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

NCT Number: NCT03344458

Document Date: Protocol Version 2: 29 January 2020

CLINICAL STUDY PROTOCOL

PRODUCT NAME/NUMBER:	TransCon hGH (ACP-011)
PROTOCOL NUMBER:	TransCon hGH CT-301EXT
IND NUMBER:	126053
EUDRACT NUMBER:	2017-003410-20
DEVELOPMENT PHASE:	3
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 DATE:	Version 1.0: 14 September 2017 Version 2.0 (Global Amendment 1): 29 January 2020
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STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Conference on Harmonisation (ICH E6) and regional regulations
- Regional subject data protection laws and regulations
- Other applicable regional and local regulations

APPROVAL SIGNATURES

SPONSOR

I agree to conduct this trial in accordance with the requirements of this Clinical Trial Protocol amendment and also in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Conference on Harmonisation (ICH E6) and regional regulations
- Regional subject data protection laws and regulations
- Other applicable regional and local regulations
- Clinical trial contractual obligations

CLINICAL TRIAL 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

PPD

PPD

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MD

PPD

Ascendis Pharma Inc.

PPD

Date

SUMMARY OF CHANGES – VERSION 2.0 (GLOBAL AMENDMENT 1), JANUARY 2020

RATIONALE

This amendment serves to clarify that investigator judgement is the foundation of reporting adverse events (AEs) associated with out-of-range laboratory values. It is recognized that IGF-1 and IGFBP3 are pharmacodynamic markers for TransCon hGH therapy and may be used to guide an investigator's recommendation to titrate the study drug dose. In prior versions of this protocol, investigators were compelled to label out-of-range IGF-1 and IGFBP3 values as "clinically significant" (regardless of presence of clinical concern, signs, or symptoms) in order to pursue dose titrations. Additionally, clinically significant laboratory values (including IGF-1 and IGFBP3) were categorically to be documented as AEs. This amendment revises the protocol language so that TransCon hGH dose titrations may occur with or without the labeling of out-of-range IGF-1 and/or IGFBP3 as "clinically significant." It also specifies that out-of-range laboratory values may constitute AEs if they induce a new/worsening diagnosis, clinical sign, or symptom, or require therapy.

Section(s)	Change	Rationale
Protocol version	Global Amendment 1.0 supersedes U.S. (country-specific) Amendment 1.0.	U.S. had a country-specific amendment (US Specific Amendment 1.0) to include protocol changes only designated in the U.S. for the GH Auto-Injector and Dual Chamber Cartridge (DCC) system. This Version 2.0 (Global Amendment 1) applies to all regions, unless otherwise specified. Thus, U.S. will continue from U.S. Amendment 1.0 to Version 2.0 (Global Amendment 1) while all other countries will move from original protocol to Version 2.0 (Global Amendment 1).Country-specific amendments will be applied, as needed, to this version and will be identified as Version 2.1 in that country.
Synopsis – Trial Design; 18.2 Schedule of Events	Clarified that interval history is included in medications and health status review.	Medications and health status review includes review of interval history that records new conditions since the last visit of the prior trial.
Synopsis – Trial Design; 8.2 Premature Subject Withdrawal; 9.6.2 Stopping/Dose	Clarified that once a subject has evidence of closed epiphyses, the subject will have completed the study and discontinue study treatment.	Evidence of closed epiphyses serves as a criterion for completing the trial.

Section(s)	Change	Rationale
Reductions; 10.1 Trial Duration		
Synopsis – Trial Design; 9.6.2 Stopping/Dose Reductions	Removed the requirement to label an IGF-1 SDS > 2 as "clinically significant" that would prompt an investigator to consider TransCon hGH dose titration.	"Clinically significant" may imply an associated diagnosis, sign, symptom; and/or requirement of additional action (another test, evaluation, or treatment). In this trial, it is not appropriate to apply the label of "clinically significant" to asymptomatic high IGF-1 SDS values and/or those associated with dose titrations.
Synopsis – Investigational Product; 9.3 Treatment Administered	Added language that 1 of the 2 vial presentations will be supplied.	At least one of the two presentations will be available for supply.
Synopsis – Criteria for Evaluation; 14.1.1 Safety Endpoints	Corrected symbol to show that IGF-1 SDS >3 will be evaluated.	Administrative change.
Synopsis – Criteria for Evaluation; 14.1.1 Safety Endpoints	Added incidence of antibodies against TransCon hGH as a safety endpoint.	Addition to the existing panel of anti-drug antibody testing.
7.3.2 Early Termination of the Trial	Left shifted second paragraph in this section.	Administrative change.
8.2 Premature Subject Withdrawal; 12.1.3 Reporting Procedures for All Adverse Events;18.2 Schedule of Events	Defined AE reporting period as up to 14 days after the final dose of TransCon hGH.	Post-treatment safety reporting period was not previously defined.
9.1.2 TransCon hGH Administered using GH Auto-Injector	Moved "in the US only".	Administrative change.
9.3 Treatment Administered	Clarified the options available to investigators when recommending TransCon hGH doses in subjects previously titrated to a bracket different than expected for weight.	Provides investigators dosing flexibility in the context of each individual subject's historical trajectory.
9.3 Treatment Administered Table 1	Displayed the dose volume (mL) when using the 22.0 mg hGH/mL vial.	Adds recommended dose volumes when using "alternative dosing" (the right-sided column of Table 1).

Section(s)	Change	Rationale
9.6.2 Stopping/Dose Reductions	Language provided that a completion visit should be performed with evidence of closed epiphyses.	Evidence of closed epiphyses would consider the subject to have completed the extension trial.
9.7 Drug Accountability	Deleted IWRS system as the only form of accountability	Study conduct has shown that paper documentation was necessary in some cases and as a back-up solution. All information will be available in IWRS, however, paper documents may be used as supporting or intermediate documentation.
10.2.1 Visit 1 and Day 1	Under "Medications and health status review", added "interval history since last visit of prior trial" and removed "disease states diagnosed since the initiation of the prior trial are considered medical history for this trial".	Medical history is inclusive of medical history collected from the prior trial and interval history collected since last visit of the prior trial.
10.2.2.5 GH Auto-Injector Data Read-Out	Updated timeframe for exchange of subject device	To align with actual timing of GH Auto-Injector implementation
10.2.3 Unscheduled Visits	Spelling correction made to "caregiver".	Administrative change.
12.1.1 Adverse Events – Definition	Removed the example "including abnormal laboratory findings" from the definition of an AE.	The protocol now clarifies that out-of-range laboratory findings may be AEs if they induce a new/worsening diagnosis, physical sign, symptom, or require therapy.
12.1.1 Adverse Events – Definition	Revised to: AEs may include: clinically significant treatment-emergent physical examination abnormalities; out-of-range lab or test result associated with a new/worsening diagnosis, clinical sign or symptom, or that require therapy.	Clarifies the AE criteria for findings from physical examinations, laboratory results, and worsening AEs.
12.1.1 Adverse Events – Definition	Added language to allow site-specific reporting preferences as it relates to mild/unrelated AEs.	While mild and unrelated AEs should not be recorded in this extension trial, this may be allowed to account for site-specific reporting preferences.
12.1.1 Adverse Events – Definition; 12.1.3	Out-of-range IGF-1, IGF-1 SDS, IGFBP3, IGFBP3 SDS—whether or not associated with a titration of the	IGF-1 and IGFBP3 are pharmacodynamic markers of TransCon hGH therapy and may be

Section(s)	Change	Rationale
Reporting Procedures for All Adverse Events	TransCon hGH dose—will not be considered an AEs unless they are associated with a diagnosis, clinical sign, or symptom, or require treatment.	used to guide an investigator's recommendation to titrate the TransCon hGH dose.
12.1.3 Reporting Procedures for All Adverse Events	Revised to: Out-of-range laboratory values or test results may constitute AEs if they induce a new/worsening diagnosis, clinical sign, or symptom, or require therapy.	Asymptomatic (and/or minimally) out-of-range laboratory or test results may not be adverse or untoward.
12.1.3 Reporting Procedures for All Adverse Events	Routine titration of chronic, concomitant medications are not considered AEs.	Children taking weight-based medications (e.g. levothyroxine) require periodic dose adjustments based on interval weight gain.
12.1.3 Reporting Procedures for All Adverse Events	Use a single, unifying diagnosis as the AE term.	A single, unifying term is more appropriate than a group of concurrent symptoms that describe one diagnosis.

SUMMARY OF CHANGES – FROM U.S. AMENDMENT 1 (14MAR2019) INCORPORATED INTO GLOBAL AMENDMENT 1

RATIONALE

The original protocol indicates that the GH Auto-Injector and dual chamber cartridges (DCC) will be introduced into the study in certain countries when ready. Due to labeling practicalities, the GH Auto-Injector will be introduced into sites in the US only. This US-specific amendment contains the procedural changes necessary to enable this introduction. In addition to the GH Auto-Injector, this US-specific amendment also includes: a new device usage questionnaire to be collected at specific timepoints; a new dosing weight bracket to account for the DCC strengths; the option for US investigators to keep subjects whose dose may have changed due to increased weight on the same dose pending IGF-1 results, and removing the requirement to re-confirm IGF-1 SDS laboratory results outside the specified range before adjusting dose.

Section(s)	Change	Rationale
Signature Page	Added 'As Amended for US only, 04 March 2019'	Administrative change
Signature page	Updated with United States Medical Monitor's name	Updated to reflect medical monitor team in United States (for which this amendment is specific)
Global	Updated name to "GH Auto-Injector" from "auto-injector"	Administrative Change
Global	Specified that GH Auto-Injector will be used in the United States (rather than 'select' countries).	GH Auto-Injector is only being rolled-out to subjects in the United States.
Global	Renamed from 'study drug' to 'investigational product'	To reflect combination GH Auto-Injector device and TransCon hGH study drug
Summary of Changes	Added Rationale and Summary of Changes table	To explain the reasons for a US-Specific Amendment and associated changes
Synopsis – Objectives; Synopsis – Criteria Evaluation; 6.2 Secondary Objectives; 14.1.4 Other endpoints	Added a secondary objective	To account for the addition of the Device Usability Questionnaire in order to assess comfort, ease-of-use, and safety, in subjects using the GH Auto-Injector
Synopsis - Trial Design	Deleted 'initially'	Administrative change. Reflects current status.
Synopsis – Trial Design – Patient-Reported Outcome Questionnaires after Visit 1	Updated timepoints of the questionnaires	Updated the new process and clarified the timepoints of the required questionnaires.

Section(s)	Change	Rationale
Synopsis – Trial Design – Patient-Reported Outcome Questionnaires after Visit 1; Section 4. List of Abbreviations 10.2.2.2; 18.2 Schedule of Events; 11.7.4 Device Usability Questionnaire; Appendix 6 – Device Usability Questionnaire	Added "Device Usability Questionnaire"	To investigate use of the GH Auto-Injector (comfort, ease-of-use, and safety) and clarify timepoints.
Synopsis – Trial Design - Ongoing Visits – TransCon hGH dose; Stopping/Dose reductions; and 9.6.1 Dose Adjustment Parameters	Updated language to include DCC presentation, weight-based dose, and tables.	Clarification of weight-based dose, dose volume, absolute milligrams of drug.
Synopsis – Trial Design – Dose Adjustment Parameters; 9.6.1 Dose Adjustment Parameters; 9.6.2 Stopping/Dose Reductions; 9.6.2 Stopping/Dose Reductions	Repeat IGF-1 testing no longer required when visit IGF-1 SDS is < 0 or > 2.0 and clinically significant	To align more closely with real-world practice where dose titrations may be recommended after a single (rather than duplicate) IGF-1 test. In the trial to date, the repeat (unscheduled) IGF-1 SDS test results have generally not provided additional meaningful information beyond the initial IGF-1 test done routinely with the scheduled study visits. Furthermore, for some subjects the repeat IGF-1 blood test have represented a time burden associated with minimal benefit. Investigators will continue to have the *option* to repeat IGF-1 tests at any time during the trial.
Synopsis – Trial Design – Dose Adjustment Parameters	For subjects previously dose-titrated, added provision to allow the maintenance of the current TransCon hGH dose until IGF-1 SDS result is available	To align more closely with real-world practice.
Global	Clarify that DCCs may be (rather than will be) supplied in the United States	Some children in the US may still use vials if they are in a weight bracket not yet served by a current DCC

Section(s)	Change	Rationale
Synopsis - Treatment regimens	Added the word "approximately" in front of 0.24 mg hGH/kg/week	This is the nominal dose; and children are in a bracket
Synopsis - Treatment regimens	Specified that weight-based dose volume or DCC adjustments will follow Table 1 and Table 2, respectively	Table 2 will be used for subjects using the GH Auto-Injector and accompanying DCCs
Planned number of subjects; Trial population; 8. Subject Population	Changed from 400 to 300	To clarify the known projected enrollment
Synopsis – Criteria for Evaluation	Deleted 'with confirmation' from Safety Endpoints on Incidence of IGF-1 SDS>2.0, 3.0	The requirement for a repeat IGF-1 test (following an initial IGF-1 SDS < 0 or > 2.0 and clinically significant) has been eliminated.
5.3 Clinical Experience	Added paragraph about CT-102 trial	Documents bioequivalence of TransCon hGH delivered by two modalities: needle/syringe versus GH Auto-Injector
5.5 Summary of Risks and Benefits	Added language	To indicate comparable safety profile
9.3 Treatment Administered Table 2	Updated weight brackets	Updates to the boundaries of the highest weight brackets were necessary to maintain the approximate weight-based dose of 0.24 mg/kg/week when administering two (duplicate) DCCs per week to achieve an absolute total TransCon hGH dose > 13.3 mg/week.
9.3 Treatment Administered	Added language	To clarify differences in Table 1 and Table 2
9.4 Dispensing and Storage	Grammatical Change	Administrative Change
10.2.2.4 Patient Reported Outcome Completion (6th week after transition to the GH Auto-Injector	Moved this section from heading 10.2.2.2	To clarify the timing of DUQ administration
10.2.2.4 GH Auto-Injector Read-out	GH Auto-Injector Data Read-Out language added	To clarify what data may be collected from the GH Auto-Injector Device after 6 months of use

Section(s)	Change	Rationale
11.7 Patient Reported Outcome Measures	Updated language	Included specific PROs
12.2.1.1 SAE Definition	Updated language regarding important medical event	To clarify an important medical event as a part of the SAE definition and reporting criteria.

2. SYNOPSIS

PRODUCT NAME/NUMBER	TransCon hGH (ACP-011) Henceforth referred to as TransCon hGH or Investigational product
PROTOCOL NUMBER	TransCon hGH CT-301EXT
IND NUMBER	126053
EUDRACT NUMBER:	2017-003410-20
DEVELOPMENT PHASE	3
PROTOCOL TITLE	**enliGHten**: A Multic**en**ter, Phase 3, Long-term, Open-**l**abel Tr**i**al Investigating Safety and Efficacy of TransCon h**GH** Admini**s**tered Once-Weekly in Children with Growth Hormone D**e**ficiency (GHD) Who Have Completed a Prior TransCo**n** hGH Clinical Trial
INDICATION	Growth failure in children due to GHD
OBJECTIVES	**Primary:** To assess long-term safety of weekly TransCon hGH in children with GHD previously treated in a phase 3 TransCon hGH trial **Secondary:** • 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 • To assess comfort, ease-of-use, and safety in subjects using the GH Auto-Injector

TRIAL DESIGN	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. 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. The final visit of the prior trial should serve as the first visit (Visit 1) of the extension trial and data collected in the prior trial 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. Following informed consent, subjects will enter the extension trial and begin or continue TransCon hGH (depending on prior trial medication). TransCon hGH will be provided in single-use glass vials and administered with syringe and needle. Once available, TransCon hGH will be supplied in dual-chamber cartridges for administration using a GH Auto-Injector in the US only. **Visit 1:** Visit 1 for the extension trial should be on the same day as the final visit of the prior trial and may occur over several days. 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. During Visit 1 (and again on Day 1, if on a subsequent day), the investigator will review all baseline data collected to determine the subject's eligibility. Data collected up through the final visit of the prior trial may be used as baseline data for the extension trial. The following will be performed for Visit 1, unless it was performed for the final visit of the prior trial: • Medications and health status review (includes review of subject diary from prior trial, interval history since last visit of prior trial, ongoing AEs from the prior trial, and current therapies) • Vital sign measurements • Height and weight measurements • Physical examination – Local tolerability assessment • Pubertal status assessment (Tanner stage, including onset of menses) (*Tanner, 1976*) • Blood collection for the following laboratory assessments*: – Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3)

	– Antibodies against human growth hormone (hGH) and polyethylene glycol (PEG) o These analyses may only be conducted after enrollment and are not required for eligibility verification. These data will be used to support evaluation of post-dose antibody detection o If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers – mPEG – Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c) – Chemistry – Hematology – Lipid panel – **Females of child-bearing potential only**: Human Chorionic Gonadotropin (hCG) *Fasting not required. Banked blood samples may be used for additional characterization of anti-drug antibody responses. • Bone age x-ray – A bone age x-ray performed within approximately the past 52 weeks may be accepsection – with appropriate documentation. However, if the last recorded bone age was > 12.0 years, and the bone age x-ray 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. • Investigational product preparation/administration training/re-training • Subject diary completion review, as needed • Patient-reported outcome questionnaires – Convenience and Overall Satisfaction domains (C&OS) of the Treatment and Satisfaction Questionnaire for Medication (TSQM-9) o For the parent (C&OS-P) – Child Sheehan Disability Scale o For the parent (CSDS-P) o **For the child ≥ 9 years old only**: (CSDS-C) • Investigational product dose adjustment (from prior trial), as needed • Investigational product and subject diary dispensing In the unusual event there is a gap of 4 to approximately 6 weeks between the assessments done for Visit 1 and Day 1 (first dose), then all of the above should be repeated, except physical exam, blood collection, and bone age x-ray.

	Patient-reported Outcome Questionnaires after Visit 1: **For subjects who were treated with Genotropin in the prior TransCon hGH CT-301 trial**: Between Visit 1 and Visit 2, immediately prior to the 6th investigational product administration, and at Visit 2, the following questionnaires will be completed by subjects/parents/legal guardians/caregivers, as applicable. • Preference Questionnaire – Parent (PQ-P) • Preference Questionnaire – Child (PQ-C): **only for subjects ≥ 9 years old (at Visit 1)** • C&OS-P • CSDS-P • CSDS-C: **only for subjects ≥ 9 years old (at Visit 1)** Note: The questionnaires to be taken before the 6th investigational product administration will be in the subject diary. At Visit 2, the questionnaires are to be completed at the clinic visit, prior to review of the subject diary, adverse events (AEs), and concomitant medications. **For all subjects who have transitioned to the GH Auto-Injector:** Immediately prior to the 6th investigational product administration using the GH Auto-Injector, and at the next scheduled clinic visit (approximately 13 weeks after transition to the GH Auto-Injector), the following patient-reported outcome questionnaires will be completed by subjects/parents/legal guardians/caregiver, as applicable. • C&OS-P • CSDS-P • CSDS-C **only for subjects ≥ 9 years old at transition to GH Auto-Injector** On the day of the 6th investigational product administration using the GH Auto-Injector (either immediately before or after the injection), and at the next scheduled clinic visit (approximately 13 weeks after transition to the GH Auto-Injector), the following questionnaire will be completed by the individual primarily preparing and performing the injection with the GH Auto-Injector. • Device Usability Questionnaire (DUQ) Note: The subject diary will include the questionnaires to be taken immediately before the 6th investigational product administration, and on the day of the 6th investigational product administration using the GH Auto-Injector. At the next scheduled visit (approximately 13 weeks after transition to the GH Auto-Injector), the questionnaires will be completed at the clinic visit, prior to review of the subject diary, AEs, and concomitant medications. **Ongoing Visits:** Visit 2 and subsequent scheduled visits every 13 weeks (±2 weeks) will be performed 5 days (±1 day) post-dose. The following will be performed:

	• Concomitant medications review • Includes review of subject diary • AE review • Includes review of subject diary • Investigational product compliance calculation • Includes review of subject diary and returned investigational product • Vital sign measurements • Height and weight measurements • Physical examination • Pubertal status assessment (Tanner stage) • Blood collection for the following laboratory assessments*: – IGF-1 and IGFBP-3 – Antibodies against hGH and PEG o If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers – **Females of child-bearing potential only:** hCG *Banked blood samples may be used for additional characterization of anti-drug antibody responses. • Investigational product dose adjustment, as needed • Investigational product and subject diary dispensing In addition to the assessments performed every 13 weeks, the following assessments will be performed every 26 weeks: • Blood collection for the following laboratory assessments*: – mPEG – Hormone/glycemic status – (TSH, FT4, FT3, morning cortisol, and HbA1c) – Chemistry – Hematology – Lipid panel *Fasting not required. The following assessment will be performed annually, and/or anytime if clinically indicated: • Bone age x-ray All attempts should be made to adhere to the planned visit schedule. Eligible subjects will receive weekly doses of TransCon hGH administered by the subject/parent/legal guardian/caregiver. **TransCon hGH Dose:**

	The starting dose of TransCon hGH (mg hGH/kg/week) in the extension trial will be the last dose in the prior trial, with volume or DCC presentation adjusted based on weight, if needed, at Visit 1. The weight-based dose will generally remain 0.24 mg hGH/kg/week, which is consistent with the pivotal phase 3 TransCon hGH CT-301 (heiGHt) trial. However, as the subject grows, the absolute dose (ie total milligrams of drug per week) will typically be increased accordingly, based on the TransCon hGH Bracketed Weight Table (eg From 0.35 mL to 0.41 mL, Table 1), or TransCon Dosing Table for the GH Auto-Injector and DCC Product (eg. From 7.6 mg to 9.1 mg, Table 2), as applicable. **Dose Adjustment Parameters:** The following parameters may be used by the investigator to adjust the TransCon hGH dose without Medical Expert pre-approval throughout the trial. • At each visit, the TransCon hGH absolute dose may be adjusted by the investigator based on the TransCon hGH Bracketed Weight Table (Table 1), or TransCon Dosing Table for the GH Auto-Injector and DCC Product (Table 2), as applicable. • Additionally, the goal for IGF-1 should be between 0 and + 2.0 SDS (unless a different target is identified in consultation with the Medical Expert). Thus, if the IGF-1 SDS measured at a visit is < 0 SDS, the dose may be increased by approximately 20% to the next higher weight bracket by the investigator. (Although the prior *requirement* has been eliminated for a second ["confirmatory"] IGF-1 SDS test prior to dose titration, a second IGF-1 SDS test collected 5 days post-dose (±1 day) remains optional at the investigator's discretion.) • Additionally, if HV is considered to be suboptimal in an adherent subject, the dose of TransCon hGH may be increased after consultation with the Medical Expert. **Stopping/Dose Reductions:** The investigator or Medical Expert may stop or reduce the dose of investigational product at any time during the trial (please notify the Medical Expert as soon as possible). For example, consideration for stopping or reducing the dose may occur in the presence of the following symptoms and laboratory abnormalities: • Severe GH-related AEs at any time during the trial • Pregnancy: A subject must be discontinued from the trial if pregnant • IGF-1 > +2.0 SDS: The TransCon hGH dose may be decreased by approximately 20% to the next lower weight bracket, unless a different target SDS is identified in consultation with the Medical Expert. See Section 9.3 for details. (Although the prior *requirement* has been eliminated for a second ["confirmatory"] IGF-1 SDS test prior to dose titration, a second IGF-1 SDS test collected 5 days post-dose (±1 day) remains optional at the investigator's discretion.)

	Any re-establishment of the prior dose due to a subsequent sub-optimal IGF-1 response should receive prior approval by the Medical Expert. In those subjects who have historically been dose titrated to a bracket different than expected for weight, the investigator may—at study visits—recommend maintenance of the current absolute dose until the visit's IGF-1 SDS values are available. Once the IGF-1 SDS values are available, the investigator may then select the most appropriate dose volume or DCC presentation. • Evidence of hypersensitivity to TransCon hGH • Evidence of clinically significant pre-diabetes or diabetes (HbA1c > 6.2% and an absolute increase of 0.5% from the prior visit HbA1c): confirmation of HbA1c level is required. Once confirmed, TransCon hGH dose may be decreased to the next lower weight bracket. If appropriate follow-up monitoring shows progressively worsening glucose intolerance, additional TransCon hGH dose adjustments may be appropriate. • Clinical evidence of benign intracranial hypertension (BIH) based on history and physical exam, including visual changes, headaches, nausea, vomiting, and/or papilledema on fundoscopy: TransCon hGH treatment should be discontinued while BIH is clinically managed **Reinstitution of TransCon hGH treatment, preferably at a lower dose, should receive prior approval by the Medical Expert.** • *De novo* diagnosis of a slipped capital femoral epiphysis should result in a dose reduction or temporary discontinuation • Identification of anti-hGH antibodies that are determined to be neutralizing If a subject has evidence of closed epiphyses (bone age > 14.0 years for females or > 16.0 years for males), the subject will have completed the study and will discontinue study treatment. If treatment is permanently discontinued for any reason, trial participation will be discontinued and a Completion Visit/Early Termination Visit (procedures indicated for Visit 5 in the Schedule of Events table, as applicable) will be performed. Completion of the trial is described in Section 10.1. Early termination is when a subject's trial participation discontinues prematurely. The Medical Expert will review all safety information on an ongoing basis. The safety data will also be periodically reviewed by an Independent Safety Committee (ISC).
PLANNED NUMBER OF SUBJECTS	Up to approximately 300
TRIAL POPULATION	Up to approximately 300 (male and female) children with GHD, completing a prior phase 3 TransCon hGH trial, still taking investigational product, who have no evidence of closed epiphyses, and meet all other entry criteria, will be invited to participate in the extension trial.

TRIAL ENTRY CRITERIA	**Inclusion Criteria** 1. Children who have completed a prior phase 3 TransCon hGH trial 2. Children who have not permanently discontinued investigational product in the prior trial 3. Written, signed, informed consent of the parent or legal guardian of the subject and written assent of the subject as required by the institutional review board/human research ethics committee/independent ethics committee (IRB/HREC/IEC) **Exclusion Criteria** 1. Poorly-controlled diabetes mellitus (HbA1c ≥ 8.0%) or diabetic complications 2. Evidence of closed epiphyses, defined as bone age > 14.0 years for females or > 16.0 years for males 3. Major medical conditions unless approved by Medical Expert 4. Known hypersensitivity to the components of the trial medication 5. Likely to be non-compliant with respect to trial conduct (in regard to the subject and/or the parent/legal guardian/caregiver) 6. Pregnancy 7. Any other reason that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule
INVESTIGATIONAL PRODUCT	Name: TransCon hGH (ACP-011) TransCon hGH is a sustained-release inactive prodrug consisting of a parent drug, unmodified 22 kDa hGH equivalent to endogenous GH, transiently bound to an inert carrier, methoxypolyethylene glycol (mPEG), via a proprietary low-molecular-weight TransCon linker. The inert mPEG acts as a carrier, extending hGH circulation time in the body through a shielding effect that minimizes GH receptor binding and renal excretion, thereby largely inactivating hGH until its release. Over a one-week period, TransCon hGH releases fully-active unmodified hGH via auto-hydrolysis of the TransCon linker in a controlled manner based on physiologic pH and temperature. As such, the TransCon technology is designed to maintain the same mode of action as daily administered hGH, with the same weekly exposure as 7 daily injections of hGH, by allowing the sustained release of unmodified recombinant hGH. TransCon hGH will be provided in glass vials requiring reconstitution with 1 mL sterile water for injection (sWFI) and administered by subcutaneous (SC) injection via syringe and needle. TransCon hGH will be supplied in 1 of the 2 following vial presentations that, after reconstitution, will result in 2 solutions: • 12.1 mg hGH/vial (11.0 mg hGH/mL after reconstitution) • 24.2 mg hGH/vial (22.0 mg hGH/mL after reconstitution)

	Once available, TransCon hGH may be supplied in dual-chamber cartridges (DCCs) for administration using a GH Auto-Injector in the US only.
REFERENCE PRODUCT(S)	None
TREATMENT REGIMENS	TransCon hGH should be administered by the subject (or parent/legal guardian/caregiver) as a once weekly SC injection of approximately 0.24 mg hGH/kg/week. The absolute total dose (volume or DCC presentation) of TransCon hGH will be adjusted according to the subject's weight using the TransCon hGH Bracketed Weight Table, or TransCon Dosing Table for the GH Auto-Injector and DCC Product, respectively. TransCon hGH dose may also be adjusted according to the level of IGF-1 SDS measured at each visit.
PLANNED TRIAL SITES	Approximately 100 sites in approximately 20 countries in Europe, the Middle East, North Africa, North America, Australia, and New Zealand that enrolled subjects in the prior phase 3 TransCon hGH trials may participate.
CRITERIA FOR EVALUATION	**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 antibodies against TransCon hGH • Incidence of IGF-1 SDS > 2.0, > 3.0 • Parameters of HbA1c and lipids • Hormone levels, including thyroid status and morning cortisol • All other hematology and chemistry parameters • Vital sign measurements **Efficacy Endpoints** The efficacy endpoints of long-term 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 **Pharmacodynamic Endpoint** • Serum IGF-1 SDS at 5 days ±1-day post-dose **Other Endpoints** • Preference for weekly TransCon hGH or daily Genotropin treatment

	• Satisfaction with weekly TransCon hGH • In subjects using the GH Auto-Injector: comfort, ease-of-use, and safety
STATISTICAL METHODS	Details of applicable statistical methods will be provided in a Statistical Analysis Plan. Baseline and demographic data will be summarized to characterize the study population. Special subgroups of interest, such as prior exposure to growth hormone and age categories will be determined, and corresponding subgroup analysis for safety and efficacy will be performed as appropriate. Prior and concomitant medication, as well as exposure to investigational product, will be summarized. Data from all clinical assessments will be summarized using descriptive statistics. Numerical variables will be summarized by mean, median, standard deviation, minimum, and maximum, while categorical variables will be summarized by counts and proportions.
SAMPLE SIZE DETERMINATION	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 investigational product, and meet eligibility criteria will be invited to participate. The sample size is determined by the prior trial sizes.
TRIAL AND TREATMENT DURATION	The trial is expected to be ongoing 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.

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4. 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
AUC	area under the curve
BIH	benign intracranial hypertension
C&OS	Convenience & Overall Satisfaction domains of the abbreviated Treatment Satisfaction Questionnaire for Medication v9
C&OS-P	Convenience & Overall Satisfaction domains of the abbreviated Treatment Satisfaction Questionnaire for Medication v9 – Parent
CFR	Code of Federal Regulations
cm	centimeter
C_{max}	maximum observed concentration
CSDS	Child Sheehan Disability Scale
CSDS-C	Child Sheehan Disability Scale – Child
CSDS-P	Child Sheehan Disability Scale – Parent
CRO	Contract Research Organization
CV	completion visit
d	day
DCC	dual chamber cartridge
DMP	data management plan
DUQ	Device Usability Questionnaire
eCRF	electronic case report form
ETV	early termination visit
FDA	Food and Drug Administration
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone-releasing hormone
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
HbA1c	hemoglobin A1c
hGH	human growth hormone
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
IM	investigator meeting
IRB	Institutional Review Board
ISC	Independent Safety Committee
IWRS	interactive web response system
kDa	kilodalton
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mPEG	methoxypolyethylene glycol
MPH	mid-parental height
ng	nanogram
PD	pharmacodynamics
PEG	polyethylene glycol
pH	power of hydrogen
PK	pharmacokinetics
PQ	Preference Questionnaire
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
SIV	site initiation visit
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
sWFI	sterile water for injection
TSQM	Treatment Satisfaction Questionnaire for Medication
TSQM-9	Abbreviated Treatment Satisfaction Questionnaire for Medication v9
TSH	thyroid stimulating hormone
WHO	World Health Organization

5. INTRODUCTION

5.1. BACKGROUND AND RATIONALE

hGH is a product of endocrine secretion of the pituitary gland, which targets tissues to promote growth in children and control metabolism in children and adults. It is secreted by somatotroph cells located in the lateral wings of the anterior pituitary gland. The most important and obvious function of hGH is growth promotion of children. Through its IGF-1 mediated effects (as well as less obvious direct effects), it stimulates cartilage and bone growth by enhancing the activity of chondroblasts and osteoblasts and promoting collagen synthesis. In addition, hGH has important metabolic functions: it exerts potent anti-insulin effects resulting in decreased glucose utilization (and resultant increased plasma glucose levels) and increased lipolysis (in contrast to the opposing actions of IGF-1 to lower plasma glucose and increase lipogenesis); these functions underlie its continued secretion into adulthood. New research continues to reveal other potential roles of hGH, including regulation of cardiac and immune function, mental agility and aging.

GHD is the result of impaired production or secretion of hGH, which can appear at any time point in life and is due to various known and unknown factors. The etiology of childhood GHD is most commonly of hypothalamic origin with impaired GHRH secretion, the most common diagnosis being isolated idiopathic GHD. GHD is a well-recognized clinical entity in adults as well. It causes abnormalities in body composition, lipid metabolism, and physical and psychosocial function, all of which improve with hGH replacement therapy.

At the present time, however, there are no commercially available sustained-release or long-acting hGH preparations. Currently hGH is available only as daily injection formulations, thus causing a significant burden and interruption of normal daily life to children and their parents, as well as compliance issues. Decreased compliance with daily hGH therapy is known to result in sub-optimal height outcomes (*Cutfield, 2011*). If a weekly long-acting hGH product were to have similar efficacy, safety, and tolerability while maintaining hGH exposure in the optimal therapeutic range as existing daily therapies, preference and satisfaction for the weekly regimen would likely exist, with improved compliance to follow.

TransCon hGH is a weekly administered hGH prodrug that liberates unmodified hGH as the active pharmaceutical ingredient through controlled auto-hydrolysis resulting in sustained release of hGH. TransCon hGH consists of hGH that is transiently conjugated to mPEG via a (TransCon) linker.

The linker that forms the bridge between the protein and mPEG moieties is stable at pH 5.0. However, after introduction into a physiological pH and temperature (ie, after injection of TransCon hGH), autohydrolysis of the linker occurs in a controlled manner that follows first-order kinetics, whereby unmodified, fully-active hGH is released. As the released hGH is completely unmodified, it is expected to have the same mode of action and tissue distribution as endogenous hGH. This is important for optimal efficacy, as a portion of hGH activity is mediated by local hGH effects in target tissue, including the growth plate and adipocytes. The release of hGH also liberates N1, -N1, -N3-trimethyl-1,3-propane-diamine, a small molecular weight compound associated with the linker. The remainder of the inactive mPEG-linker component of TransCon hGH is cleared from the body through natural mechanisms for other high molecular weight molecules.

The exposure-toxicity relationship of PEG in animals and humans has been well investigated and metabolism/excretion of PEG is well understood, indicating that the PEG associated with a biological molecule represents an acceptable benefit-risk ratio to humans (*Webster, 2007)*. Detailed information is provided in the Investigator's Brochure.

The Sponsor initiated the TransCon hGH development program with TransCon hGH (ACP-001), in which the carrier was 80 kDa mPEG, and for which four clinical trials were conducted: two phase 1 trials in healthy adults, one phase 2 trial in adult GHD, and one 6-month phase 2 trial in pediatric GHD. Upon completion of the TransCon hGH (ACP-001) phase 2 clinical program, the Sponsor modified the TransCon hGH product by replacing the 80 kDa mPEG with a 40 kDa mPEG, with the understanding that this difference in mPEG would not significantly affect the autohydrolytic release of hGH, the prolonged half-life, or the inactive nature of the parent TransCon hGH product. The linker component and hGH remained the same between TransCon hGH (ACP-001) and TransCon hGH (ACP-011); the only change was the reduction in mPEG carrier size. This change resulted in TransCon hGH (ACP-011), a drug product that is functionally equivalent in PK, PD, and safety/tolerability to its predecessor, but with lower viscosity and higher product concentration that enables smaller injection volumes and the use of a small-gauge needle. Additionally, the PEG exposure was reduced by ≥ 50%.

5.2. RELEVANT FINDINGS FROM NONCLINICAL STUDIES

Nonclinical pharmacology and toxicology studies have been conducted to support the clinical development program involving weekly SC administration of TransCon hGH (ACP-011) in children with growth hormone deficiency. All pivotal nonclinical safety studies either have been or are being conducted in compliance with Good Laboratory Practices (GLP) and the program as a whole follows recommendations provided by ICH guidance and product specific guidance from health authorities. The nonclinical program has assessed both the parent prodrug and the products of autohydrolysis (hGH, the remainder mPEG-linker [measured as mPEG40], and TMPD) as well as IGF-1, the PD biomarker for hGH.

Please refer to the current Investigator's Brochure for detailed information pertaining to the nonclinical program supporting conduct of this clinical trial.

5.3. CLINICAL EXPERIENCE

A phase 1 clinical trial of TransCon hGH (ACP-001) in healthy male volunteers has been conducted as a randomized, double-blind, dose-escalation trial versus placebo and daily hGH (Omnitrope) investigating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) response in 44 healthy male subjects. No negative effects of the test drug were detected when compared to placebo and the active comparator (Omnitrope). The test product was well tolerated at up to 0.24 mg hGH/kg when injected once subcutaneously to 28 healthy male subjects.

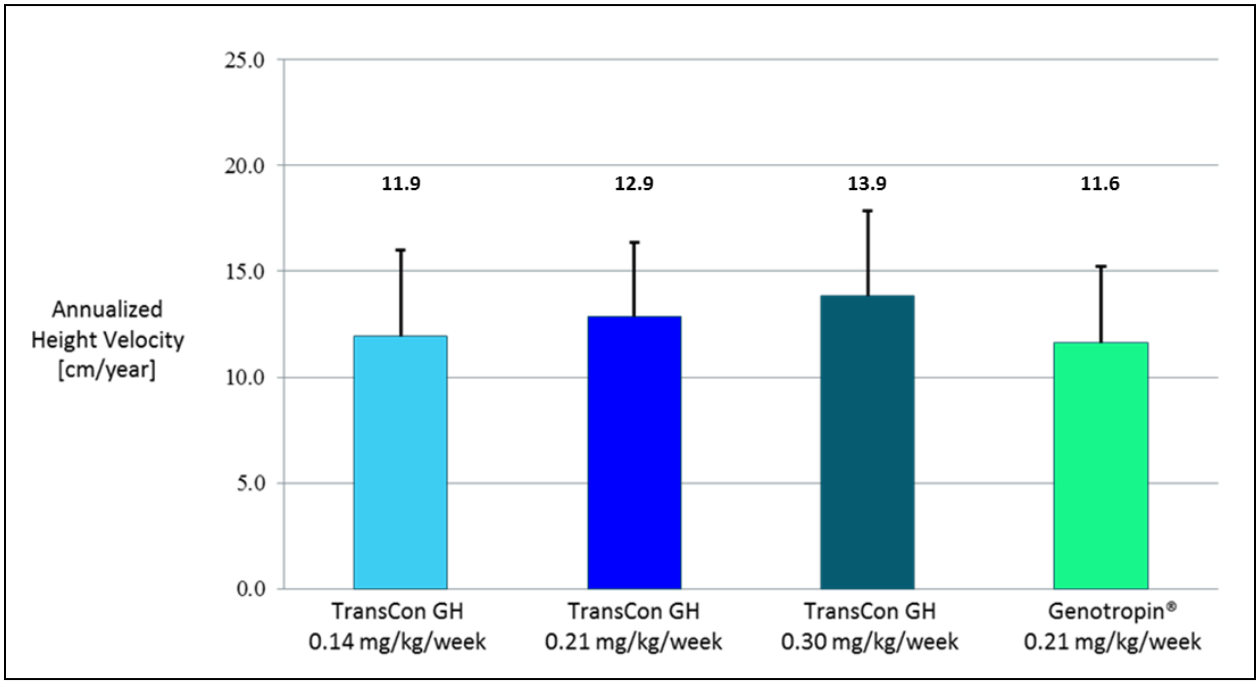
A second phase 1 single-dose trial investigated the safety and tolerability of TransCon hGH (ACP-001) at 2 different dose-levels, 0.30 mg hGH/kg and 0.36 mg hGH/kg, respectively, in 24 male and female healthy subjects. ACP-001 was well tolerated with no safety concerns.

A phase 2 clinical trial in adult subjects with GHD was a randomized, open-label, active-controlled trial of 3 dose levels of TransCon hGH (ACP-001) (0.02, 0.04 and 0.08 mg

hGH/kg/week) compared to daily hGH (Omnitrope 0.04 mg hGH/kg/week divided into 7 equal daily doses) over 4 weeks. A total of 37 subjects were randomized. ACP-001 was well tolerated with no safety concerns. Detailed information is given in the Investigator's Brochure.

A phase 2 clinical trial in pediatric subjects with GHD has been conducted as a multicenter, randomized, open-label, active-controlled, parallel-group trial of 3 doses of TransCon hGH (ACP-001; 0.14, 0.21 and 0.30 mg hGH/kg/week) compared to daily hGH (Genotropin 0.21 mg hGH/kg/week divided into 7 equal daily doses) over 26 weeks. 55 subjects were randomized, of whom 53 received investigational product (12 subjects in the 0.14 mg hGH/kg/week, 14 subjects in the 0.21 mg hGH/kg/week and 14 subjects in the 0.30 mg hGH/kg/week TransCon hGH cohorts and 13 subjects in the 0.21 mg hGH/kg/week Genotropin cohort). Mean annualized HV among the 3 dose levels administered weekly ranged from 11.9 cm for the 0.14 mg/kg/week dose to 12.9 cm for the 0.21 mg hGH/kg/week dose to 13.9 cm for the 0.30 mg hGH/kg/week dose, which were all comparable to 11.6 cm for the active comparator, daily injections of Genotropin at a 0.21 mg hGH/kg/week dose (Figure 1).

Figure 1: Annualized Height Velocity (Mean +SD) in 53 Subjects After 26 Weeks of TransCon hGH vs. Genotropin Treatment



cm = centimeter; kg = kilogram; mg = milligram

No reports of drug-related serious or unexpected AEs were observed. AEs were generally mild and observed at the same level and nature compared between the 3 TransCon hGH cohorts and the Genotropin cohort. Injection site reactions were generally mild and transient and were observed at a rate that was similar to the daily hGH control arm. There were no observations of injection site nodule formation or lipoatrophy. Low immunogenicity (a single subject with a low titer) was consistent with published data for daily hGH. No neutralizing antibodies were

detected. Maximum and average hGH blood concentration were comparable between equivalent weekly doses of TransCon hGH and daily hGH.

The clinical safety profile of ACP-001 was overall comparable to daily hGH. Headache and fatigue were the most frequent drug-related AEs during the phase 2 adult growth hormone deficiency (AGHD) trial and were reported in all treatment groups. No AEs were judged to be definitely drug-related.

TransCon hGH (ACP-011) was found to be bioequivalent (with comparable PK, PD, safety and tolerability) in a Phase 1 single center, randomized, open-label trial to evaluate comparability of PK and PD parameters of ACP-001 and ACP-011.

In a trial completed in 2018, TransCon hGH (ACP-011) administered by two modalities (syringe/needle versus GH Auto-Injector) was confirmed to be bioequivalent (with comparable PK, PD, safety and tolerability) in a phase 1, randomized, open-label, single-dose, crossover study in healthy adult males.

A global phase 3 trial, called the TransCon hGH CT-301 (heiGHt) trial in children with GHD, was initiated in September 2016 and is ongoing. The heiGHt trial is a randomized, open-label, active-controlled phase 3 registration trial that is designed to enroll approximately 150 children with GHD who have not previously been treated. The inclusion criteria require subjects to be pre-pubertal children with bone age that is at least six months less than chronological age, impaired height that is either greater than or equal to two standard deviations (SD) below the population mean or at least 1.5 SD below mid-parental height (MPH), GHD diagnosis confirmed by two different GH stimulation tests, and IGF-1 that is greater than or equal to one SD below the population mean. Subjects will receive either once-weekly TransCon hGH (0.24 mg hGH/kg/week) or daily injections of Genotropin at 34 µg/kg/day (0.24 mg hGH/kg/week) with a 2:1 randomization in a non-inferiority design. The primary endpoint of the trial is height velocity after 52 weeks of treatment. Other key endpoints include an annualized HV at earlier time points, change in height standard deviation scores over 52 weeks, normalization of IGF-1 SDS, change in serum IGF-1 and IGFBP-3 levels, and change in IGF-1 and IGFBP-3 SDS.

A second phase 3 trial called the TransCon hGH CT-302 (fliGHt) trial in children with GHD was initiated in 2017. Approximately 150 subjects (ages 3 to 17 years old) enrolled in fliGHt will have been treated previously with commercial hGH (from 13 weeks to 130 weeks) and will switch to TransCon hGH. In addition, children with GHD who are 6 months to < 3 years old may or may not have been previously treated with commercial hGH. The treatment period in fliGHt is 6 months. The primary outcome is safety and tolerability.

5.4. TRIAL RATIONALE

In comparison to the heiGHt and fliGHt trials, the primary objective of this extension trial is to assess the long-term safety of weekly TransCon hGH (ACP-011) in children with GHD previously treated in a TransCon hGH trial. Additionally, when the GH Auto-Injector, a unique device developed specifically for the administration of TransCon hGH, becomes available, subjects will be switched from the administration of TransCon hGH by syringe and needle to the GH Auto-Injector in the US only.

Preference and satisfaction for dosing with TransCon hGH or Genotropin will also be evaluated.

5.5. SUMMARY OF POTENTIAL RISKS AND BENEFITS

TransCon hGH (ACP-011) is an investigational medicinal hGH prodrug product with a proposed once-weekly dosing regimen designed to overcome the inconvenience and suboptimal compliance of daily hGH injections. The safety and efficacy profile is anticipated to be comparable to currently approved daily hGH products, while maintaining exposure (C_{max} and AUC) in the optimal therapeutic range. Moreover, the biodistribution is designed to be the same as with established daily hGH products. Obviating the need for daily injections should increase compliance and therefore long-term efficacy, which would be of great benefit to pediatric patients with GHD *(European Union, 2008*).

TransCon hGH administered by the GH Auto-Injector is expected to have a comparable safety profile to TransCon hGH administered by syringe and needle as well as to daily hGH formulations.

6. OBJECTIVES

6.1. PRIMARY OBJECTIVE

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

6.2. SECONDARY OBJECTIVES

- To assess annualized HV with long-term dosing 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 with long-term dosing of weekly TransCon hGH treatment
- To evaluate the 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
- In subjects using the GH Auto-Injector: to assess comfort, ease-of-use, and safety

7. TRIAL DESIGN

7.1. OVERALL TRIAL DESIGN AND PLAN

7.1.1. Trial Design

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. 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. The final visit of the prior trial should serve as the first visit of the

extension trial and data collected in the prior trial will serve as baseline data for 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 GH Auto-Injector in the US only.

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.

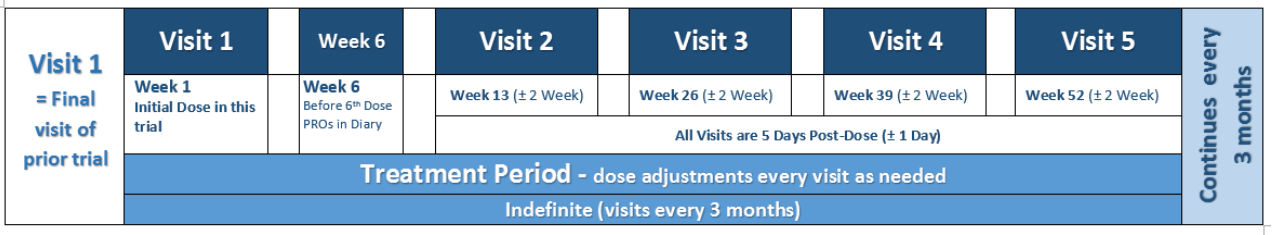
The trial consists of:

1. Visit 1 – the final visit of the prior trial should be the first visit of this extension trial, but a period up to approximately 6 weeks between the final visit of the prior trial and the first dose in the extension trial is acceptable
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.

The overall trial design is shown in Figure 2.

Figure 2 Overall Trial Design



7.1.2. Measures Taken to Minimize Bias

All subjects' visits should be performed at approximately the same time of day. Also, assessments should be performed in a similar fashion at each visit, using a calibrated

wall-mounted stadiometer. Subjects' height in particular will preferably be measured by the same auxologist and either with the subject always barefoot or in thin foot covers.

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

- Investigators will be trained about the importance of subject retention
- Investigators will be instructed to encourage subjects to complete all trial visits, until they complete the trial
- The Informed Consent Form (ICF) and Assent Form will include a statement educating subjects and parents/legal guardians/caregivers about the scientific importance of their data
- 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
- Visit windows allow flexibility for clinic attendance (see Section 10.2).
- Every effort will be made to contact subjects/parents/legal guardians/caregivers or other family members to maintain contact with the clinic

7.2. TRIAL SITES

The trial will be conducted at approximately 100 sites. All centers will be specialized treatment centers in the management of pediatric GHD.

7.3. TERMINATION RULES

7.3.1. Early Termination of Subjects

Valid reasons for which a subject's participation in the clinical trial may be discontinued include the following:

- Withdrawal of consent by the subject or parent/legal guardian
- Subject is lost-to-follow-up

For procedures to be performed for subjects discontinuing trial participation, refer to Section 8.2.

7.3.2. Early Termination of the Trial

The Sponsor reserves the right to discontinue or suspend the trial at any time in the event of any of the following:

- Inefficacy of the investigational product
- Occurrence of AEs unknown to date with respect to their nature, severity, and duration, or an unexpected incidence of known AEs such that the Sponsor has determined that continued treatment with TransCon hGH presents an unreasonable and significant risk of illness or injury
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of subjects

- Cancellation of drug development

Sponsor reserves the right to discontinue or suspend the trial for any reason, in which case, provisions will be made to ensure patients will receive continued treatment with commercially available hGH

The Sponsor may stop this trial at a particular site for any of the following reasons:

- Serious and/or persistent non-compliance with the protocol or clinical trial conduct
- Careless or premeditated false documentation in the electronic case report form (eCRF)
- Inadequate cooperation between the investigator and Sponsor
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation

8. SUBJECT POPULATION

Up to approximately 300 (male and female) children with GHD, completing a prior phase 3 TransCon hGH trial, still taking investigational product, who have no evidence of closed epiphyses, and meet all other entry criteria, will be invited to participate in the extension trial.

8.1. TRIAL ENTRY CRITERIA

8.1.1. Inclusion Criteria

1. Children who have completed a prior phase 3 TransCon hGH trial
2. Children who have not permanently discontinued investigational product in the prior trial
3. Written, signed, informed consent of the parent or legal guardian of the subject and written assent of the subject as required by the IRB/HREC/IEC

8.1.2. Exclusion Criteria

1. Poorly-controlled diabetes mellitus (HbA1c ≥ 8.0%) or diabetic complications
2. Evidence of closed epiphyses, defined as bone age > 14.0 years for females or > 16.0 years for males
3. Major medical conditions unless approved by Medical Expert
4. Known hypersensitivity to the components of the trial medication
5. Likely to be non-compliant with respect to trial conduct (in regard to the subject and/or the parent/legal guardian/caregiver)
6. Pregnancy
7. Any other reason that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule

8.2. PREMATURE SUBJECT WITHDRAWAL

Early withdrawal occurs when an enrolled subject ceases participation in the trial, regardless of the circumstances, prior to the expected completion of the trial, which in this study is until a) the product is approved and commercially available, b) the Sponsor makes alternative arrangements for continued subject access to hGH treatment, or c) treatment for pediatric growth hormone deficiency is no longer considered appropriate. Additionally, the investigator may discontinue the treatment of a subject at any time if considered to be in the subject's best interest. If treatment is permanently discontinued for any reason, trial participation should be discontinued. If the subject completes the trial or discontinues prematurely, a Completion Visit/Early Termination Visit should be performed. See Section 7.3.1 for a list of valid reasons for early termination of subjects from the trial.

For trial discontinuations, the investigator should schedule a Completion Visit/Early Termination Visit to collect data, particularly AE data reported up to 14 days after the final dose of TransCon hGH (if applicable), and to collect blood for laboratory evaluations. This visit should contain all assessments from Visit 5 (Week 52, see Schedule of Events, Section 18.2), as applicable, and will be documented in the eCRF together with the reason(s) for trial discontinuation.

8.3. SUBJECT REPLACEMENT CRITERIA

Subjects who terminate early will not be replaced.

9. TREATMENTS

9.1. INVESTIGATIONAL PRODUCT

9.1.1. TransCon hGH Administered with Syringe and Needle

TransCon hGH will be provided as a lyophilized powder in single-use glass vials. The following materials for investigational product reconstitution and administration will be provided to the investigational sites and distributed by the investigator to the subject/parent/legal guardian/caregiver:

- Instructions for Use
- Sterile water for injection
- Syringes for administration
- Needles for reconstitution and administration

TransCon hGH will be dispensed to subjects/parents/legal guardians/caregivers in sufficient amounts to provide the subject with enough investigational product until the next dispensing visit.

9.1.2. TransCon hGH Administered using GH Auto-Injector

Once the GH Auto-Injector is available (in the US only), thorough training of investigational product preparation and administration will occur at the next regularly scheduled visit. TransCon hGH will be provided as a lyophilized powder in single-use dual-chamber cartridges

(DCCs). The DCC contains lyophilized drug product in one chamber and sWFI diluent in the other chamber. The GH Auto-Injector, through a series of steps, automatically reconstitutes the investigational product. The following materials for investigational product reconstitution and administration will be provided to the investigational sites and distributed by the investigator to the subject/parent/legal guardian/caregiver:

- Instructions for Use
- Appropriate DCC for subject weight and dose
- GH Auto-Injector
- Needle for administration

TransCon hGH will be dispensed to subjects/parents/legal guardians/caregivers in sufficient amounts to provide the subject with enough investigational product until the next dispensing visit.

9.2. LABELING

All investigational product will be labeled according to GMP and local requirements. Subjects/parents/legal guardians/caregivers will be provided with dosing and storage instructions. Investigational product labels will comply with regulatory requirements of each country and will be printed in the local language.

9.3. TREATMENT ADMINISTERED

For administration using syringe and needle, TransCon hGH will be provided as a lyophilized powder in single-use glass vials to be reconstituted with 1 mL sWFI. One of two concentrations will be available, the low concentration for lighter weight subjects, the high concentration for higher weight subjects (when available):

- 12.1 mg hGH/vial (11.0 mg hGH/mL when reconstituted)
- 24.2 mg hGH/vial (22.0 mg hGH/mL when reconstituted)

Table 1 shows the weight ranges and corresponding drug concentration and volume to be administered to all subjects, regardless of weight, with an average dose of 0.24 ± 0.02 mg hGH/kg/week. If the concentration suggested in the preferred dosing column is unavailable, alternative dosing should be followed. It is imperative that investigators **do not** calculate a weight-based dose but rather follow the chart and administer the exact volume (based on weight) of the given concentration as indicated.

Table 1 TransCon hGH Bracketed Weight Table

	DOSING		ALTERNATIVE DOSING[a]	
Weight (kg)	Drug Concentration (reconstituted)	Volume (mL)	Drug Concentration (reconstituted)	Volume (mL)
5.5-6.6	11.0 mg hGH/mL	0.13	22.0 mg hGH/mL	0.07
6.7-7.9	11.0 mg hGH/mL	0.16	22.0 mg hGH/mL	0.08
8.0-9.5	11.0 mg hGH/mL	0.19	22.0 mg hGH/mL	0.10
9.6-11.4	11.0 mg hGH/mL	0.23	22.0 mg hGH/mL	0.11
11.5-13.9	11.0 mg hGH/mL	0.27	22.0 mg hGH/mL	0.14
14.0-16.4	11.0 mg hGH/mL	0.33	22.0 mg hGH/mL	0.17
16.5-19.9	11.0 mg hGH/mL	0.39	22.0 mg hGH/mL	0.20
20.0-23.9	11.0 mg hGH/mL	0.47	22.0 mg hGH/mL	0.24
24.0-28.9	22.0 mg hGH/mL	0.29	11.0 mg hGH/mL	0.57
29.0-34.9	22.0 mg hGH/mL	0.35	11.0 mg hGH/mL	0.69
35.0-41.9	22.0 mg hGH/mL	0.41	11.0 mg hGH/mL	0.83
42.0-50.9	22.0 mg hGH/mL	0.50	11.0 mg hGH/mL	0.50 + 0.50
51.0-60.5	22.0 mg hGH/mL	0.60	11.0 mg hGH/mL	0.60 + 0.61
60.6-73.4	22.0 mg hGH/mL	0.73	11.0 mg hGH/mL	0.73 + 0.73
73.5-87.7	22.0 mg hGH/mL	0.88	11.0 mg hGH/mL	0.88 + 0.88

[a] to be used only when drug availability requires

hGH = human growth hormone; kg = kilogram; mg = milligram; mL = milliliter

TransCon hGH will be injected SC into the left and right buttock, left and right thigh, and left and right abdomen by the subject/parent/legal guardian/caregiver. To minimize local side effects, it is recommended to rotate the six injection sites in a subsequent manner (eg, right thigh, right abdomen, right buttock, left thigh, left abdomen, left buttock).

The reason for administering the exact volume as per Table 1 (rather than calculating the exact dose) is as follows. When the GH Auto-Injector, a unique device developed specifically for the administration of TransCon hGH, becomes available, subjects will be switched from the administration of TransCon hGH by syringe and needle to the GH Auto-Injector in the US only.

With the GH Auto-Injector, TransCon hGH will be provided in single-use DCCs as detailed in Section 9.1.2. Multiple DCC presentations (dose strengths) will be available containing approximately 20% incremental increases in dose to support increasing weight ranges. Thus, each DCC will contain a specific quantity of TransCon hGH to support a specific weight range consistent with Table 1, as shown in Table 2.

Dosing based on fixed volumes or DCCs for weight ranges with 20% bracketing ensures that all subjects will receive an average of 0.24 mg hGH/kg/week over the course of the trial.

Table 2 TransCon hGH (ACP-011) Dosing Table for the GH Auto-Injector and DCC Product

Subject Weight (kg)	DCC Dose Strengths (mg hGH)
11.5 – 13.9	3.0
14.0 – 16.4	3.6
16.5 – 19.9	4.3
20.0 – 23.9	5.2
24.0 – 28.9	6.3
29.0 – 34.9	7.6
35.0 – 41.9	9.1
42.0 – 50.9	11.0
51.0 - 60.4	13.3
60.5 – 69.9	7.6 + 7.6
70.0-84.9	9.1 + 9.1
85.0– 100.0	11.0 + 11.0

hGH = human growth hormone; kg = kilogram; mg = milligram

After the GH Auto-Injector is available (in the US only), for subjects whose weight is below the ranges listed in Table 2, TransCon hGH will continue to be administered using syringe and needle. Once the subject's weight has reached a weight range listed in Table 2, TransCon hGH will be administered using the GH Auto-Injector.

Please note that there are slight differences in the boundaries of the highest weight brackets in Table 2 versus Table 1. These differences are necessary to maintain the approximate weight-based dose of 0.24 mg hGH/kg/week, when administering two (duplicate) DCCs per week to achieve an absolute total TransCon hGH dose > 13.3. mg/week.

For those subjects who have historically been dose-titrated to a bracket different (higher or lower) than expected for weight, and have had interval weight gain into a higher bracket, the investigator has the option to either:

- Increase the absolute dose according to Table 1 or Table 2. For example, a subject who has been one weight-bracket-below-expected can stay one bracket-below-expected. A subject who weighed 15 kg at a prior visit has been taking a dose volume (vial) or absolute dose (DCC) one bracket lower than expected for weight (taking 0.27 mL of the 11.0 mg hGH/mL vial, rather than the expected 0.33 mL; or taking 3.0 mg DCC rather than 3.6 mg DCC). At the current visit, he weighs 17 kg (a higher weight bracket) so is eligible to increase to 0.33 mL (vial) or 3.6 mg (DCC), which are still one weight bracket lower than indicated in Table 1 or Table 2.
- **Or**, maintain the current dose volume (vial) or absolute dose (DCC) until the visit's IGF-1 SDS values are available. Once the IGF-1 SDS values are available, the investigator may then select the most appropriate dose volume or DCC presentation.

- Please refer to the Investigator's Brochure for complete details on the composition and characteristics of TransCon hGH.

9.4. DISPENSING AND STORAGE

TransCon hGH must be kept in a locked area at the clinic with access limited to designated trial staff and stored according to its labeling. The sWFI supplied for reconstitution of TransCon hGH should also be stored according to its labeling. All products will be temperature monitored, as appropriate.

TransCon hGH and sWFI will be dispensed to the subjects/parents/legal guardians/caregivers by trial staff to be stored according to its labeling.

Further details are provided in the Pharmacy Manual and Instructions for Use.

9.5. SELECTION OF TRIAL DOSES

TransCon hGH is an inactive prodrug. The phase 2 pediatric GHD trial with TransCon hGH demonstrated that a dose of 0.21 mg hGH/kg/week provided similar hGH exposure, efficacy (annualized HV), and safety/tolerability compared to the equivalent weekly dose of Genotropin, with PD demonstrating normalization of IGF-1 SDS. This trial also demonstrated comparable tolerability and safety and numerically greater annual HV with a 0.30 mg hGH/kg/week dose of TransCon hGH. Treatment guidelines support an hGH dose of 0.24 mg hGH/kg/week (*Grimberg, 2016*) . The TransCon hGH 0.24 mg hGH/kg/week dose is currently being studied in the phase 3 heiGHt Trial. This is also the target dose of this extension trial, however, if dose adjustments for a subject were made in the prior trial, that dose will be carried through to the extension trial. Importantly, IGF-1 levels, along with other safety parameters discussed in Section 9.6, will be measured at every visit and, if needed, changes in dosing will be allowed.

9.6. DOSE ADJUSTMENTS

9.6.1. Dose Adjustment Parameters

The following parameters may be used by the investigator to adjust the TransCon hGH dose without Medical Expert pre-approval.

- At each visit, the TransCon hGH dose volume (vial) or DCC dose strength may be adjusted by the investigator based on the TransCon hGH Bracketed Weight Table (vial) or TransCon hGH Dosing Table for the GH Auto-Injector and DCC Product (See Section 9.3).
- Additionally, the goal for IGF-1 should be between 0 and + 2.0 SDS (unless a different target is identified in consultation with the Medical Expert). Thus, if the IGF-1 SDS measured at a visit is < 0 SDS, the dose may be increased by approximately 20% to the next higher weight bracket by the investigator (See Section 9.3) (Although the prior *requirement* has been eliminated for a second ["confirmatory"] IGF-1 SDS test prior to dose titration, a second IGF-1 SDS test collected 5 days post-dose (±1 day) remains optional at the investigator's discretion.)
- Additionally, if HV is considered to be suboptimal in an adherent subject, the dose of TransCon hGH may be increased after consultation with the Medical Expert.

9.6.2. Stopping/Dose Reductions

The investigator or Medical Expert (and, if needed, with the ISC review) may stop or reduce the dose of investigational product for an individual subject at any time during the trial (please notify the Medical Expert as soon as possible). For example, consideration for stopping or reducing the dose may occur in the presence of the following symptoms and laboratory abnormalities:

- Severe hGH-related AEs at any time during the trial (eg, peripheral edema, severe headache, intracranial hypertension or other adverse drug reaction and/or abnormal laboratory values).
- Pregnancy: A subject must be discontinued from the trial if pregnant.
- IGF-1 > +2.0 SDS: The TransCon hGH dose may be decreased by approximately 20% to the next lower weight bracket, unless a different target SDS is identified in consultation with the Medical Expert. See Section 9.3 for details. (Although the prior *requirement* has been eliminated for a second ["confirmatory"] IGF-1 SDS test prior to dose titration, a second IGF-1 SDS test collected 5 days post-dose (±1 day) remains optional at the investigator's discretion.)

Any re-establishment of the prior dose due to a subsequent sub-optimal IGF-1 response should receive prior approval by the Medical Expert.

- In those subjects who have historically been dose titrated to a bracket different than expected for weight, the investigator may—at study visits—recommend maintenance of the current absolute dose until the visit's IGF-1 SDS values are available. Once the IGF-1 SDS values are available, the investigator may then select the most appropriate dose volume or DCC presentation.
- Evidence of hypersensitivity to TransCon hGH
- Evidence of clinically significant pre-diabetes or diabetes (HbA1c > 6.2% and an absolute increase of 0.5% from the prior visit HbA1c): Confirmation of HbA1c level is required. Once confirmed, TransCon hGH dose may be decreased to the next lower weight bracket. If appropriate follow-up monitoring shows progressively worsening glucose intolerance, additional TransCon hGH dose adjustments may be appropriate.
- Clinical evidence of BIH based on history and physical exam, including visual changes, headaches, nausea, vomiting, and/or papilledema on fundoscopy: TransCon hGH treatment should be discontinued while BIH is clinically managed.

Reinstitution of TransCon hGH treatment, preferably at a lower dose, should receive prior approval by the Medical Expert.

- *De novo* diagnosis of a slipped capital femoral epiphysis should result in a dose reduction or temporary discontinuation.
- Identification of anti-hGH antibodies that are determined to be neutralizing

If a subject has evidence of closed epiphyses by assessment of bone age x-ray (bone age >14.0 years for females or >16.0 years for males), and therefore pediatric growth hormone therapy is no longer considered appropriate, the subject will discontinue study treatment and be considered to have completed the study. If a Visit 5/CV/ETV was just conducted in accordance with

evaluating bone age x-ray results, this visit will be the CV and AE data should be reported up to 14 days after the final dose of TransCon hGH.

If treatment is permanently discontinued, for any reason, trial participation will be discontinued. For additional details, refer to Section 8.2.

9.7. DRUG ACCOUNTABILITY

Trial site staff will be supplied with the investigational product and ancillary supplies to distribute as required to subjects/parents/legal guardians/caregivers. Dedicated site staff will be responsible for investigational product and associated procedures, as well as ancillary supplies, exercising accepted medical and pharmaceutical practices. Investigational product and ancillary supplies must be kept in an appropriate, secure area at the trial site and stored according to conditions specified on the product labels.

The trial will use an Internet-based interactive web response system (IWRS) to capture drug inventory and accountability data, including receipt of drug inventory and supplies by the site, distribution to subjects, return to the site from subjects, and return to the Sponsor (or destruction with the Sponsor's approval). Each investigational product delivery to the site must be confirmed, including date, quantity, and batch/pack number. Each drug dispensed by the site to a subject must include date and amount of drug dispensed. Each drug returned to the site by a subject must include date and amount of unused drug returned.

The computer system complies with all applicable regulatory requirements for record keeping and record retention in clinical trials (21 CFR Part 11 and ICH E6 GCP) as do paper systems.

The system is designed so that changes to any record do not obscure the original information. The audit record will clearly indicate that a change was made and clearly provide a means to locate and read the prior information. All changes to the data have an electronic audit trail in accordance with 21 CFR 11.10(e). Electronic signatures will be used in accordance with 21 CFR Part 11.

Upon completion or termination of the trial, the investigator will, until further notice, keep remaining investigational product and ancillary supplies, along with a copy of the inventory records from the IWRS.

IMPORTANT: Under no circumstances will the investigator allow investigational products to be used other than as directed by this protocol.

9.8. TREATMENT COMPLIANCE

Treatment compliance will be assessed based on drug accountability and review of the subject diary. Subjects/parents/legal guardians/caregivers will be instructed to return all empty investigational product vials and/or DCCs at all study visits after Visit 1. The completed subject diary, which captures the date, time, person administering investigational product, injection site and dose of investigational product, should be returned at each site visit. All investigational product, used and unused, shall be returned at the end of the subject's participation in the trial or at the visit following investigational product discontinuation.

9.9. PRIOR AND CONCOMITANT THERAPIES

9.9.1. Prior Therapy

Prior therapy taken during the prior trial will be captured and recorded.

9.9.1.1. Previous hGH Therapies

Subjects who were treated with Genotropin in the prior TransCon hGH CT-301 trial should be instructed NOT to take their regular dose of Genotropin on the day of Visit 1.

9.9.2. Permitted and Prohibited Therapies

Concomitant therapy is considered any medication other than the investigational product that is administered from the first dose of investigational product administration up until the end of the trial. Any change in documented, permitted concomitant medication must be recorded in the eCRF, noting the type of medication, the dose, start date, stop date (if applicable), and indication. If the administration of a prohibited concomitant medication becomes necessary, participation in the trial may be discontinued prematurely for that subject, based on a decision made jointly by the investigator and Medical Expert.

9.9.2.1. Permitted Therapies

1. 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).
2. Treatment for diabetes
3. Over-the-counter vitamins, minerals, or other dietary supplements only if their use is agreed to by the investigator.

9.9.2.2. Prohibited Therapies

1. Weight-reducing drugs or appetite suppressants, unless used for management of attention-deficit/hyperactivity disorder (ADHD)
2. hGH therapies other than TransCon hGH

10. TRIAL PROCEDURES

10.1. TRIAL DURATION

Each subject's participation is expected to last up until:

- the product is approved and commercially available,
- alternative arrangements have been made for continued subject access to hGH treatment, or
- treatment for pediatric growth hormone deficiency is no longer considered appropriate (including—but not limited to—when there is evidence of closed epiphyses [bone age >14.0 years for females; > 16.0 years for males]).

When any of the 3 criteria is met, the subject will be considered to have completed the extension trial. The total duration of participation for each subject in the trial will therefore depend on the conditions listed above and may be different in different countries and regions.

10.2. TRIAL PERIODS AND VISITS

Following confirmation of eligibility, enrolled subjects will begin attending morning visits every 13 weeks (±2 weeks):

- **Visit 1:** Week 1 (Day 1 is the 1st weekly dose)
- **Visit 2:** Week 13 (±2 weeks), 5 days (±1 day) after the 11th, 12th, 13th, 14th or 15th dose
- **Visit 3:** Week 26 (±2 weeks), 5 days (±1 day) after the 24th, 25th, 26th, 27th or 28th dose

This pattern will continue until completion of the trial. All visits should be in the morning for consistent height measurements. Attempts should be made to adhere to the planned visit schedule. It is suggested that the site staff provide dosing, diary, and visit reminders (eg, phone calls) to subjects/parents/legal guardians/caregivers between visits, especially for those subjects who transitioned from Genotropin to TransCon hGH.

An overview of all visits is provided in the Schedule of Events (Section 18.2).

For detailed descriptions of assessments refer to Section 11.

10.2.1. Visit 1 and Day 1

Prior to any protocol related activities or evaluations, informed consent will be obtained from each potential subject in accordance with GCP and regional regulatory requirements. Informed consent may be obtained during the prior trial. The format and content of the ICF must be approved by the appropriate IRB/HREC/IEC prior to implementation. Release of medical information authorization should also be obtained at the time of informed consent.

Visit 1 of the extension trial should be the same day as the final visit of the prior trial and may occur over several days. To continue uninterrupted treatment with hGH, Day 1 (the first weekly dose) should occur on the day of Visit 1 if the subject is entering after completion of the TransCon hGH CT-301 trial (heiGHt trial), or as soon as possible thereafter. If the subject is entering after completion of the TransCon hGH CT-302 (fliGHt trial), they should remain on their dosing schedule and take their dose approximately two days after 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.

During Visit 1 (and again on Day 1, if on a subsequent day), the investigator will review all baseline data collected to determine the subject's eligibility. Data collected up through the final visit of the prior trial may be used as baseline data for the extension trial. The following will be performed for Visit 1 of the extension trial:

1. Medications and health status review
   - Medical history from the prior trial will be carried forward into this trial

- Ongoing AEs from the prior trial will be followed until resolution or stabilization
- Review of subject diary from the prior trial
- Current therapies
- Interval history since last visit of prior trial

2. Vital sign measurements
3. Height and weight measurements
4. Physical examination
   - Local tolerability assessment. **For subjects who were treated with Genotropin in the prior TransCon hGH CT-301 trial**, Visit 1 injection site examinations to the daily hGH treatment areas should be explicitly documented so as to differentiate from any new reactions that occur during the extension trial.
5. Pubertal status assessment (Tanner stage, including onset of menses)
6. Blood collection for the following laboratory assessments*:
   - IGF-1 and IGFBP-3
   - Antibodies against hGH and PEG
     - These analyses may only be conducted after enrollment and are not required for eligibility verification. These data will be used to support evaluation of post-dose antibody detection
     - If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers
   - mPEG
   - Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c)
   - Chemistry
   - Hematology
   - Lipid panel
   - **Females of child-bearing potential only**: hCG

   *Fasting not required. Banked blood samples may be used for additional characterization of anti-drug antibody responses.
7. Bone age x-ray
   - A bone age x-ray performed within approximately the past 52 weeks may be acceptable with appropriate documentation. However, if the last recorded bone age was > 12.0 years, and the bone age x-ray 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.

8. Investigational product preparation/administration training/re-training
   - May also be performed at other visits, as needed
   - Includes review of the TransCon hGH Instructions for Use (also provided to the subject/parent/legal guardian/caregiver for reference throughout the trial)
   - When the GH Auto-Injector is available, thorough onsite training of investigational product preparation and administration will occur at the earliest regularly scheduled visit (including the 1st visit upon transition of the GH Auto-Injector in the US where the GH Auto-Injector will be used.
   - Includes instructions that administration of investigational product should occur at approximately the same time of day on the same day of the week throughout the trial. Details regarding adjustment of a subject's established dose day/time are provided in the trial manual.
9. Subject diary completion review, as needed
   - May also be performed at other visits, as needed
   - Includes reminder to complete Week 6 PRO questionnaires prior to 6th dose of investigational product
   - In those subjects using the GH Auto-Injector: includes reminder to complete the Device Usability Questionnaire (DUQ) on the day of 6th dose using the GH Auto-Injector
10. Patient-reported outcome questionnaires
   - Convenience and Overall Satisfaction domains (C&OS) of the Treatment and Satisfaction Questionnaire for Medication (TSQM-9)
     - For the parent (C&OS-P)
   - Child Sheehan Disability Scale
     - For the parent (CSDS-P)
     - **For the child ≥ 9 years old only**: (CSDS-C)
11. Investigational product dose adjustment (from prior trial), as needed
   - Investigational product volume is based on weight measurement obtained at Visit 1 and the Bracketed Weight Table for TransCon hGH, or the GH Auto-Injector dosing table
12. Investigational product and subject diary dispensing

In the unusual event there is a gap of 4 to approximately 6 weeks between the assessments done for Visit 1 and Day 1 (first dose), then all of the above should be repeated except physical exam, blood collection, and bone age x-ray.

Following Visit 1, TransCon hGH will be administered by subject/parent/legal guardian/caregiver as a once weekly SC injection. Once weekly healthcare services may be offered for the first 4 weeks of a new treatment (eg, subjects beginning TransCon hGH in this trial) to accommodate home administration of TransCon hGH. Extended support may be offered until subjects/parents/legal guardians/caregivers are comfortable assuming responsibility for

administration of the investigational product. See Section 9.3 for details regarding TransCon hGH administration and Section 9.6 for details regarding dose adjustments.

10.2.2. Week 6, Visit 2 and scheduled visits every 13 weeks ongoing

- For subjects who were treated with Genotropin in the TransCon hGH CT-301 trial, immediately prior to the 6th investigational product administration (Week 6), patient-reported outcome questionnaires within the subject diary will be completed
- Visit 2 and subsequent scheduled visits every 13 weeks (±2 weeks) will be performed 5 days (±1 day) post-dose

Subjects should adhere to the planned visit schedule. It is suggested that site staff provide dosing, diary, and visit reminders (eg, phone calls) to subjects/parents/legal guardians/caregivers between the visits, especially for those subjects who transitioned from Genotropin to TransCon hGH and for those that transitioned from vial and syringe to the GH Auto-Injector.

10.2.2.1. Patient-Reported Outcome Completion (Week 6 within Diary; Visit 2 at Clinic Visit)

For subjects who were treated with Genotropin in the prior TransCon hGH CT-301 trial: Between Visit 1 and Visit 2, immediately prior to the 6th investigational product administration and at Visit 2, the following patient-reported outcome questionnaires will be completed by subjects/parents/legal guardians/caregivers, as applicable. At Week 6, the questionnaires will be completed in the subject diary. At Visit 2, the questionnaires will be completed at the clinic visit, prior to review of the subject diary, AEs, and concomitant medications.

- PQ-P
- PQ-C: **only for subjects ≥ 9 years old (at Visit 1)**
- C&OS-P
- CSDS-P
- CSDS-C: **only for subjects ≥ 9 years old (at Visit 1)**

10.2.2.2. Visit 2, Visit 4, Visit 6 and every 6 months ongoing (even-numbered visits)

The following assessments will be performed at Visit 2, Visit 4, Visit 6, and every 6 months ongoing (even-numbered visits):

1. Concomitant medications
   - Includes review of subject diary
2. AE review
   - Includes review of subject diary
3. Investigational product compliance calculation
   - Includes review of subject diary and returned investigational product
4. Vital sign measurements

5. Height and weight measurements
6. Physical examination
7. Pubertal status assessment (Tanner stage)
8. Blood collection for the following laboratory assessments*:
   - IGF-1 and IGFBP-3
   - Antibodies against hGH and PEG
     - If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers
   - Females of child-bearing potential only: hCG

   *Banked blood samples may be used for additional characterization of anti-drug antibody responses
9. Investigational product dose adjustment, as needed
10. Investigational product and subject diary dispensing

An overview of all visits is provided in Section 18.2.

10.2.2.3. Visit 3, Visit 5, Visit 7 and every 6 months ongoing (odd-numbered visits)

The following assessments will be performed at Visit 3, Visit 5, Visit 7, and every 6 months ongoing (odd-numbered visits), unless otherwise indicated:

1. Concomitant medications
   - Includes review of subject diary
2. AE review
   - Includes review of subject diary
3. Investigational product compliance calculation
   - Includes review of subject diary and returned investigational product
4. Vital sign measurements
5. Height and weight measurements
6. Physical examination
7. Pubertal status assessment (Tanner stage)
8. Blood collection for the following laboratory assessments*:
   - IGF-1 and IGFBP-3
   - Antibodies against hGH and PEG
     - If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers
   - mPEG

- Hormone/glycemic Status (TSH, FT4, FT3, morning cortisol, and HbA1c)
- Chemistry
- Hematology
- Lipid panel
- **Females of child-bearing potential only**: hCG
  *Fasting not required. Banked blood samples may be used for additional characterization of anti-drug antibody responses.

9. Investigational product dose adjustment, as needed
10. Investigational product & subject diary dispensing

An overview of all visits is provided in the Schedule of Events, Section 18.2.

10.2.2.4. Patient-Reported Outcome Completion (6th week after transition to the GH Auto-Injector) and Device Usability Questionnaire

For all subjects who have transitioned to the GH Auto-Injector (6th week of GH Auto-Injector Use): Immediately prior to the 6th dose of the GH Auto-Injector, and at the next scheduled clinic visit (approximately 13 weeks after transition to the GH Auto-Injector), patient-reported outcomes questionnaires will be completed by subjects/parents/legal guardians/caregivers, as applicable. At 6 weeks after transition to the GH Auto-Injector, the questionnaires will be completed in the subject diary. At the next scheduled clinic visit (approximately 13 weeks after transition to the GH Auto-Injector), the questionnaires will be completed at the clinic visit, prior to review of the subject diary, AEs, and concomitant medications. The questionnaires are:

- C&OS-P
- CSDS-P
- CSDS-C: **only for subjects ≥ 9 years old (at time of transition to GH Auto-Injector)**

In addition, on the day of the 6th dose using the GH Auto-Injector (either immediately before or after the 6th dose) and at the next scheduled clinic visit (approximately 13 weeks after transition to GH Auto-Injector), the following questionnaire will be completed by the individual primarily responsible for preparing and performing the injection with the GH Auto-Injector.

- DUQ

10.2.2.5. GH Auto-Injector Data Read-Out

After approximately 3 to 6 months of subjects being on the auto-injector, there is a potential that new devices may be shipped to the sites so that the subject may exchange their device and receive a new one. The used devices may be sent to Ascendis for data download and analysis, which will include no clinical or personal data. The device serial number may be logged to the subject's study ID, but not any patient identifiers.

The potential data collected by the device are as follows:

1. Injection Log
   - A log entry of this type is stored after each successful injection.
2. Other Data Log
   - Timestamp
   - Dose size
3. Other information
   - Charge time
   - Battery level
   - Motor stop position
   - Position of first rubber stopper (used cartridge detect)
4. Errors Log

   An error log entry will contain the data:
   - Timestamp
   - Error code (eg “self-test error” or “injection user abort”)
   - Additional error information that depends on the “error code”
5. Reset Log

   If a reset occurs, it is logged.
   - Timestamp
   - Reset cause (eg “watchdog” or “software”)
   - Additional reset information

10.2.2.6. Annual Assessments

The following will be performed annually (Visit 5, Visit 9, etc.) and/or anytime if clinically indicated

- Bone age x-ray

10.2.3. Unscheduled Visits

Unscheduled visits are those visits that occur between regularly scheduled visits and are performed to assess a previously noted AE, abnormal laboratory value(s), and/or clinical findings. In such cases, the subject/parent/legal guardian/caregiver will be contacted to arrange an unscheduled visit. Only focused assessments (guided by the reason for the visit) will occur at these visits.

10.2.4. Completion/Early Termination Visits

If treatment is permanently discontinued for any reason, trial participation will be discontinued and a Completion Visit/Early Termination Visit (procedures indicated for Visit 5 in the Schedule of Events table, as applicable) will be performed. Completion of the trial is described in Section 10.1. Early termination is when a subject's trial participation discontinues prior to completion of the trial.

10.2.5. Follow-up

Once participation in this extension trial is completed, there will be no follow-up visit except as required to follow serious adverse event (SAEs) that are determined to be related to the investigational product (See Section 12.1.3).

11. ASSESSMENTS

11.1. VITAL SIGN MEASUREMENTS

Subject should rest for at least 5 minutes before assessment. For younger subjects for whom this may not be possible, attempts should be made to measure vital signs when subject is calm. The following vital signs should be measured:

- Heart Rate
- Blood Pressure
- Respiratory Rate
- Body Temperature

11.2. WEIGHT MEASUREMENT

Weight should be measured at each visit by the same auxologist at approximately the same time of day on the same calibrated weight scale (to minimize bias and reduce variability). Subjects should be wearing light clothing and no shoes. For subjects who cannot stand independently, a calibrated pediatric/infant weight scale should be used.

11.3. HEIGHT MEASUREMENT

Height should be measured at each visit, preferably by the same auxologist, at approximately the same time of day using a wall-mounted stadiometer (to minimize bias and reduce variability), the accuracy of which has been verified prior to each visit using a validated metallic calibration rod.

Children < 2 years old should be measured in a recumbent position using a length board placed on a flat, stable surface such as a table. Note: despite previous height measurements being performed on a length board, once a subject is 2 years old, the subsequent measurements should be performed on a stadiometer.

For subjects ≥ 2 years old, obtain the height measurement on a wall-mounted stadiometer following the general guidance below:

- The subject should not stretch prior to height determination

- The subject should be standing without shoes and socks. Thin foot covers over bare feet may be worn.
- The subject should be wearing only light clothing so that the subject's pose can be observed
- The subject's gaze should be forward and in a horizontal position (Frankfurt plane)
- The subject's heels should be placed together. If the subject has genu valgum (knock-knee), the knees must be in contact with each other and the heels as close to each other as possible
- The subject's heels, buttocks, shoulders, and occiput of the cranium should all be in contact with the stadiometer
- Upward pressure should be applied to the subject's mandibular rami (jaw)
- The subject's shoulders should be relaxed, and pressure applied to the abdomen to reduce lordosis (spine curvature)
- The counterweight head is lowered until it is in contact with the highest part of the subject's head
- The height measurement is read at the horizontal level with the counter to the nearest 0.1 cm
- The subject should step away from the stadiometer and **repeat the previous steps 2 more times.** Repeated determinations must be within 0.5 cm of each other otherwise three new measurements must be performed and recorded.

For subjects < 2 years old, obtain the height measurement on a length board following the general guidance below (*WHO, 2008*):

- The subject should be undressed (diaper/underwear is acceptable)
- The parent/legal guardian/caregiver or another individual should place the subject supine on the length board with the subject's head against the fixed headboard, compressing the hair
- The subject's head should be positioned so that an imaginary vertical line from the ear canal to the lower border of the eye socket is perpendicular to the board. The subject's eyes should be looking straight up
- The auxologist should stand on the side of the length board, clearly able to see the measuring tape. If possible, the subject's parent/legal guardian/caregiver or another individual should stand behind the headboard and hold the subject's head in position.
- The subject should lie straight along the board, with shoulders touching the board and without arching the spine
- The subject should not change position during measurement
- Gentle pressure should be applied to the subject's knees to straighten the legs as far as possible
- While the subject's knees are being held with one hand, the footboard should be pulled with the other hand until flat against the subject's feet, toes pointing upwards

- Measurement of the subject's length is read and recorded in centimeters to the last completed 0.1 cm

11.4. PHYSICAL EXAMINATION

A physical examination should be performed to include injection site examination to assess for local tolerability. **For subjects who were treated with Genotropin in the prior TransCon hGH CT-301 trial,** Visit 1 injection site examinations to the daily hGH treatment areas should be explicitly documented so as to differentiate from any new reactions that occur during the extension trial.

11.5. FUNDOSCOPY

A standard fundoscopy may be performed to rule out blurred disc margins as indicated by subject symptoms. Fundoscopy may be performed throughout the trial as needed at the investigator's discretion.

11.6. PREGNANCY TEST

Testing for hCG should be performed for female subjects of child-bearing potential. Subjects who are sexually active must use an effective form of contraception.

11.7. PATIENT-REPORTED OUTCOME MEASURES

All Patient-Reported Outcomes (including PQ, CSDS, and C&OS) 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 – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (***Guidance for Industry, 2009***).**

11.7.1. 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 timing of the preference questionnaires is listed in Section 10.2.2.1.

11.7.2. 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 (*Whiteside, 2009*). 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.

The timing of the questionnaires to be completed after Visit 1 is listed in Section 10.2.2.1 and Section 10.2.2.2.

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

The original 14-item Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4 is a reliable and valid instrument to assess patients' satisfaction with medication, providing scores in four domains – Side Effects, Effectiveness, Convenience and Overall Satisfaction. In naturalistic studies, administering the TSQM with the Side Effects domain could provoke the physician to assess the presence or absence of adverse events in a way that is clinically atypical, carrying the potential to interfere with routine medical care. As a result, a TSQM-9, derived from the TSQM Version 1.4 but without the Side Effects domain was created (*Bharmal, 2009*). This measure is being adapted further for this trial with the removal of the Effectiveness domain since effectiveness of hGH is not subjective and will be assessed with objective measures in this and other trials evaluating TransCon hGH. Thus, only C&OS of the TSQM-9 will be used.

At Visit 1 for all subjects, the parent/legal guardian/caregiver will complete the C&OS-P. The timing of the questionnaires to be completed after Visit 1 is listed in Section 10.2.2.1 and Section 10.2.2.2.

11.7.4. 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 data will supplement the GH Auto-Injector ease-of-use and functionality data gathered from a previous phase 1 clinical trial (comparing TransCon hGH administered by GH Auto-Injector and by syringe/needle), as well as data gathered during the formative and summative usability studies conducted in the device design and development phases. The data will also be analyzed as part of this current trial's overall assessment of safety and efficacy.

The DUQ was designed for use by children and/or adults. It consists of eight statements that the subject or caregiver (ie, whomever is designated as the individual primarily responsible for preparing and performing the injection with the GH Auto-Injector) is asked to rank on a scale indicating level of agreement. The statements relate to the level of comfort, ease-of-use, and safety.

This timing of DUQ administration is outlined in Section 10.2.2.4.

11.8. SUBJECT DIARY

The subject diary will be provided to the subject/parent/legal guardian/caregiver at the clinic visits and should be completed weekly on the day of investigational product administration. The data captured within the subject diary includes:

- Date and time of administration
- Dose of investigational product
- Person preparing and giving injection
- Location of injection on subject's body
- Assessment of local tolerability

- Changes to medications or subject's health

The subject diary should be reviewed by trial staff at every trial visit as part of concomitant medication review, adverse event reporting and investigational product compliance.

11.9. BONE X-RAY

Documentation of a bone age x-ray performed within approximately the past 52 weeks with appropriate documentation may be acceptable to show open epiphyses. However, if subject's prior documented bone age was > 12.0 years, and the bone age x-ray 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.

11.10. LABORATORY ASSESSMENTS

Blood will be collected at each visit for assessments as listed in the Schedule of Events (Section 18.2), and described in Section 10.2. The total blood volume collected in a 3-month period will be up to approximately 18 mL, and the total collected in a 6-month period will be up to approximately 30 mL.

Detailed blood sampling, processing and assaying of samples will be provided in the laboratory manual.

11.11. LOCAL TOLERABILITY ASSESSMENT

Local tolerability is defined as an injection site reaction deemed abnormal from those ordinarily observed in SC injections (including pain, intensity, or duration), and will be collected on an AE form, as appropriate. Between visits, local tolerability will be evaluated and documented by the subject/parent/legal guardian/caregiver in the subject diary.

At clinic visits, assessment of local tolerability will be performed by injection site examination by trial staff (documented as part of the physical exam), in conjunction with subject diary review.

11.11.1. Reporting Local Tolerability as an Adverse Event

For the purpose of this trial, injection site reactions should not be documented as AEs unless the reaction:

- impacts the subject's ability to perform daily activities, or
- requires medical therapy (not including prophylactic therapy)

12. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING

12.1. ADVERSE EVENTS

12.1.1. Definition

An 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, 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.

Possible AEs associated with TransCon hGH are listed in the Investigator's Brochure or the accompanying Reference Safety Information. The adverse reactions associated with commercially available daily hGH-containing products that may or may not be observed with use of TransCon hGH are:

- Sudden death in pediatric patients with Prader-Willi syndrome; risk factors include morbid obesity, history of upper airway obstruction or sleep apnea, and unidentified respiratory infection
- Intracranial tumors, particularly meningiomas, in teenagers/young adults treated with brain irradiation as children
- Injection site reactions/rashes (as well as rare, generalized hypersensitivity reactions)
- Skin atrophy and lipoatrophy
- **Note:** Rotating the injection site (see Section 9.3) is expected to decrease the risk of skin atrophy or lipoatrophy.
- Headaches
- Glucose intolerance, including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus
- Intracranial hypertension with papilledema, visual changes, headache, nausea, and/or vomiting
- Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes (including carpal tunnel syndrome/paresthesias)
- Hypothyroidism (central [secondary] hypothyroidism may first become clinically evident or worsen in patients with GHD during hGH treatment)
- Slipped capital femoral epiphysis (occurs more frequently in patients with endocrine disorders or in patients undergoing rapid growth)
- **Note:** Any subject with the onset of a limp or complaints of hip or knee pain should be carefully evaluated for a slipped capital femoral epiphysis.
- Progression of pre-existing scoliosis due to rapid growth (hGH has not been shown to increase the occurrence of scoliosis)

  Note: Any subjects with a history of scoliosis should be monitored for progression of scoliosis.
- Pancreatitis - Cases of pancreatitis have been reported rarely in children and adults receiving hGH treatment, with some evidence supporting a greater risk in children compared with adults. Pancreatitis should be considered in any hGH-treated subject, especially a child, who develops persistent severe abdominal pain.

AEs may include:

- Clinically significant treatment-emergent physical examination abnormalities
- Out-of-range lab or test results associated with new/worsening diagnosis, clinical sign, or symptom; or that require therapy

In this trial, all AEs that are considered mild and not related to investigational product will not be recorded on the AE CRF; this is with the exception of site-specific reporting preferences. In addition, the following out-of-range laboratory values—whether or not associated with a titration of the TransCon hGH dose—will not be considered AEs unless they are associated with a sign or symptom: IGF-1, IGF-1 SDS, IGFBP3, IGFBP3 SDS. In this trial, IGF-1 and IGFBP3 are pharmacodynamic markers of TransCon hGH therapy and may be used to guide an investigator's recommendation to titrate the TransCon hGH dose.

The Medical Expert will review all safety information on an ongoing basis. The key safety data will also be reviewed periodically by an ISC in accordance with its governing charter.

12.1.2. Severity, Causality, and Outcome Assessment

12.1.2.1. Severity Rating

The following guideline must be used by the investigator to grade the intensity of an AE:

Mild – The subject is aware of the sign or symptom but tolerates it easily. The event is of little concern to the subject and/or of little or no clinical significance. The event is not expected to have any effect on the subject's health or well-being. The event may or may not require medical intervention.

Moderate – The event causes the subject enough discomfort for it to cause interference with or change some of the subject's usual activities. The event is of some concern to the subject and poses some risk to the subject's health or well-being. The event may require medical intervention.

Severe – The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up.

Life-threatening – The subject is at immediate risk of death from the event as it occurred.

12.1.2.2. Causality Rating

The principal investigator will assess the causal relationship between the investigational product and the event using the following guideline:

Definite – This causality category applies to those AEs which the investigator feels are clearly related to the investigational product. An AE may be categorized as definitely related to the investigational product when the event meets the first 4 (or more) of the following criteria:

- The event follows a reasonable temporal sequence from investigational product administration

- The event cannot be reasonably explained by known characteristics of the subject's clinical status, environmental or toxic factors, or other therapies administered
- The event disappears or decreases in severity upon cessation of the investigational product. [There are important exceptions when an AE may not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (eg, tardive dyskinesia)]
- The event follows a known response pattern to the investigational l product
- The event reappears upon re-challenge (if applicable)

Probable – This causality category applies to those AEs which the investigator feels a high degree of certainty are related to the investigational product. An AE may be categorized as probably related to the investigational product when the event meets the first 3 (or more) of the following criteria:

- The event follows a reasonable temporal sequence from investigational product administration
- The event cannot be reasonably explained by known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered
- The event disappears or decreases in severity upon cessation of the investigational product. [There are important exceptions when an AE may not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (eg, tardive dyskinesia]
- The event follows a known response pattern to the investigational product
- The event reappears upon re-challenge (if applicable)

Possible – This causality category applies to those AEs in which the investigator feels there is a reasonable, although not probable, connection with the investigational product. An AE may be categorized as possibly related to the investigational product when the event meets the first 2 (or more) of the following criteria:

- The event follows a reasonable temporal sequence from investigational product administration
- The event is possibly explained by known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject
- The event follows a known response pattern to the investigational product

Unlikely– This causality category applies to those AEs in which the investigator feels there is unlikely a connection with the investigational product. An AE may be categorized as unlikely related to the investigational product when the event meet the first 2 (or more) of the following criteria:

- The event does not follow a reasonable temporal sequence from investigational product administration
- The event may readily be explained by known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject

- The event does not follow a known response pattern to the investigational product

Unrelated/Not Related – This category is applicable to those AEs in which the investigator feels there are clearly extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under Definite, Probable, Possible, or Unlikely, as noted above.

12.1.2.3. Outcome Assessment

Subjects will be followed until AEs have either resolved, subjects have returned to their baseline status, or subjects are deemed stable or commensurate with ongoing disease processes. One of 6 AE outcomes listed below must be recorded:

Resolved – The subject has fully recovered from the event and has returned to baseline status without residual observable effects.

Resolved with sequelae – The subject has recovered from the event with some residual observable effects.

Ongoing – The subject has not recovered from the event and observable effects remain, regardless of whether the event is changing or stable and persistent.

Death Due to This Event – The subject died because of the event

Death Due to Other Event – The subject had not recovered from the event at the time of death

Lost to Follow-up – The subject had not recovered from the event at the time of last contact

12.1.3. Reporting Procedures for All Adverse Events

At each visit, all AEs will be documented in response to a general question about the subject's well-being and whether any possible changes in well-being have occurred since the previous visit. Additionally, at each visit, site staff will review subject diary data with the subject and parent/legal guardian/caregiver, to determine if diary entries reflect any AEs. There will be no direct questioning to solicit possible AEs. AEs reported up to 14 days after the final dose of TransCon hGH will be captured. AEs, including SAEs, will be documented through the end of the subject's participation in the trial. All AEs ongoing at the completion of the study or Early Termination Visit must be followed until the event is resolved or deemed stable by the investigator. In this trial, all AEs that are considered mild and not related to investigational product will not be reported on the AE CRF. In addition, the following out-of-range laboratory values—whether or not associated with a titration of the TransCon hGH dose—will not be considered AEs unless they are associated with a clinical sign or symptom: IGF-1, IGF-1 SDS, IGFBP3, IGFBP3. In this trial, IGF-1 and IGFBP3 are pharmacodynamic markers of TransCon hGH therapy and may be used to guide an investigator's recommendation to titrate the TransCon hGH dose. Reportable AEs must be recorded on the appropriate eCRF. Reportable AEs either observed by the investigator or reported by the subject must be recorded regardless of causality.

The following attributes must be documented for each reported AE:

- Subject ID
- Description

- Onset date (if AE was present on Day 1, include whether onset was prior to or after first dose of investigational product)
- Resolution date, if applicable
- Severity
- Causality (relationship to investigational product)
- Outcome
- Action taken
- Determination of "serious" (or not)

Any ongoing AEs from the prior trial will be followed until resolution or stabilization. Any changes to the conditions documented as medical history during the trial and that meet the above AE definition should be recorded as AEs so that a complete safety profile of the investigational product is obtained. See Section 12.2.2 for additional reporting procedures for serious AEs.

Any change from baseline health status that meets the above AE definition and occurs from the time of the first administration of investigational product until the completion of the study or the Early Termination Visit will be recorded as an AE.

Out-of-range laboratory values or test results may constitute AEs if they:

- induce a new/worsening diagnosis, clinical sign, or symptom, or
- require therapy.

Routine titration of chronic, concomitant medications (eg, increase of levothyroxine dose due to interval weight gain and without associated signs/symptoms of overt hypothyroidism) would not be considered as AEs. Whenever possible, an AE should be recorded as a specific diagnosis or syndrome rather than as a sign, symptom, or out-of-range laboratory value. If there is not a diagnosis, the event term should be the clinical sign or symptom. Based on an investigator's clinical judgement, multiple concurrent symptoms should be grouped together as a single, unifying diagnosis (e.g. headache, fever, cough, and coryza constitute a probable viral upper respiratory tract infection, and this single AE term is more appropriate than listing each symptom as a separate AE).

Care should also be taken to record the most medically appropriate term (eg, hypertension for elevated blood pressure that persists and requires chronic treatment and follow-up, or increased blood pressure for elevated blood pressure that occurs for a limited time and does not persist or require ongoing treatment).

AEs will be documented at the maximum intensity experienced. If a previously recorded AE or condition recorded as part of medical history increases in severity or frequency, it will be recorded as a new AE.

All AEs will be considered ongoing until they have completely resolved or, in the case of a condition recorded as part of medical history, returned to baseline status prior to investigational product administration. At study completion or the Early Termination Visit, all AEs should have a statement regarding resolution.

Any SAE that is determined to be related to the investigational product will be followed until resolution or stabilization.

Any undesirable medical occurrence resulting from an accidental overdose is an AE and should be recorded and reported on the appropriate eCRF page. Regardless of classification as an AE or not, *all* overdoses should be documented, and the subject(s) monitored. Since accidental overdoses with the investigational product could have serious clinical consequences and/or represent a compliance issue, they should be reported to the Medical Expert immediately and evaluated by the Sponsor.

12.2. SERIOUS ADVERSE EVENTS AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

12.2.1. Definitions

12.2.1.1. Serious Adverse Event Definition

In addition to severity and causality ratings, each AE is to be classified by the investigator as "serious" or "not serious."

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" here refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of an existing hospitalization

  Note: Hospitalization for an elective procedure, for a routinely scheduled treatment, or scheduled in advance of trial participation are not considered SAEs.
- Results in persistent or significant disability/incapacity, or disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

  Note: This applies if a subject exposed to an investigational product gives birth to a child with a congenital anomaly or birth defect.
- Is an important medical event

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in this definition.

Events **not** considered to be SAEs are hospitalizations for:

- Routine treatment or monitoring of the investigational product or indication under study not associated with any deterioration in condition

- Treatment that was elective or planned prior to enrollment for a pre-existing condition unrelated to the investigational product or indication under study that has not worsened
- Admission to a hospital for general care not associated with any deterioration in condition
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Suspected Unexpected Serious Adverse Reaction Definition

A suspected unexpected serious adverse reaction (SUSAR) is any AE for which there is evidence to suggest a causal relationship between the drug and the AE, and which is assessed as both unexpected and serious. A suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or Reference Safety Information as associated with TransCon hGH, or if it is not listed at the specificity or severity that has been observed. The final determination of expectedness will be assessed by the Sponsor.

Non-Serious Adverse Events Leading to Discontinuation

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

12.2.2. Reporting

All initial and follow-up information regarding SAEs or SUSARs must be reported by the investigator to the Sponsor or its representatives within 24 hours of discovery, including those related to protocol-mandated procedures and regardless of suspected causality. Reporting must not be delayed by waiting for additional information. The minimum information required for reporting an SAE are the AE term (diagnosis) and the investigator's initial causality assessment. Additional information can be reported to the Sponsor or its representatives as a follow-up report.

The Sponsor (or its representatives) is responsible for reporting within the time frame required by applicable regulations all SUSARs to:

- Investigators
- Central IRBs/HRECs/IECs
- National ethics committees (if applicable)
- Appropriate regulatory authorities

It is the investigators' responsibility to comply with the requirements of their local IRB/HREC/IEC for reporting SUSARs, other SAEs, and any new and/or relevant safety information provided by the Sponsor or its representatives. At minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

13. SAFETY MONITORING

The Sponsor will conduct an ongoing review of all trial data, with particular attention given to laboratory findings, AEs, and concomitant medications. Any important safety trends or other findings considered related to the investigational product will be reported to the investigators and to regulatory authorities. In particular, the Sponsor will notify investigators and regulatory authorities of AEs that:

- Fulfill the criteria for SUSARs
- Occur at a meaningfully greater frequency than described in the current Investigator's Brochure or Reference Safety Information

14. STATISTICS

The Statistical Analysis Plan (SAP) will provide a detailed description of the planned statistical analyses. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record.

14.1. TRIAL ENDPOINTS

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

14.1.2. Efficacy Endpoints

The efficacy endpoints of long-term 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

14.1.3. Pharmacodynamic Endpoint

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

14.1.4. Other Endpoints

- Preference for weekly TransCon hGH or daily Genotropin treatment
- Satisfaction with weekly TransCon hGH
- Comfort, ease-of-use, and safety in subjects using the GH Auto-Injector

14.2. SAMPLE SIZE DETERMINATION

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 investigational product, and meet eligibility criteria will be invited to participate. The sample size is determined by the prior trial sizes.

14.3. ANALYSIS POPULATIONS

The analysis population includes all subjects who receive at least one dose of investigational product.

14.4. STATISTICAL ANALYSES

Baseline and demographic data will be summarized to characterize the study population. Subgroups of interest, such as prior exposure to hGH and age categories, will be determined and corresponding subgroup analyses for safety and efficacy will be performed as appropriate. Prior and concomitant medication, as well as exposure of investigational product, will be summarized.

Data from clinical assessments will be summarized using descriptive statistics. Numerical variables will be summarized by mean, median, standard deviation, minimum, and maximum while categorical variables will be summarized by counts and proportions.

15. TRIAL CONDUCT

15.1. SITE INITIATION

Prior to participation, investigational sites and investigators will be evaluated for continued appropriate qualifications and ability to execute the trial. Each investigational site must undergo appropriate training on the trial protocol and ancillary trial procedures and documents through participation in a Site Initiation Visit (SIV) or Investigator Meeting (IM). Protocol and GCP training must take place before any subjects are enrolled at a site. SIVs and IMs will include, but may not be limited to, investigational product preparation and administration procedures, data collection requirements, and subject eligibility requirements.

15.2. SCREEN FAILURES

Screen failures are not expected because there is no screening period in this trial.

15.3. MAINTENANCE OF ENROLLMENT LOGS

Procedures for maintenance of enrollment logs are discussed in the trial manual.

15.4. DATA HANDLING AND RECORD KEEPING

15.4.1. Collection of Data

Data will be collected in the eCRF. The eCRF is an integral part of the trial and subsequent reports. It must be used to capture all trial-specific data collected and must be kept current to reflect subject status during the course of the trial. Only a Subject Identification Number will be used to identify the subject. The investigator must keep a separate subject identification code list with subject names and medical record numbers (or other personal identifiers).

The trial will use an Internet-based remote data entry system to collect clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 GCP. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The system is configured based on the requirements from the Sponsor. Source documents are to be retained to enable a reconstruction and evaluation of the trial. Source documents include the hospital files and trial worksheets provided by the Sponsor. Data will be recorded in the trial worksheets as appropriate to complete and/or clarify the source data.

The design of the computerized system complies with all the applicable regulatory requirements for record keeping and record retention in clinical trials (21 CFR Part 11 and ICH E6 GCP) to the same degree of confidence as is provided with paper systems. Clinical investigators must retain either the original or a certified copy of all source documents sent to the Sponsor or its representatives, including query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly provides a means to locate and read the prior information. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

15.4.2. Coding Dictionaries

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A complete description of data to be collected is provided in the trial documentation.

15.4.3. Data Handling

Data will be entered in a timely manner and in accordance with a trial management plan.

15.4.4. Direct Access to Source Data/Documents

The investigator/trial site is to provide direct access to source data/documents for trial-related monitoring, audits, IRB/HREC/IEC review, and regulatory inspection.

15.4.5. Record Keeping

The investigator is responsible for maintaining adequate records to fully document the conduct of the trial consistent with that noted in ICH E6, including but not limited to the following:

1. All versions of the Investigator's Brochure
2. Signed Protocol and Amendments in effect during the conduct of the trial
3. Signed ICFs
4. Source documents, including adequate case histories, questionnaires, and subject diaries
5. Signed, dated, and completed eCRFs and documentation of data corrections
6. Notification of SAEs and related reports
7. Dated and documented IRB/HREC/IEC approvals and approval by regulatory authorities, as required
8. Normal laboratory reference ranges
9. Laboratory certifications
10. Curricula Vitae of all clinical investigators
11. Completed Forms FDA 1572
12. SIV documentation
13. Delegation of Authority Log
14. Subject Screening & Enrollment Log(s), Subject Identification Code List
15. Investigational product accountability documentation
16. Signed agreements between involved parties
17. Relevant communication, including that related to monitor site visits (eg, letters, meeting notes, notes from telephone calls)
18. Interim, annual, or final reports to IRBs/HREC/IEC and regulatory authorities, as required
19. Audit certificate(s), if applicable

15.5. DATA QUALITY CONTROL

15.5.1. Monitoring Procedures

The Sponsor and/or its representative may make periodic visits to the investigational site to assess compliance with trial procedures and regulatory requirements; to ensure that the safety, welfare, and privacy of subjects are being protected; and to verify the accuracy and integrity of the trial data. In addition, independent Quality Assurance site audits may be conducted as verification of the quality and compliance of trial conduct.

The Sponsor and/or its representative will periodically review the trial data to ensure that data are being appropriately collected and reported. Queries and corrections will be made as needed.

15.5.2. Data Management

Sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and Contract Research Organization (CRO)'s standard operating procedures (SOPs). A comprehensive data management plan (DMP) will be developed including a data management overview, description of database contents, annotated eCRFs, user acceptance testing procedures, query contacts, and consistency checks.

Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the trial manual.

15.6. AUDITING PROCEDURES

In addition to the routine monitoring procedures, a GCP Quality Assurance audit may be initiated by the Sponsor. The investigator has to ensure that subjects/parents/legal guardians are aware of and consent to personal information being reviewed during the data verification process as a part of monitoring/auditing/inspection by the Sponsor, properly authorized agents of the Sponsor, or competent authorities. In addition, participation and personal information is treated as strictly confidential to the extent that applicable law permits and to which it is not publicly available. The purpose of audits and inspections is to evaluate compliance with the principles of GCP, international and local regulatory requirements, and the trial protocol. The audit or inspection may include, for example, a review of all source documents, drug records, original clinic medical notes, and some or all of the facilities used in the trial.

The audits may be conducted by the Sponsor or Sponsor's selected agent in accordance with Sponsor's SOP or SOPs of the selected and properly authorized agent. A competent authority may also wish to conduct an inspection during the trial or after its completion. If an inspection is requested by a competent authority, the investigator must inform the Sponsor immediately that this request has been made. The investigator and his/her institution will permit all monitoring, audits, and regulatory inspections, providing direct access to source data.

15.7. LABORATORY QUALITY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the central laboratories. Some serum or plasma samples may be used for bioanalytic test validation.

The laboratories will provide a list of reference ranges for applicable analyses before trial start. These will be held in the investigator site file and the trial master file. The methods employed for each assay should be available on request. Any change in the laboratory procedures, reference values, etc., during the trial must promptly be communicated to the Sponsor. The laboratories may also be audited by the Sponsor or by competent authorities.

15.8. TRIAL TERMINATION OR COMPLETION

The investigator should notify the IRB/HREC/IEC in writing of the completion or early termination of the trial. Upon trial completion or termination, applicable regulatory reporting requirements will be followed. The Sponsor reserves the right to terminate the trial at any time for any reason.

15.9. CHANGES TO THE PROTOCOL

Changes in any portion of this protocol must be documented in the form of an amendment from the Sponsor and must be approved by the investigational site's IRB/HREC/IEC and regulatory authorities, as required, before the amendment is implemented. However, in the event of apparent immediate hazard to a subject, a deviation from the protocol is allowed to eliminate the hazard. In this case, the deviation and the reason for it must be submitted for approval as required by regional regulations to the applicable IRB/HREC/IEC and regulatory authorities, along with a proposed protocol amendment if appropriate.

Protocol amendments may only be made with prior written approval of the Sponsor and/or its representative and documented approval or favorable opinion from applicable regulatory authorities or regional IRB/HREC/IEC, as required. The investigator must send a copy of the documented approval to the Sponsor and/or its representative.

15.10. OTHER CHANGES IN TRIAL CONDUCT

Changes in trial conduct are not permitted. Any unforeseen changes in trial conduct will be recorded in the clinical study report.

15.11. USE OF INFORMATION AND PUBLICATION

The data and information generated in this trial are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required prior to disclosing any information related to this trial. Publication of the results will be based on appropriate analyses and review of the complete data. Authorship will be determined based on enrollment of eligible subjects or contribution to the design, conduct, or interpretation of the trial. Publication of any data of this trial without prior Sponsor approval is not permitted.

16. ETHICAL AND LEGAL CONSIDERATIONS

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- GCPs as outlined in ICH E6 and regional regulations
- Declaration of Helsinki
- Regional required subject data protection laws and regulations
- Applicable regional regulations

16.1. INDEPENDENT SAFETY COMMITTEE

Independent oversight of this trial will be provided by an ISC. Its duty is to regularly review the progress of the trial and assess accumulating safety data. After each meeting, it will advise the Sponsor on the continuing safety of current trial subjects and on the continuing validity and scientific merit of the trial. All decisions about the conduct of the trial will rest solely with the Sponsor. The ISC will consist of at least 1 pediatric endocrinologist and 1 physician of another relevant medical discipline, all with experience in clinical studies, who will operate based on the ISC Charter agreed to by all ISC members. The Charter will define data content and review frequency.

The Sponsor may attend the ISC meetings.

The ISC is empowered to recommend the following courses of action with respect to continuing the trial:

1. the trial should continue without modification
2. the trial should continue but with modification to the protocol, or with additional data presentation needed
3. trial enrollment and treatment administration should be temporarily suspended pending further data evaluation, or
4. the trial should be terminated because of safety concern

The responsibility for the final decision regarding the ISC-recommended course of action will rest with the Sponsor.

16.2. INFORMED CONSENT

The draft ICF must be reviewed by the Sponsor and/or its representative prior to submission to a regional IRB/HREC/IEC for approval. A copy of the ICF approved by the review board must be forwarded to the Sponsor and/or its representative.

The ICF (and subject information sheet, if applicable) documents the trial-specific information the investigator provides to the subject and the subject's agreement to participate. The investigator or designee will fully explain in layman's terms the nature of the trial along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The ICF and subject information sheet must be appropriately signed and dated before the subject undergoes any trial-related procedure. The original and any amended signed and dated ICFs and subject information sheets must be retained at the trial site with a copy of each provided to the subject.

16.3. IRB/HREC/IEC APPROVALS

The Principal Investigator at each site is responsible for obtaining approval from the appropriate regional IRB/HREC/IEC for the final protocol, Sponsor-approved ICF and subject information sheet (if applicable), and any advertisements to recruit subjects. Written approval of these documents must be obtained from the committee before any subject is enrolled at a trial site.

The Principal Investigator is also responsible for the following interactions with the regional IRB/HREC/IEC:

1. Obtaining review board approval for any protocol amendments and ICF revisions before implementing the changes
2. Providing the review board with any required information before or during the trial
3. Submitting progress reports to the review board as required during the conduct of the trial, requesting re-review and approval of the trial as needed, and providing copies of all review board re-approvals and relevant communication to the Sponsor and/or its representative
4. Notifying the review board of all serious and unexpected AEs related to the investigational product reported by the Sponsor and/or its representative, as required
5. Notifying the review board of the end of trial participation, in accordance with regional guidelines and regulations

16.4. SUBJECT COMPENSATION FOR ADVERSE EFFECTS ON HEALTH

The Sponsor and/or its representative will adhere to regional regulations regarding clinical trial compensation of subjects whose health is adversely affected by taking part in the trial.

16.5. FINANCE AND INSURANCE

Will be described in trial documents.

17. REFERENCES

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Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-1 treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-1 deficiency. Horm Res Paediatr. 2016;86(6):1-37.

Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (December 2009).

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Webster R, Didier E, Harris P, et al. PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. Drug Metab Dispos. 2007;35(1):9-16

Whiteside SP. Adapting the Sheehan disability scale to assess child and parent impairment related to childhood anxiety disorders. J Clin Child Adolesc Psychol. 2009 Sep;38(5):721-730.

World Health Organization. Training course on child growth assessment. Geneva, WHO, 2008.

18. ATTACHMENTS

18.1. SIGNATURE OF AGREEMENT

In signing this protocol, the investigator agrees to:

1. Conduct the trial in accordance with the relevant, current protocol and make changes only after notifying the Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human subjects
2. Comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice plus appropriate regional regulatory laws and requirements
3. Personally conduct or supervise the described investigation
4. Inform any subjects or persons used as controls that the investigational products are being used for investigational purposes
5. Ensure requirements relating to obtaining informed consent and regional ethical or institutional review board approval have been met
6. Report to the Sponsor or its representative any AEs that occur in the course of the investigations, as specified in Section 12.
7. Read and understand the Investigator's Brochure, including potential risks and side effects of the investigational product
8. Ensure all associates, colleagues, and employees assisting in the conduct of the trial are informed of their obligations in meeting their commitments
9. Maintain adequate and accurate records and make these available for inspection by the Sponsor and/or its representative or any regulatory agency authorized by law
10. Promptly report to the regional ethical or institutional review board all changes in research activity and all unanticipated problems involving risks to human subjects or others
11. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements
12. Administer investigational product only to subjects who meet trial entry criteria and are enrolled in the trial and only according to the guidelines set forth in this protocol

SIGNATURE OF AGREEMENT

I have read and understand the information in this clinical trial protocol, including the potential risks and side effects of the investigational product, and agree to personally conduct or supervise the described investigation(s) in accordance with the relevant, current protocol(s) and will deviate from the protocol only after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to inform all subjects that the investigational product is being used for experimental purposes, and I will ensure that the requirements related to obtaining informed consent are met. I agree to report to the Sponsor any adverse events that occur in the course of the investigation(s).

1. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments.
2. I will not make any changes in the research without IRB/HREC/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
3. I agree to maintain all information in this document and regarding the stud(ies) as confidential and to use it only for the purpose of conducting the stud(ies). I agree not to forward this document to any other party without the prior written authorization of the Sponsor.

Investigator:

Printed Name and Title: _____

Signature: _____

Date: _____

18.2. SCHEDULE OF EVENTS

	VISIT 1[1]	VISIT 2	VISIT 3	VISIT 4	VISIT 5/CV/ETV[2]
	Week 1 Day 1	**Week 13 (± 2 weeks)**	**Week 26 (± 2 weeks)**	**Week 39 (± 2 weeks)**	**Week 52 (± 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 review[3]	x				
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
Investigational product preparation/administration training	x				
Training on GH Auto-Injector[9]	(x)	(x)	(x)	(x)	(x)
Subject diary training	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			
DUQ[11]		x			
Investigational product dose adjustment[13]	x	x	x	x	x
Local tolerability assessment[14]	x	x	x	x	x
Investigational product & subject diary dispensing	x	x	x	x	x
Investigational product 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 10.2.2.5). 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] Medications and health status: Interval history only to be recorded in case of new disease states since the last visit of the prior trial; 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 GH Auto-Injector is available, transition to the GH Auto-Injector will occur in the US (only) 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 investigational product, and in clinic at Visit 2, prior to review of the subject diary, AEs, and concomitant medications. For subjects transitioning to the GH 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 GH Auto-Injector, and again in clinic at the following scheduled visit, prior to review of the subject diary, AEs, and concomitant medications. Additionally, for subjects transitioning to the GH Auto-Injector, the DUQ will be completed within the subject diary on the day of the 6th dose of investigational product, and in clinic at Visit 2, 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 GH Auto-Injector, as applicable.

[13] Dose adjustments at visits are typically 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] Investigational product compliance includes review of subject diary and returned investigational product.

[16] AE review includes review of subject diary and physical examination of injection sites. AEs that are considered mild and not related to investigational product will not be reported on the AE CRF. AEs reported up to 14 days after the final dose of TransCon hGH will be captured.

19. APPENDICES

Preference Questionnaire – Child

Preference Questionnaire – Parent

Child Sheehan Disability Scale – Child

Child Sheehan Disability Scale – Parent

Convenience & Overall Satisfaction Domains of the Treatment Satisfaction Questionnaire for Medication - 9 – Parent

Device Usability Questionnaire

APPENDIX 1. PREFERENCE QUESTIONNAIRE – CHILD

enliGHten Visit ____ **ID #** | | | | | |

PQ-CHILD

Date: | | | | | | | 2 | 0 | 1 | |
Day Month Year

INSTRUCTIONS

Please complete ONLY if you are 9 years old or older. Your growth hormone treatment is the injections (shots) you take to help you grow. The following questions are about your experience (how you think and feel) about your growth hormone treatment that you were using before starting this study compared to your current treatment in this study.

- Please read each question carefully.
- There are no "right" or "wrong" answers. THIS IS NOT A TEST.
- If you are not sure how to answer a question, pick the answer that is closest to how you feel.
- If you mark a box by mistake, draw a single line through the wrong response box and then mark the box you want.

1. **Which treatment do you prefer (like better)?** *(Choose ONLY one answer)*
   - ❑ Injections (shots) I am CURRENTLY taking in this study (once a week)
   - ❑ Injections (shots) I was taking BEFORE starting this study (once a day)
   - ❑ I don't have a preference (I like them both the same) ➡ SKIP to question #4 on next page.

2. **Overall, I prefer (like better) the treatment I chose in question 1 because:** *(Check as many answers as you like)*
   - ❑ How often I need to get injections (number of shots a week)
   - ❑ It helps me grow better
   - ❑ Less injection pain
   - ❑ Less afraid about getting injections
   - ❑ Less bruising, redness, and/or swelling
   - ❑ Less worry about missing a dose
   - ❑ Less burning, stinging, and/or soreness
   - ❑ Less embarrassed
   - ❑ Less annoyed by the injections
   - ❑ Less interference with (getting in the way of) my activities
   - ❑ Easier to get the injection ready to take
   - ❑ Easier to give the injection
   - ❑ Easier to store (keep somewhere when you are not using it)

enliGHten Visit ____ **ID #** | | | | | | |

PQ-CHILD (Continued)

3. **Of all the reasons you checked in question 2, which ONE is the MOST IMPORTANT to you?** *(Choose ONLY one answer)*
   - ❑ How often I need to get injections (number of shots a week)
   - ❑ It helps me grow better
   - ❑ Less injection pain
   - ❑ Less afraid about getting injections
   - ❑ Less bruising, redness, and/or swelling
   - ❑ Less worry about missing a dose
   - ❑ Less burning, stinging, and/or soreness
   - ❑ Less embarrassed
   - ❑ Less annoyed by the injections
   - ❑ Less interference with (getting in the way of) my activities
   - ❑ Easier to get the injection ready to take
   - ❑ Easier to give the injection
   - ❑ Easier to store (keep somewhere when you are not using it)

4. **When you finish this study, which treatment would you prefer to continue taking?** *(Choose ONLY one answer)*
   - ❑ Injections (shots) I am CURRENTLY taking in this study (once a week)
   - ❑ Injections (shots) I was taking BEFORE starting this study (once a day)
   - ❑ I don't have a preference (I like them both the same)

5. **If you have a friend who needs medicine to help them grow, which treatment would you tell them to use?** *(Choose ONLY one answer)*
   - ❑ Injections (shots) I am CURRENTLY taking in this study (once a week)
   - ❑ Injections (shots) I was taking BEFORE starting this study (once a day)
   - ❑ I don't have a recommendation (they could use either)

6. **How easy was it for you to remember what it felt like when you were taking shots <u>every day</u> to help you grow?** *(Choose ONLY one answer)*
   - ❑ Very easy to remember
   - ❑ Easy to remember
   - ❑ Not easy to remember
   - ❑ I don't remember at all

APPENDIX 2. PREFERENCE QUESTIONNAIRE – PARENT

enliGHten Visit ____ **ID #** | | | | | |

PQ-PARENT

Date: | | (Day) | | | | (Month) | 2 | 0 | 1 | | (Year) Initials: | | | |

INSTRUCTIONS

The following questions are about your child's experience with their growth hormone treatment that they were using before starting this study compared to their current treatment in this study. Check the response box that most closely represents **YOUR opinion and experience.**

- Please read each question carefully.
- There are no "right" or "wrong" answers.
- If you are not sure how to answer a question, mark the box that is closest to your experience.
- If you mark a box by mistake, draw a single line through the wrong response box and then mark the box you want.

1. **Which treatment do you prefer?** *(Choose ONLY one answer)*
   - ❑ Injections my child is CURRENTLY taking in this study (once a week)
   - ❑ Injections my child was taking BEFORE starting this study (once a day)
   - ❑ I don't have a preference (SKIP to question #4)

2. **Overall, I prefer the treatment I chose in question 1 because:** *(Check as many answers as you like)*
   - ❑ How often my child needs to get injections (number of injections a week)
   - ❑ It helps my child grow better
   - ❑ My child seems to have less injection pain
   - ❑ My child seems less afraid about getting injections
   - ❑ My child seems to have less bruising, redness, and/or swelling
   - ❑ My child seems less worried about missing a dose
   - ❑ My child seems to have less burning, stinging, and/or soreness
   - ❑ My child seems less embarrassed
   - ❑ My child seems less annoyed by the injections
   - ❑ Easier to prepare my child emotionally for injections
   - ❑ Less interference with my child's activities
   - ❑ Easier to prepare the injection
   - ❑ Easier to give the injection
   - ❑ Easier to store
   - ❑ I am less afraid about giving my child injections
   - ❑ I am less worried about missing a dose
   - ❑ I am less embarrassed
   - ❑ I am less emotionally impacted
   - ❑ Less interference with my activities

enliGHten Visit ____ **ID #** | | | | | | |

PQ-PARENT(Continued)

3. **Of all the reasons you checked in question 2, rank the THREE MOST IMPORTANT** *(Write 1 on the line for most important, 2 for second most important, 3 for third most important)*

___How often my child needs to get injections (number of injections a week)
___It helps my child grow better
___My child seems to have less injection pain
___My child seems less afraid about getting injections
___My child seems to have less bruising, redness, and/or swelling
___My child seems less worried about missing a dose
___My child seems to have less burning, stinging, and/or soreness
___My child seems less embarrassed
___My child seems less annoyed by the injections
___Easier to prepare my child emotionally for injections
___Less interference with my child's activities
___Easier to prepare the injection
___Easier to give the injection
___Easier to store
___I am less afraid about giving my child injections
___I am less worried about missing a dose
___I am less embarrassed
___I am less emotionally impacted
___Less interference with my activities

4. **Which treatment would you prefer your child continues using after the study ends?** *(Choose ONLY one answer)*

❑ Injections my child is CURRENTLY taking in this study (once a week)
❑ Injections my child was taking BEFORE starting this study (once a day)
❑ I don't have a preference

5. **If you knew another child who needed growth hormone treatment, which treatment would you recommend?** *(Choose ONLY one answer)*

❑ Injections my child is CURRENTLY taking in this study (once a week)
❑ Injections my child was taking BEFORE starting this study (once a day)
❑ I don't have a recommendation

APPENDIX 3. CHILD SHEEHAN DISABILITY SCALE – CHILD

enliGHten Visit ____ **ID #** | | | | | |

CSDS-CHILD

Date: | | | | | | | 2 | 0 | 1 | |
Day Month Year

Instructions:

Complete ONLY if you are 9 years old or older.

Now I want to know how much your growth hormone injections (shots) have messed things up for you. How much have they stopped you from doing things you want to do?

Please mark ONE circle for each question.

1. How much have your growth hormone injections (shots) messed things up with school and homework:

Not at all — A little bit — Some — A lot — Very, very much

0 1 2 3 4 5 6 7 8 9 10

2. How much have your growth hormone injections (shots) messed things up with friends:

Not at all — A little bit — Some — A lot — Very, very much

0 1 2 3 4 5 6 7 8 9 10

3. How much have your growth hormone injections (shots) messed things up at home:

Not at all — A little bit — Some — A lot — Very, very much

0 1 2 3 4 5 6 7 8 9 10

APPENDIX 4. CHILD SHEEHAN DISABILITY SCALE – PARENT

enliGHten Visit ____ **ID #** | | | | | |

CSDS-PARENT

Date: | | (Day) | | | (Month) | 2 | 0 | 1 | | (Year) Initials: | | | |

Instructions:

Please mark the number in the circle that corresponds to how much your child's growth hormone deficiency (GHD) treatments are currently interfering with various areas of life.

Please mark ONE circle for each question.

1. The GHD treatments have disrupted <u>your child's</u> **schooling**:

2. The GHD treatments have disrupted <u>your child's</u> **social life**:

3. The GHD treatments have disrupted <u>your</u> **work**:

4. The GHD treatments have disrupted <u>your</u> **social life**:

5. The GHD treatments have disrupted <u>your</u> **family life/home responsibilities**:

APPENDIX 5. CONVENIENCE & OVERALL SATISFACTION DOMAINS OF THE TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION - 9 – PARENT

enliGHten Visit ____ **ID #** | | | | | |

C&OS-PARENT

Date: | | | | | | | | | | Initials: | | | |
Day Month Year

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication your child is taking in this clinical trial. We are interested in your evaluation of the convenience of the medication and your overall satisfaction with the medication *over the last two to three weeks* or *since your child last used it.*

For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

2. How easy or difficult is it to plan when your child will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

3. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

enliGHten Visit ____ **ID #** | | | | | | |

C&OS-PARENT (Continued)

4. Overall, how confident are you that taking this medication is a good thing for your child?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

5. How certain are you that the good things about your child's medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

6. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

APPENDIX 6. DEVICE USABILITY QUESTIONNAIRE

enliGHten ID #	Visit #___/Week ___ after transition to GH Auto-Injector	

Device Usability Questionnaire

Date: ☐☐ ☐☐☐ 2 0 ☐☐

Day Month Year

INSTRUCTIONS

Please have the individual primarily preparing and performing the injection with the GH Auto-Injector rank the following statements:

The following questions are about your experience (how you think and feel) about using the GH Auto-Injector to give your medicine in this study.

1. **The GH Auto-Injector does not cause a lot of pain or discomfort**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree
2. **I can unpack, use, and inject the medicine without difficulty or making a mistake**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree
3. **I can unpack, use, and inject the medicine in a short amount of time**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree
4. **I can use the GH Auto-Injector to inject medicine without touching blood**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree

enliGHten ID # **Visit #___/Week ____ after transition to GH Auto-Injector**

Device Usability Questionnaire (Continued)

5. **The GH Auto-Injector leaves little to no marks on the skin**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree
6. **It is easy for me to see that the medicine has been properly injected**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree
7. **The GH Auto-Injector tells me easily if I received my medicine or if there was a problem by sounds and lights**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree
8. **The GH Auto-Injector has not caused an injury where I had to see a doctor for help**
   - ❑ Strongly Agree
   - ❑ Somewhat Agree
   - ❑ Neither Agree nor Disagree
   - ❑ Somewhat Disagree
   - ❑ Strongly Disagree

enliGHten ID #	**Visit #___/Week ____ after transition to GH Auto-Injector**

Device Usability Questionnaire (Continued)

Please provide any other comments below.

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Date this page was completed _____

Initials of the person completing this page: _____

- ❑ Caregiver/Parent
- ❑ Child