiency (GHD)

NCT Number: NCT03305016

Document Date: SAP: 14 March 2019

STATISTICAL ANALYSIS PLAN

Protocol Title:	**fliGHt:** A Multicenter, Phase 3, Open-Label, 26-Week Trial Investigating the Sa**f**ety, To**l**erab**i**lity and Efficacy of TransCon h**GH** Admini**s**tered Once Weekly in Children with Growth Hormone Deficiency (GHD)
Protocol Number:	TransCon hGH CT-302
Compound:	TransCon hGH
Phase:	3
Sponsor:	Ascendis Pharma, Inc. 500 Emerson Street Palo Alto, California 94301
SAP Author:	[redacted]
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LIST OF ABBREVIATIONS

ΔHSDS	change in height standard deviation score
µg	microgram
ACP-001	TransCon PEG80 hGH
ACP-011	TransCon PEG40 hGH
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
AGHD	adult growth hormone deficiency
ANCOVA	Analysis of Covariance
AUC	area under the curve
BIH	benign intracranial hypertension
BLQ	Below the Limit of Quantification
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
CFR	Code of Federal Regulations
Cm	centimeter
C_{max}	maximum observed concentration
CSDS-C	Child Sheehan Disability Scale – Child
CSDS-P	Child Sheehan Disability Scale – Parent
DCC	dual chamber cartridge
DMP	data management plan
eCRF	electronic case report form
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone-releasing hormone
HbA1c	hemoglobin A1c
HREC	Human Research Ethics Committee
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
ISC	Independent Safety Committee
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mPEG	methoxypolyethylene glycol
MPH	mid-parental height
PD	pharmacodynamics
PEG	polyethylene glycol
PK	pharmacokinetics
PQ-C	Preference Questionnaire – Child
PQ-P	Preference Questionnaire – Parent
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
SUSAR	suspected unexpected serious adverse reaction
TMPD	N1, -N1, N3-trimethyl-1,3-propanediamine
TSQM	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-302 (fliGHt: A Multicenter, Phase 3, Open-Label, 26-Week Trial Investigating the Safety, Tolerability and Efficacy of TransCon hGH Administered Once Weekly in Children with Growth Hormone Deficiency (GHD)), Amendment 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-302 and its amendment, and Case Report Forms (CRFs) for Protocol TransCon hGH CT-302.

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 the safety and tolerability of weekly TransCon hGH in children with GHD from 6 months to 17 years old, inclusive

2.2. SECONDARY OBJECTIVES

- To assess annualized height velocity (HV) in children with GHD at 26 weeks of weekly TransCon hGH treatment
- To assess the proportion of subjects with IGF-1 SDS in the normal range of 0.0 to +2.0 at 26 weeks of weekly TransCon hGH treatment
- To evaluate change in height standardized score (ΔHSDS) in children with GHD at 26 weeks of weekly TransCon hGH treatment
- To determine the incidence of antibodies against TransCon hGH (anti-hGH and anti-PEG) in children with GHD over 26 weeks of weekly TransCon hGH treatment

- To assess the expected C_{max} of TransCon hGH in children with GHD ≥ 6 months to < 3 years old
- To assess the preference for weekly TransCon hGH or commercially available daily hGH treatment
- 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, open-label, 26-week trial of weekly TransCon hGH in children 6 months to 17 years old, inclusive, with GHD. Study population will include approximately 150 male and female children who at Visit 1 are 3 to 17 years old, inclusive, diagnosed with GHD, weigh no more than 80 kg, have open epiphyses, and have received at least 0.20 mg hGH/kg/week of daily hGH treatment for ≥ 13 weeks but ≤ 130 weeks. Additionally, children with GHD who at Visit 1 are ≥6 months but <3 years old, weigh at least 5.5 kg, and are either hGH treatment-naive or have been treated with daily hGH (≥ 0.20 mg hGH/kg/week) for ≤130 weeks. TransCon hGH will be provided as a lyophilized powder dosed at 0.24 mg hGH/kg/week in single-use glass vials and administered with syringe and needle.

The trial will be conducted at up to approximately 50 sites specialized in the management of pediatric GHD.

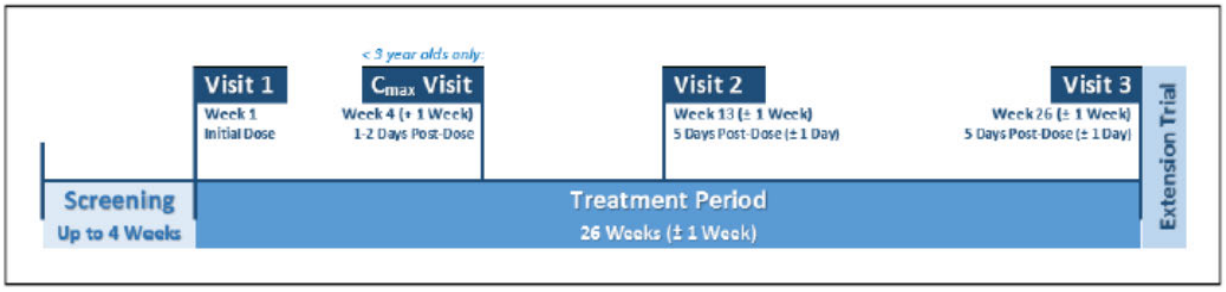
The trial consists of:

1. Screening Period – up to approximately 4 weeks
2. Treatment Period – up to 27 weeks of dosing

The total duration of participation for each subject in the trial will therefore be up to approximately 31 weeks (Figure 1). The scheduled visits are listed in Table 1.

Each subject who successfully completes the trial on study drug will be invited to participate in the CT-301EXT (extension) Trial designed to assess long-term safety and efficacy.

Figure 1: Overall Trial Design



3.2. SAMPLE SIZE

A sample size of 150 provides at least 95% probability to observe AEs with a 2% or more incidence rate for a 26-week follow up. It also enables the combined safety database of the clinical program (a sample size of approximately 300) to have at least 95% probability to observe AEs with an incidence rate of 1% or more.

As recruiting subjects <3 years old will prove challenging, an exact sample size for this cohort has not been pre-determined.

Table 1: Schedule of Events

	Screening	Visit 1	C_{max} Visit[1]	Visit 2	Visit 3/ET[2]
	Weeks -4 to -1	Week 1	Week 4 (+ 1 Week)	Week 13 (± 1 Week)	Week 26 (± 1 Week)
	Morning	Pre-Dose, Morning	1-2d Post-Dose, Morning	5d ± 1d Post-Dose, Morning	5d ± 1d Post-Dose, Morning
INFORMED CONSENT	x				
MEDICAL HISTORY	x				
CONCOMITANT MEDICATION	x	x	x	x	x
VITAL SIGNS MEASUREMENTS[3]	x	x		x	x
HEIGHT[4] & WEIGHT	x	x		x	x
LIMITED PHYSICAL EXAMINATION	x	x		x	x
PUBERTAL STATUS ASSESSMENT	x	x		x	x
BONE AGE X-RAY[5]	x				
FUNDOSCOPY[6]	x				x
BLOOD SAMPLE COLLECTION	x[7]		x[8]	x[9]	x[10]
STUDY DRUG & SUBJECT DIARY DISPENSING		x		x	
DRUG PREPARATION TRAINING		x		x	
SUBJECT DIARY TRAINING		x			
CSDS-P		x[11]		x[12]	x
CSDS-C[13]		x[11]		x[12]	x
C&OS-P		x[11]		x[12]	x
ON-SITE STUDY DRUG ADMINISTRATION		x			
LOCAL TOLERABILITY ASSESSMENT[14]		x			
PQ-P[15]				x[12]	
PQ-C[13 15]				x[12]	
ADVERSE EVENTS[16]			x		
STUDY DRUG COMPLIANCE[17]			x		
DOSE ADJUSTMENT[18]				x	

[1] Subjects <3 years old at Visit 1 will perform the C_{max} Visit. Subjects ≥3 years old at Visit 1 will NOT perform the C_{max} Visit.
[2] An Early Termination Visit should be performed for all subjects exiting the trial and should include all procedures listed for Visit 3. Stopping study drug does NOT require
[3] 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
[4] Height should be measured at each visit at approximately the same time of day, preferably by the same auxologist.
[5] Locally read bone age x-ray only required at Screening if subject is at Tanner stage 4 and an x-ray performed within the past 52 weeks with a bone age delay of ≥ 6 months is
[6] Fundoscopy may also be performed at any time, if clinically indicated.
[7] Blood samples collected at Screening will be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. The analyses of antibodies against hGH and PEG may only be conducted after enrollment and are not required for eligibility verification. Data will be used to support evaluation of post-dose antibody detection. Female subjects of child-bearing potential will also have blood samples tested for hCG.
[8] Blood samples collected at the Cmax Visit will be tested for the following: hGH, IGF-1 and IGFBP-3, and hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c).
[9] Blood samples collected at Visit 2 will be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Subjects < 3 years old at Visit 1 will also have blood samples tested for mPEG. Female subjects of child-bearing potential will also have blood samples tested for hCG.
[10] Blood samples collected at Visit 3 will be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Subjects ≥ 9 years old at Visit 1 will also have blood samples tested for TMPD. Subjects < 3 years old at Visit 1 will also have blood samples tested for mPEG. Female subjects of child-bearing potential will also have blood samples tested for hCG.
[11] At Visit 1, the CSDS-P, CSDS-C, and C&OS-P should only be completed for subjects treated with daily hGH prior to enrollment.
[12] CSDS-P, CSDS-C, C&OS-P, PQ-P, and PQ-C will be completed (as applicable) within the subject diary immediately prior to the 6th dose of study drug and again at Visit 2.
[13] CSDS-C and PQ-C should only be completed by subjects ≥ 9 years old at Visit 1.
[14] Local tolerability assessment at the injection site to be performed at time of injection and 15 minutes, 1 hour, and 2 hour post-dose.
[15] PQ-P and PQ-C should only be completed for subjects treated with daily hGH prior to enrollment.
[16] AE review includes review of subject diary and physical examination of injection sites.
[17] Study drug compliance includes review of subject diary and returned study drug.
[18] Dose adjustments at visits are based on subject weight at visits. However, dose adjustments may occur between visits per protocol Section 9.6.

3.3. STUDY ENDPOINTS

3.3.1. Safety Endoints

The safety endpoints as measured throughout the 26 weeks of weekly TransCon hGH treatment include the following:

- Incidence of AEs
- Local tolerability, as assessed by the subject/parents/legal guardians/caregivers and trial staff
- 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 as measured at 26 weeks of weekly TransCon hGH treatment include the following:

- Annualized HV
- ΔHSDS
- 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. C_{max}/Pharmacodynamic Endpoints

- Expected C_{max} of hGH in subjects <3 years old
- Serum IGF-1 SDS at 1-2 days post-dose in subjects <3 years old
- Serum IGF-1 SDS at 5 days ±1 day post-dose in all subjects

3.3.4. Other Endpoints

- Preference for TransCon hGH or commercially available daily hGH treatment
- Satisfaction with treatments for GHD: daily hGH and weekly TransCon hGH
- Impact of taking treatments for GHD: daily hGH and weekly TransCon hGH

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 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

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

Baseline will be defined as the most recent non-missing assessment (including repeated and unscheduled assessments) before the study drug administration.

5.2. HANDLING OF MISSING DATA

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

For the prior daily hGH treatment, if the day of first daily hGH treatment is missing, then impute the day to the 1st of that month. If both day and month are missing, then impute to Jan 1 of the year (eg, Jan 1, 2018). The duration will then be derived from the imputed date.

For Analysis of Covariance (ANCOVA) modeling, the following imputation will be done for the missing covariates:

- 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.
- If growth hormone stimulation data is missing at diagnosis, a value of 5 ng/mL will be used by convention.
- If subject took prior hGH treatment, but dose or duration is missing, the mean dose level will be used. If the prior hGH treatment date is completely missing and can't be imputed based on the rules stated before, the mean duration will be used for ANCOVA analysis.

For medication with missing start or end date, the following rules will be used to determine if it is prior or concomitant medication.

- If the start date is completely missing, but the end date is available and it is before the first dose date, then it will be counted as prior medication. Otherwise, it will be counted as both prior and concomitant medication.
- If both the start date and end date are completely missing, and it is ongoing, it will be counted as both prior and concomitant medication.
- If the start or end day is partially missing, Day 1 of the month will be used to determine if it is prior or concomitant medication. If both day and month of start date are missing, Jan 1 will be used to determine if it is prior or concomitant medication.

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 during the treatment-emergent period (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

Enrolled subjects will attend a total of 3 morning trial visits:

- Visit 1 will be considered Week 1, Day 1 (first day/week of dosing)
- Visit 2 will be performed during Week 13 (±1 week), 5 days (±1 day) post-dose

  If during Week 12, Visit 2 must occur on Days 82 to 84
  If during Week 13, Visit 2 must occur on Days 89 to 91
  If during Week 14, Visit 2 must occur on Days 96 to 98

- Visit 3 will be performed during Week 26 (±1 week), 5 days (±1 day) post-dose

  If during Week 25, Visit 3 must occur on Days 173 to 175
  If during Week 26, Visit 3 must occur on Days 180 to 182
  If during Week 27, Visit 3 must occur on Days 187 to 189

Subjects <3 years old at Visit 1 will have a total of 4 morning trial visits including the above 3 visits and the addition of:

- C_{max} Visit to be performed during Week 4 (+1 week), 1-2 days after the 4th or 5th dose

  If during Week 4, C_{max} Visit must occur on Days 23-24
  If during Week 5, C_{max} Visit must occur on Days 30-31

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	**Screening**	**Visit 1**	**C_{max} Visit**	**Visit 2**	**Visit 3/ET**
Week	Weeks -4 to -1	Week 1	Week 4 (+ 1 Week)	Week 13 (± 1 Week)	Week 26 (± 1 Week)
Target Day		Day 1	Day 29	Day 92	Day 183
Range		Day 1	Day 2 - 60	Day 61 - 137	Day 138 - EOS

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, 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.

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))
Height Standard Deviation 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 over 26 weeks	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 – first treatment date +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/Total Duration of Treatment (week)

5.5. ANALYSIS POPULATION

The Screened Population includes all the subjects who are screened for this study and have any data captured in the EDC.

The Full Analysis Set includes all subjects who receive at least one dose of study drug during the trial and who have any follow-up data. 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 screened for the trial, the reasons for screen failure, 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 major protocol deviations.

7. DEMOGRAPHICS AND OTHER CHARACTERISTICS

7.1. DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Descriptive summaries of the baseline demographic and other disease characteristics will be summarized for the Full Analysis Set.

- Baseline Demographics and disease characteristics:
  - Age (years) at Visit 1
  - 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])
  - Gender
  - Race
  - Ethnicity
  - Region (North America and Oceania)
  - Absolute height (cm)
  - Height SDS
  - Weight (kg)
  - Body mass index (BMI) (kg/m^2)
  - Pubertal status (Tanner stage)
  - Mother's height (cm)
  - Father's height (cm)
  - Mid-parental height SDS
  - Delta Mid-parental height SDS: subject height SDS subtract mid parental height SDS
  - IGF-1
  - IGF-1 SDS
  - IGFBP-3
  - Deficiencies of Other Pituitary Axes
  - Prior use of hGH therapy (Yes/No)
  - Current use of hGH (name, dose and duration)

- Disease Characteristics at diagnosis (prior to starting daily growth hormone therapy)
  - Age at diagnosis
  - IGF-1 SDS at diagnosis
  - IGFBP-3 SDS at diagnosis
  - Peak stimulated GH
  - Peak stimulated GH levels ≤5 ng/mL, >5 ng/mL
  - Bone age at diagnosis/delay in bone age
  - Results of karyotype testing
  - Other pituitary deficiencies 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 2016 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.

For medication with missing dates, the rules stated in Section 5.2 will be applied to determine if the medication is a prior or concomitant medication.

7.3.1. Prior Medication

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

7.3.2. Concomitant Medication

Concomitant medication is defined as medication taken after the first study treatment and during the trial.

Permitted Concomitant Medications

- Replacement therapy for other non-GH pituitary deficiencies.
- Glucocorticoid therapy for indications other than adrenal replacement (eg, asthma)
- 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 26 weeks of weekly 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 (eg, in combination with another drug), route of administration, formulation, or dose, including an overdose.

An AE is considered treatment emergent, ie, Treatment Emergent Adverse Event (TEAE), is any AE that was first occurred or worsened after the first study dose 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. LOCAL TOLERABILITY

Local tolerability is defined as an injection site reaction deemed abnormal from those ordinarily observed in SC injections (including pain, intensity, or duration).

At Visit 1, assessment of local tolerability will be performed by trial staff using the Local Tolerability Scale at the time of the first study drug injection and 15 minutes, 1 hour and 2-hour post-dose. At the same time, and as part of subject diary training, the subjects/parents/legal guardians/caregivers will document their assessment of local tolerability in the subject diary, within which injection site pain will be rated by the Wong-Baker FACES Pain Rating Scale.

Between visits, local tolerability will be evaluated and documented by the subject/parent/legal guardian/caregiver in the subject diary.

At Visit 2 and Visit 3, assessment of local tolerability will be performed by injection site examination by trial staff local tolerability will be summarized based on the investigator's and subject/parents/legal guardians assessment of redness, bruising, swelling and pain.

Descriptive summary variables such as pain scale, redness, bruising and swelling will be produced for each assessment at each time point. A data listing of investigator's and subject/parents/legal guardian assessment will also be provided.

8.3. ANTIBODIES

The appropriateness of the approach taken to analyze and report anti-drug antibody data should be evaluated on a case-by-case basis (*Assay Development [Draft Guidance] 2016*), following recent regulatory guidance and a white paper (*Shankar 2014*). 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 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.

8.4. 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.

8.5. CLINICAL LABORATORY EVALUATIONS

Descriptive summaries of actual (absolute) values and changes from 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.

For each laboratory parameter, if applicable, shifts in assessments of abnormality from baseline to each post-baseline visit will be presented (shift tables).

8.6. 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.

8.7. EXPOSURE AND COMPLIANCE

Summary tables 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 observed 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.

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.

8.8. OTHER ASSESSMENTS

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

Weight and pubertal status are measured at screening and at Visits 1, 2 and 3. Summary tables will be produced for these assessments by visit.

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

Bone age and delay in bone age are measured at screening. Listing will 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. An ANCOVA will be used to analyze by visit annualized height velocity. The model will include baseline age, peak GH levels (log transformed) at diagnosis, delta mid-parental height SDS, prior GH dose level (log transformed), and duration (log transformed) as covariates, and gender as a factor.

Summary tables including data and listings will be presented for all height measured during the trial.

9.2. ΔHSDS

Height Standard Deviation Score (HSDS) is derived based on the rules stated in Section 5.4. The by visit change from baseline of the HSDS will be analyzed by ANCOVA model including baseline age, peak GH (log transformed) at diagnosis, delta mid-parental height SDS, prior GH dose level (log transformed), and duration (log transformed) as covariates, and gender as a factor.

Summary tables and Figures will be provided for HSDS and change from baseline in HSDS at each time point. Listings will also be generated for all the HSDS information.

9.3. IGF-1 SDS AND IGFBP-3 SDS

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

- 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 by visit post baseline values and change from baseline in IGF-1 SDS and IGFBP-D SDS will be analyzed by ANCOVA model, including baseline age, peak GH (log transformed) at diagnosis, baseline (of the corresponding variable), prior GH dose level (log transformed), and duration (log transformed) as covariates, and gender as a factor.

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 also 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 may also be summarized based on the following subgroups if the sample size allows.

- 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
- Baseline GH-stim strata (≤5 ng/mL and >5 ng/mL)
- Prior exposure to hGH therapy (Yes/No)

10. PHARMACOKINETIC AND PHARMACODYNAMICS ANALYSES

The following Pharmacokinetic (PK) and Pharmacodynamic (PD) endpoints are assessed, and two of them are only in subjects who are less than 3 years old at Visit 1:

- Expected C_{max} of hGH in subjects <3 years old
- Serum IGF-1 SDS at 1-2 days post-dose in subjects <3 years old
- Serum IGF-1 SDS at 5 days ±1 day post-dose in all subjects

In general, the PK/PD parameters will be summarized using descriptive statistics (number of subjects, arithmetic mean, arithmetic SD, arithmetic SEM, arithmetic CV, median, minimum, and maximum, and geometric mean and geo CV, if applicable)

10.1. ANALYSIS OF PK ANALYTES

Blood samples for measurement of PK analytes are to be collected as according the schedule in Table 1, Schedule of Events (Section 3.1). Blood samples will be processed to serum for quantitation of hGH, and PEG (measured as total methoxypolyethylene glycol, 40 KDa [mPEG40]); and to plasma for quantification of N1, -N1, N3-trimethyl-1,3-propanediamine (TMPD).

Furthermore, if warranted, TransCon hGH, hGH and PEG serum levels may be analyzed at any visit in any subject to support the interpretation of immunogenicity titers (anti-hGH and anti-PEG antibodies).

C_{max} of hGH, which is the maximum observed serum concentration, will be calculated for Subjects <3 years old at Visit 1 (C_{max} Visit). 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 visit for each analyte.

10.2. ANALYSIS OF PD ANALYTES

Blood samples for measurement of PD analytes are to be collected as according to the schedule in Table 1, Schedule of Events (Section 3.1). Blood samples will be processed for serum IGF-1 and IGFBP-3.

SD-scores for IGF-1 and IGFBP-3 will be calculated based on absolute serum concentration data applying published IGF-1 and IGFBP-3 age and gender-specific Standard Deviation Score (SDS) reference ranges (*Bidlingmaier 2014*, *Friedrich 2014*).

Absolute and baseline-corrected serum concentration data will be listed and summarized by time point.

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
- Impact of taking daily hGH and TransCon hGH
- Satisfaction with daily hGH and weekly TransCon hGH over time

11.1. PREFERENCE QUESTIONNAIRE

The Preference Questionnaires are administered to subjects who were treated with daily hGH prior to enrollment in the trial. The parent/legal guardian/caregiver will complete the PQ-P for all subjects. For subject>=9 years old at Visit 1, will also 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

At Visit 1, the Child Sheehan Disability Scale (CSDS) assessment is administered to subjects who were treated with daily hGH prior to enrollment. At all other time points, the CSDS is administered to all subjects, regardless of whether they were hGH-experienced or hGH-naïve.

The parent/legal guardian/caregiver will complete the CSDS-P for all subjects. For subjects >= 9 years old at Visit 1 will also complete the CSDS-C.

At Week 6, immediately prior to the 6th dose of study drug, the CSDS-P and the CSDS-C (as applicable) will be completed within the Subject Diary. At approximately Week 13 and Week 26, the CSDS-P and the CSDS-C (as applicable) will be completed at Visits 2 and 3.

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 subjects who were treated with daily hGH prior to enrollment. At all other time points, the C&OS 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).

At Week 6, immediately prior to the 6th dose of study drug, the C&OS will be completed within the Subject Diary. At approximately Week 13, the C&OS will be completed at Visit 2.

C&OS-P contains two sections including convenience section (items 1-3) and global satisfaction section (items 4-6). 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 convenience score and global satisfaction score at each time point will be summarized. Listings will also be provided for C&OS -P.

12. REFERENCES

Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (Draft Guidance), April 2016:
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