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

NCT Number: NCT03305016

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CLINICAL STUDY PROTOCOL

AMENDMENT 1

PRODUCT NAME/NUMBER:	TransCon hGH (ACP-011)
PROTOCOL NUMBER:	TransCon hGH CT-302
IND NUMBER:	126053
DEVELOPMENT PHASE:	3
PROTOCOL TITLE:	**fliGHt:** A Multicenter, Phase 3, Open-Label, 26-Week Trial Investigating the Safety, Tolerability and Efficacy of TransCon hGH Administered Once Weekly in Children with Growth Hormone Deficiency (GHD)
PROTOCOL DATE:	29 August 2017
SPONSORED BY:	Ascendis Pharma Endocrinology Division A/S Tuborg Boulevard 5, DK-2900, Hellerup, Denmark
Sponsor Medical Monitor (Medical Expert)	[redacted]
Sponsor Medical Monitor (Medical Expert)	[redacted]

AMENDMENT 1 SUMMARY OF CHANGES

Rationale

An administrative amendment to the original protocol was required to separately list pregnancy as an exclusion criterion to clarify that, under no circumstance, will pregnant individuals be allowed to participate in this trial. As such an amendment was required, the following administrative changes were also incorporated:

Section(s)	Change	Rationale
Title Page 1. Approval Signatures	[redacted]	New Medical Director assigned to study
Global	Change of bone age x-ray requirement at Screening to only those subjects at Tanner stage 4	Update to align with standard of care
Global	Change of requirement in previous bone age x-ray (to be used in place of a Screening x-ray) from being < 13.0 years for females or < 15.0 years for male to requiring a bone age delay of ≥ 6 months	Update to align with standard of care
Global	[redacted]	[redacted]
Global	[redacted]	[redacted]
Inclusion Criteria (1.b.i.)	Addition of impaired height for children < 2 years old to be based on 2006 WHO Child Growth Standards	Clarification of standardization based on CDC guidance

Section(s)	Change	Rationale
5.3 Clinical Experience	Changed "heiGHt Trial…was initiated in August 2016" to "heiGHt Trial…was initiated in September 2016"	Reflection of initiation to be based on submission of the protocol to a regulatory authority rather than finalization of protocol
9.3 Treatment Administered (Table 1)	Addition of "(reconstituted)" following Drug Concentration	Clarification of dose as the IP label reads either "12.1 mg hGH" or "24.2 mg hGH"
10.2.1 Screening (Medical History)	Changed "Prior height measurements over the 52 weeks prior to daily hGH treatment" to "Prior height measurements over the 52 weeks prior to diagnosis"	Inclusion of children < 3 years old who may not have started hGH treatment
11. ASSESSMENTS	Addition of 11.2 Weight Measurement	Provide similar guidelines for measuring weight as measuring height
11.3 Height Measurement	Change "Height should be measured at each visit by the same auxologist at approximately the same time of day (to minimize bias and reduce variability) using a wall-mounted, stadiometer…" to "Height should be measured at each visit by the same auxologist at approximately the same time of day using the same wall-mounted stadiometer (to minimize bias and reduce variability)…"	Clarification of guideline to reduce variability between height measurements
11.3 Height Measurement	Update use of a length board versus a stadiometer to be based on the subject's age at the time of measurement rather than the subject's age at Visit 1	Update to align with CDC/WHO guidance and standard of care

Section(s)	Change	Rationale
11.7.3 Convenience & Overall Satisfaction Domains of the Treatment Satisfaction Questionnaire for Medication	Change "OS&C" to "C&OS"	Correct misspelling
15.2 Screen Failures	Change "Subjects who fail to meet the eligibility criteria at any point during Screening are defined as Screening Failures" to "Subjects who fail to meet the eligibility criteria at any point prior to administration of first study drug dose are defined as Screening Failures."	Clarification of definition of Screen Failures
18.2 Schedule of Events	Removal of days for each study visit	Removal of unnecessary details and incorrect days provided for Week 13 and 26
[redacted]	[redacted]	[redacted]

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

1. APPROVAL SIGNATURES

1.1 Sponsor

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

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

[redacted]

29 Aug 2017
Date

29 Aug 2017.
Date

29 Aug 2017
Date

2. SYNOPSIS

PRODUCT NAME/NUMBER	TransCon hGH (ACP-011) Henceforth referred to as TransCon hGH or Study Drug
PROTOCOL NUMBER	TransCon hGH CT-302
IND NUMBER	126053
DEVELOPMENT PHASE	3
PROTOCOL TITLE	**fliGHt:** A Multicenter, Phase 3, Open-Label, 26-Week Trial Investigating the Sa**f**ety, To**l**erabi**l**ity and Efficacy of TransCon h**GH** Adminis**t**ered Once Weekly in Children with GHD
INDICATION	Growth failure in children due to GHD
OBJECTIVES	**Primary:** • To assess the safety and tolerability of weekly TransCon hGH in children with GHD from 6 months to 17 years old, inclusive **Secondary:** • To assess annualized height velocity (HV) in children with GHD at 26 weeks of weekly TransCon hGH treatment • To assess the proportion of subjects with IGF-1 standard deviation score (SDS) in the normal range of 0.0 to +2.0 at 26 weeks of weekly TransCon hGH treatment • To evaluate the change in height standard deviation scores (ΔHSDS) in children with GHD at 26 weeks of weekly TransCon hGH treatment • To determine the incidence of antibodies against TransCon hGH (anti-hGH and anti-PEG) in children with GHD over 26 weeks of weekly TransCon hGH treatment • To assess the expected maximum observed concentration (C_{max}) of TransCon hGH in children with GHD ≥ 6 months to < 3 years old • To assess the preference for weekly TransCon hGH or commercially available daily hGH treatment • To assess the treatment satisfaction of weekly TransCon hGH over time
TRIAL DESIGN	This is a multicenter phase 3, open-label, 26-week trial of weekly TransCon hGH in children 6 months to 17 years old, inclusive, with GHD. Children ≥ 6 months to < 3 years old with GHD may be hGH-treatment naïve or have been treated with daily hGH (≥ 0.20 mg hGH/kg/week) for ≤ 130 weeks. Children ≥ 3 to 17 years old, inclusive, must have been treated with daily hGH (≥ 0.20 mg hGH/kg/week) for

	≥ 13 weeks but ≤ 130 weeks and be without evidence of closed epiphyses. TransCon hGH will be provided as a lyophilized powder in single-use glass vials and administered with syringe and needle. **Screening:** Following informed consent, subjects will enter the Screening Period (up to approximately 4 weeks) to determine eligibility. The following will be performed during screening: 1) Medical history a. Data supporting a diagnosis of GHD b. Pituitary deficiencies c. Other relevant diagnoses d. Prior height measurements e. Prior and current therapies 2) Vital sign measurements 3) Height and weight measurements 4) Limited physical examination 5) Pubertal status assessment (Tanner stage) (*Tanner 1976*) 6) **Tanner stage 4 only:** Bone age x-ray (if an x-ray performed within the past 52 weeks with a bone age delay of ≥ 6 months is not available) 7) Fundoscopy (to rule out blurred disc margins) 8) Blood collection for the following laboratory assessments*: a. Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) b. Antibodies against human growth hormone (hGH) and polyethylene glycol (PEG) c. Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c) d. Chemistry e. Hematology f. Lipid panel g. **Females of child-bearing potential only:** Human Chorionic Gonadotropin (hCG) * Banked blood samples may be used for additional characterization of anti-drug antibody responses **Visit 1:** Subjects meeting all entry criteria will return to the clinic for Visit 1. Subjects will be dispensed TransCon hGH to be administered weekly (preferably in the evening) by the parent/legal guardian/caregiver or the

	subject, with the exception of the first dose being administered in the clinic at Visit 1. All subjects, regardless of their dose of hGH prior to trial entry, will start TransCon hGH at 0.24 mg hGH/kg/week, with volumes administered based on the bracketed weight chart for TransCon hGH. The following will be performed: 1) Patient-reported outcome questionnaires **Only completed for subjects treated with daily hGH prior to enrollment:** a. Child Sheehan Disability Scale – Parent (CSDS-P) b. **≥ 9 years old only:** Child Sheehan Disability Scale – Child (CSDS-C) c. Convenience & Overall Satisfaction domains (C&OS) of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) – Parent (C&OS-P) 2) Review changes from baseline status 3) Concomitant medication review 4) Vital sign measurements 5) Height and weight measurements 6) Limited physical examination 7) Pubertal status assessment (Tanner stage) 8) Study drug and subject diary dispensing and training 9) On-site study drug administration 10) Local tolerability assessment **C_{max} Visit:** ***Only completed by subjects < 3 years old at Visit 1*** *Week 4 (+1 week),* ***1-2*** *days after 4th or 5th injection* The following will be performed: 1) Concomitant medications Includes review of subject diary 2) AE review Includes review of subject diary 3) Blood collection for the following laboratory assessments: a. Expected C_{max} of hGH b. IGF-1 and IGFBP-3 c. Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c) Immediately prior to the 6th study drug administration, the following questionnaires will be completed by subjects/parents/legal guardians, as applicable, in the subject diary: 1) Preference Questionnaire – Parent (PQ-P)

	Only completed for subjects treated with daily hGH prior to enrollment 2) **≥ 9 years old only:** Preference Questionnaire – Child (PQ-C) **Only completed for subjects treated with daily hGH prior to enrollment** 3) CSDS-P 4) **≥ 9 years old only:** CSDS-C 5) C&OS-P **<u>Visit 2 & Visit 3:</u>** *Week 13 (±1 week), 5 days (±1 day) after 12th, 13th, or 14th injection, respectively* *Week 26 (±1 week), 5 days (±1 day) after 25th, 26th, or 27th injection, respectively* The following will be performed: 1) **At Visit 2 only:** Patient-reported outcome questionnaires Completed prior to subject diary review, adverse events (AEs) review, and concomitant medication review a. PQ-P **Only completed for subjects treated with daily hGH prior to enrollment** b. **≥ 9 years old only:** PQ-C **Only completed for subjects treated with daily hGH prior to enrollment** c. C&OS-P 2) Patient-reported outcome questionnaires Completed prior to subject diary review, AEs review, and concomitant medication review a. CSDS-P b. **≥ 9 years old only:** CSDS-C 3) Concomitant medications Includes review of subject diary 4) AE review Includes review of subject diary 5) Study drug compliance calculation Includes review of subject diary and returned study drug 6) Vital sign measurements 7) Height and weight measurements 8) Limited physical examination 9) Pubertal status assessment (Tanner stage) 10) Blood collection for the following laboratory assessments*: a. IGF-1 and IGFBP-3 b. Antibodies against hGH and PEG

	c. **< 3 years old only:** mPEG d. **At Visit 3 and ≥ 9 years old only:** TMPD (N1,-N1,-N3-trimethyl-1,3-propane-diamine; a small molecular weight leaving group associated with the linker) e. Hormone/glycemic Status (TSH, FT4, FT3, morning cortisol, and HbA1c) f. Chemistry g. Hematology h. Lipid panel i. **Females of child-bearing potential only:** hCG * Banked blood samples may be used for additional characterization of anti-drug antibody responses 11) **At Visit 2 only:** Study drug dose adjustment, as needed 12) **At Visit 2 only:** Study drug & subject diary dispensing 13) **At Visit 3 only:** Fundoscopy (to rule out blurred disc margins) **TransCon hGH Dose:** TransCon hGH will be dosed at 0.24 mg hGH/kg/week. This dose was selected due to variable compliance with daily dosing regimens and to be consistent with the pivotal phase 3 heiGHt Trial that has been ongoing since November 2016. The initial volume of TransCon hGH administered will be calculated using the weight measurement obtained at Visit 1 and the TransCon hGH bracketed weight chart. **Dose Adjustment Parameters:** The following parameters may be used by the investigator to adjust the TransCon hGH dose without Medical Monitor pre-approval. At Visit 2, the TransCon hGH dose may be adjusted by the investigator based on the TransCon hGH bracketed weight table. 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 Monitor). Thus, if the IGF-1 SDS measured at Visit 2 (or the C_{max} Visit, as applicable) is < 0 SDS, and following confirmation of IGF-1 level as < 0 SDS by a second measurement collected 5 days post-dose (±1 day), the dose may be increased by approximately 20% to the next higher weight bracket by the investigator.

	Stopping/Dose Reductions: The investigator (with Medical Monitor pre-approval) or Medical Monitor (and, if needed, with the Independent Safety Committee [ISC] review) may stop or reduce the dose of study drug at any time during the trial in the presence of the following symptoms and laboratory abnormalities: • Severe hGH-related AEs at any time during the trial • Pregnancy **Subjects who are sexually active must use an effective form of contraception** • IGF-1 > +2.0 SDS: Following confirmation of IGF-1 level as > +2.0 SDS by a second measurement collected 5 days post-dose (±1 day), TransCon hGH dose may be decreased by approximately 20% to the next lower weight bracket, unless a different target is identified in consultation with the Medical Monitor **Any re-establishment of the original dose (0.24 mg hGH/kg/week) due to a subsequent sub-optimal IGF-1 response should receive prior approval by the Medical Monitor.** • Substantially reduced IGF-1 and growth response or evidence of a hypersensitivity to TransCon hGH • Evidence of clinically significant pre-diabetes or diabetes (HbA1c > 6.2% measured at Visit 2 and an absolute increase of 0.5% from Screening HbA1c): Following confirmation of HbA1c level, TransCon hGH dose may be decreased by approximately 20% 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 Monitor.** • *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

	Any subject who discontinues treatment should be encouraged to remain in the trial and attend all subsequent trial visits. If, however, trial participation is discontinued (ie, consent is withdrawn), an Early Termination Visit (all procedures of Visit 3) should be performed. The Medical Monitor will review all AEs, including serious adverse event (SAE) reports. The safety data will also be periodically reviewed by an ISC.
PLANNED NUMBER OF SUBJECTS	Approximately 150
TRIAL POPULATION	• Approximately 150 male and female children who at Visit 1 are 3 to 17 years old, inclusive, diagnosed with GHD, weigh no more than 80 kg, have open epiphyses, and have received at least 0.20 mg hGH/kg/week of daily hGH treatment for ≥ 13 weeks but ≤ 130 weeks • Additionally, children with GHD who at Visit 1 are ≥ 6 months but < 3 years old, weigh at least 5.5 kg, and are either hGH treatment-naïve or have received at least 0.20 mg hGH/kg/week of daily hGH treatment for ≤ 130 weeks
TRIAL ENTRY CRITERIA	**Inclusion Criteria** 1) Investigator-determined GHD diagnosis together with at least one of the following prior to the historical initiation of daily hGH therapy: a. 2 Growth Hormone (GH) stimulation test(s) with peak GH level of ≤10 ng/mL b. Impaired height defined as at least one of the following: i) ≥ 2 SD below the mean height for chronological age and sex when compared to the relevant growth charts: (1) 2006 WHO Child Growth Standards for < 2 years old (2) 2000 CDC Growth Charts for the United States for ≥ 2 years old ii) ≥ 1.5 SDS below mid-parental height c. IGF-1 level ≥ 1 SD below the mean IGF-1 level standardized for age and sex according to the local laboratory reference values d. Bone age x-ray ≥ 6 months less than chronological age e. Diagnosis of at least one additional pituitary hormone deficiency f. Congenital hypopituitarism due to congenital hypothalamic-pituitary defect (eg, ectopic posterior pituitary, pituitary hypoplasia, abnormal stalk, septo-optic dyplasia) or genetic defect (eg, GH1, POU1F1, or PROP1) 2) 6 months to 17 years old, inclusive, at Visit 1

	a. If 3 to 17 years old, are taking daily hGH at a dose of ≥ 0.20 mg hGH/kg/week for at least 13 weeks but no more than 130 weeks prior to Visit 1 b. If ≥ 6 months but < 3 years old, are either hGH treatment-naïve or are taking daily hGH at a dose of ≥ 0.20mg hGH/kg/week for no more than 130 weeks prior to Visit 1 3) Tanner stage < 5 at Visit 1 4) Open epiphyses (bone age ≤14.0 years for females or ≤16.0 years for males) 5) 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 **Exclusion Criteria** 1) Weight of < 5.5 kg or > 80 kg at Visit 1 2) Females of child-bearing potential* (until non-clinical developmental toxicity studies have been completed and confirm participation by females of child-bearing potential to be acceptable) *Although subjects who are of child-bearing potential at the time of enrollment will be exclusionary, subject who begin menses *during* the trial may continue. 3) History of malignant disease 4) Any clinically significant abnormality likely to affect growth or the ability to evaluate growth (eg, chronic diseases or conditions such as renal insufficiency, spinal cord irradiation, hypothyroidism, active celiac disease, malnutrition, or psychosocial dwarfism) 5) Poorly-controlled diabetes mellitus (HbA1c >8.0%) or diabetic complications 6) Known neutralizing antibodies against hGH 7) Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids or oral glucocorticoids, with the exception of hormone replacement therapies for hypopituitarism: hypothyroidism (thyroxine), adrenal insufficiency (hydrocortisone), hypogonadism (sex steroids), diabetes insipidus (desmopressin) **Note:** Children with multiple hormonal deficiencies must be on replacement therapy for at least 13 weeks prior to Visit 1. If taking thyroid replacement therapy, child must be considered clinically euthyroid. If taking glucocorticoid replacement therapy, temporary adjustment, as appropriate, is acceptable. 8) Requiring inhaled glucocorticoid therapy (eg, asthma) at doses higher than those listed below for longer than 4 weeks during the 12 months prior to Visit 1.*

	• Budesonide: 400 µg/d • Fluticasone: 264 µg/d • Beclomethasone: 504 µg/d • Flunisolide: 1000 µg/d • Mometasone: 211 µg/d • Ciclisonide: 264 µg/d *Although need for high-dose inhaled glucocorticoid therapy at the time of enrollment into this trial will be exclusionary, subjects who initiate high-dose inhaled glucocorticoid therapy for asthma *during* the trial may continue. 9) Concomitant administration of one of the following: • Chronic oral glucocorticoids used for more than 3 months of the 12 months prior to Visit 1, other than as replacement therapy for congenital hypopituitarism • Weight-reducing drugs or appetite suppressants, unless used for management of attention-deficit/hyperactivity disorder (ADHD) 10) Major medical conditions, unless approved by Medical Monitor 11) Pregnancy 12) Presence of contraindications to hGH treatment 13) Known or suspected HIV-positive status 14) Known hypersensitivity to the components of the trial medication 15) Likely to be non-compliant with respect to trial conduct (in regards to the subject and/or the parent/legal guardian/caregiver) 16) Participation in any other trial of an investigational agent within 30 days prior to Visit 1 17) Prior exposure to investigational hGH 18) 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 a 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 power of hydrogen (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 2 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)
REFERENCE PRODUCT(S)	None
TREATMENT REGIMENS	TransCon hGH should be administered by the subject (or parent/legal guardian/caregiver) as a once weekly (preferably in the evening) SC injection of 0.24 mg hGH/kg/week. The total dose (volume) of TransCon hGH will be adjusted according to the subject's weight using the TransCon hGH bracketed weight chart at Visit 2. TransCon hGH dose may also be adjusted according to the level of IGF-1 SDS measured at Visit 2 (and/or the C_{max} Visit, as applicable).
PLANNED TRIAL SITES	Up to approximately 50 sites
CRITERIA FOR EVALUATION	**Safety Endpoints** The safety endpoints as measured throughout the 26 weeks of weekly TransCon hGH treatment include the following: • Incidence of AEs • Local tolerability, as assessed by the subject/parents/legal guardians/caregivers and trial staff • Incidence of antibodies against hGH, including neutralizing antibodies • Incidence of antibodies against PEG • Incidence of IGF-1 SDS ≥ 2.0, ≥ 3.0 with confirmation • Parameters of HbA1c and lipids • Hormone levels, including thyroid status and morning cortisol • All other hematology and chemistry parameters • Vital sign measurements

	Efficacy Endpoints The efficacy endpoints as measured at 26 weeks of weekly TransCon hGH treatment include the following: • Annualized HV • ΔHSDS • Proportion of subjects with IGF-1 SDS of 0 to +2.0. Additionally, cut points of -2.0 to +2.0 and -1.0 to +2.0 will be assessed. • Change in IGF-1 SDS • Change in IGFBP-3 SDS **C_{max}/Pharmacodynamic Endpoints** • Expected C_{max} of hGH in subjects < 3 years old • Serum IGF-1 SDS at 1-2 days post-dose in subjects < 3 years old • Serum IGF-1 SDS at 5 days ±1 day post-dose in all subjects **Other Endpoint** • Preference for TransCon hGH or commercially available daily hGH treatment • Satisfaction with weekly TransCon hGH
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 study drug, 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.
SAMPLE SIZE DETERMINATION	A sample size of 150 subjects provides at least 95% probability to observe AEs with a 2% or more incidence rate. It also enables the combined safety database of the clinical program (a sample size of approximately 300 exposed to TransCon hGH for at least 6 months) to have at least 95% probability to observe AEs with a 1% or more incidence rate. As recruiting subjects < 3 years old will prove challenging, an exact sample size for this cohort has not been pre-determined.

TRIAL AND TREATMENT DURATION	The total duration of the trial for an individual subject is up to approximately 31 weeks (up to approximately 4 weeks of screening plus up to 27 weeks of treatment). After successful completion, subjects may be eligible to enter the CT-301EXT (extension) trial that will provide treatment with weekly TransCon hGH treatment until: a) product approval and commercial availability in the local market; b) the Sponsor makes alternative arrangements for continued patient access; or c) treatment 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 9-item Treatment Satisfaction Questionnaire for Medication
C&OS-P	Convenience & Overall Satisfaction domains of the abbreviated 9-item Treatment Satisfaction Questionnaire for Medication – Parent
CFR	Code of Federal Regulations
cm	centimeter
C_{max}	maximum observed concentration
CSDS	Child Sheehan Disability Scale
CSDS-C	Child Sheehan Disability Scale – Child
CSDS-P	Child Sheehan Disability Scale – Parent
CRO	Contract Research Organization
d	day
DCC	dual chamber cartridge
dL	deciliter
DMP	data management plan
E coli	*Escherichia coli*
EC	Ethics Committee
eCRF	electronic case report form
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone-releasing hormone
HbA1c	hemoglobin A1c

hCG	human chorionic gonadotropin
hGH	human
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
SGA	small for gestational age
SHOX	short stature homeobox
SIV	site initiation visit
SOP	standard operating procedures

SUSAR	suspected unexpected serious adverse reaction
sWFI	sterile water for injection
T_{max}	time to maximum observed concentration
TMPD	N1,-N1,-N3-trimethyl-1,3-propane-diamine
TQSM	Treatment Satisfaction Questionnaire for Medication
TSQM-9	Abbreviated 9-item Treatment Satisfaction Questionnaire for Medication
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 secretion of hGH is pulsatile in nature; the majority of secretory pulses (up to 70% of daily secretion) occur with the first episode of slow-wave sleep. During childhood hGH levels are relatively stable until puberty, when the hGH pulse amplitude is elevated with no change in the frequency of pulses; afterwards hGH pulse levels gradually decline through adulthood. hGH production and secretion are regulated by multiple factors; growth hormone-releasing hormone (GHRH) and ghrelin are the most significant stimulators, while somatostatin is the strongest inhibitor.

The hGH gene cluster is located on human chromosome 17q22-24, encoding a 191 amino-acid protein of 22 kDa and a less abundant 20 kDa hGH molecule (as well as related proteins). hGH stimulates the hepatic production and release of IGF-1 which in turn acts on target tissues and is likely responsible for most, but not all, activities of hGH. IGF-1 is also produced by growth cartilage in response to hGH, where it acts locally as a paracrine-autocrine growth factor. hGH also has direct effects in the growth plate (eg, stimulation of chondrogenesis, in concert with IGF-1 action) and in adipocytes (eg, lipolysis, in opposition to IGF-1 mediated lipogenesis). IGF-1 is found in association with specific IGF-binding proteins whose main functions are to extend IGF-1 half-life in circulation, transport IGF-1 to target cells, and modulate its biological actions.

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.

Fifty years have passed since the human pituitary hGH extract was purified and the first GHD patient was successfully treated. Contamination with infectious agents (Creutzfeld-Jakob prions) led to discontinuation of its use in 1985 (*Kemp 2014*). A recombinant human growth hormone (somatropin) was then produced by introducing the human DNA sequence into *Escherichia coli* (*E coli*) and later produced in other cell lines; it first became commercially available in 1985. The product is identical to natural hGH with 191 amino acids. Since then, several hundred thousand children have received hGH for growth impairment. In addition, hGH has been successfully used to treat growth impairment associated with a number of conditions such as Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, short stature homeobox (SHOX) deficiency, Noonan syndrome, idiopathic short stature, and children born small for gestational age (SGA). The safety and efficacy profile of daily hGH preparations in pediatric and adult populations is well established and deemed satisfactory.

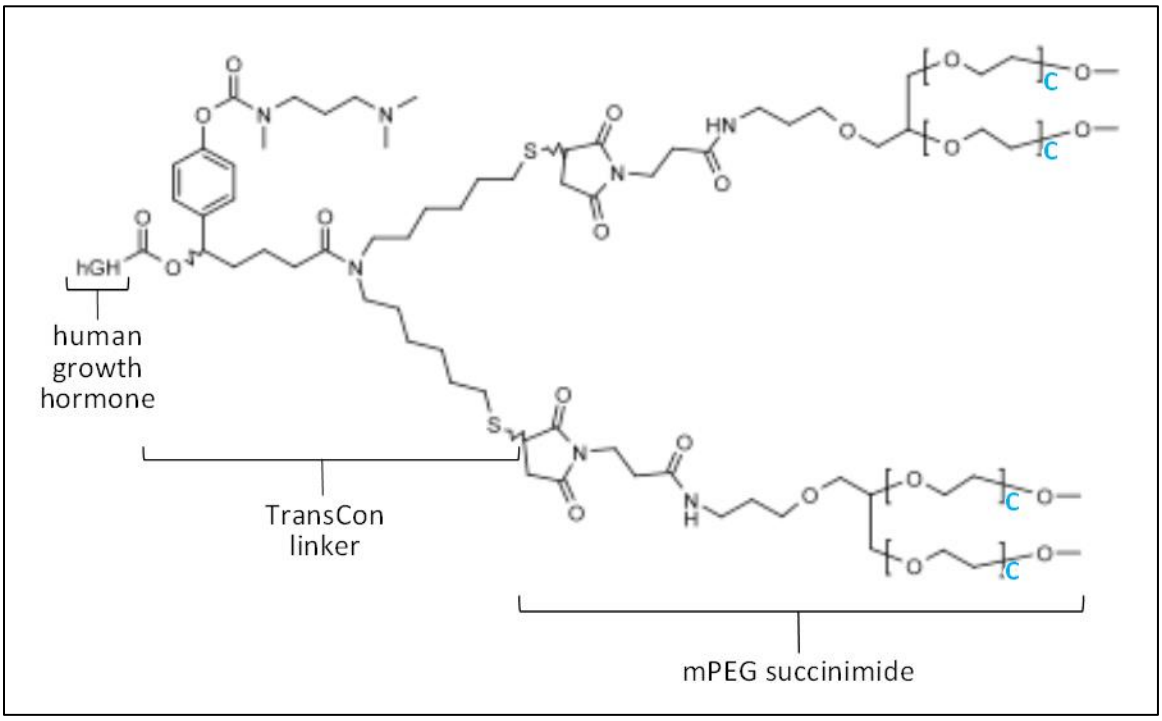
At the present time, however, there are no commercially available sustained-release or long-acting hGH preparations. Currently hGH is available only as daily injection formulations, thus causing a significant burden and interruption of normal daily life to children and their parents, as well as compliance 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.

To address this unmet need, the Sponsor developed TransCon hGH, part of the company's proprietary pipeline of drugs that utilize TransConjugation (ie, transiently attaching proteins or small molecules to a carrier) to create an inactive prodrug. The prodrug is stable during storage, but, after subcutaneous injection, the prodrug enters the bloodstream where the active ingredient (hGH) undergoes sustained release under physiological temperature and pH in a controlled and predictable manner. This ensures an extended in vivo half-life and more constant drug concentration levels than observed when using traditional conjugation methods (eg, permanent PEGylation). TransConjugation technology is designed to provide several key benefits to pharmaceutical product development:

1) Efficacy/safety profiles similar to daily hGH therapy
2) Extended in vivo half-life of hGH while maintaining exposure in the optimal therapeutic range

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 (Figure 1).

Figure 1
Structure of TransCon PEG40 hGH (ACP-011)



hGH = human growth hormone; mPEG = methoxypolyethylene glycol, c = 250

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 has 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 known 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 PEG80 hGH (ACP-001), in which the carrier was 80 kDa mPEG, and for which 4 clinical trials were conducted: 2 phase 1 trials in healthy adults, 1 phase 2 trial in adult GHD, and 1 6-month phase 2 trial in pediatric GHD. Acceptable safety, pharmacokinetics (PK), and pharmacodynamics (PD) were shown in these trials. Importantly, safety, tolerability, and efficacy comparable to Genotropin were shown in the phase 2 pediatric GHD trial, as well as comparable exposure (C_{max} and area under the curve (AUC)) when compared to the same weekly dose of daily hGH.

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 both PK and PD 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 PK and PD models have supported the suitability of TransCon hGH (ACP-011) for once-weekly treatment of patients.

Overall, the toxicity studies with TransCon PEG40 hGH did not identify any unexpected findings or significant concerns, following either weekly repeat dosing in cynomolgus monkey for up to 26 weeks, for up to 5 weeks in the rat, or following in utero exposure in rat, or during critical phases of pre- and post-natal development in rat. TransCon hGH (ACP-011) and derived hydrolysis products were not genotoxic when assessed in a standard battery of genotoxicity tests, and no adverse effects were observed in stand-alone safety pharmacology studies in the rat. Following weekly repeat dosing for up to 26 weeks at dose levels 20-fold above the expected therapeutic dose, a minimal increased body weight gain was observed in the juvenile cynomolgus monkey. Non-adverse test article-related microscopic findings, interpreted as exaggerated pharmacology, were limited to the mammary glands in both male and female animals. The findings included small amounts of exudate, ductal dilation, vacuolation, mononuclear cell infiltrate, and minimal lobular hyperplasia in females only, and only at the 4.8 mg hGH/kg dose level. Hyperplasia is a recognized finding at high growth hormone doses in monkeys, presumably reflecting cross-reactivity with the prolactin receptor.

Additionally, the nonclinical safety pharmacology program for TransCon hGH (ACP-011) did not identify adverse effects on the function of the central nervous, pulmonary, or cardiovascular systems. No effects on the cardiovascular system were observed in the adult or juvenile

cynomolgus monkey studies after once-weekly dosing for up to 26 weeks at doses up to 4.8 mg hGH/kg/week (highest dose tested). In all studies, multiple time points were selected to ensure adequate coverage of the T_{max} of the parent prodrug and the autohydrolysis products. Furthermore, an in vitro hERG assay was performed as part of the TransCon hGH (ACP-001) nonclinical safety program and was deemed relevant by FDA and BfArM to support development of TransCon hGH (ACP-011). In this study (Study 790652), the application of partly hydrolyzed TransCon hGH (ACP-001) containing released hGH (nominal concentration of 72 µg/mL), remainder mPEG80-linker (nominal concentration of 289 µg/mL), and TMPD (nominal concentration of 235 ng/mL) did not produce a statistically significant effect on the hERG ion channel tail current.

Comprehensive QSAR assessments evaluating the potential carcinogenicity, genotoxicity and cardiotoxicity of TMPD have been performed. Based on these evaluations, mainly employing FDA data sets of modules built by the ICSAS group of the CDER branch of the FDA in 2010, it was concluded that structural elements of TMPD do not show evidence of carcinogenicity, genotoxicity or cardiotoxicity (MultiCASE 2011).

DEREK did not identify any alerts linked to mutagenicity, genotoxicity, carcinogenicity, hERG channel inhibition, or any of the DEREK rapid prototype clinical related endpoints such as bradycardia, hepatotoxicity or nephrotoxicity. Leadscope investigations were marginally positive in the E coli mutagenicity model but negative in the mouse lymphoma model. TMPD was not predicted to be carcinogenic in rodent models (CTS 2011).

Additionally, TransCon hGH has been studied in two Phase 1 trials in adults (ACP 001 PK/PD-001, and ACP 001 CT-003), a Phase 2 trial in adults with GHD (ACP 001 CT-002), and a 26-week Phase 2 trial in treatment-naïve children with GHD (ACP 001 CT-004). Electrocardiograms in each of these trials did not demonstrate any drug-relate cardiotoxicity.

The nonclinical data are provided in further detail in the Investigator's Brochure.

5.3 Clinical Experience

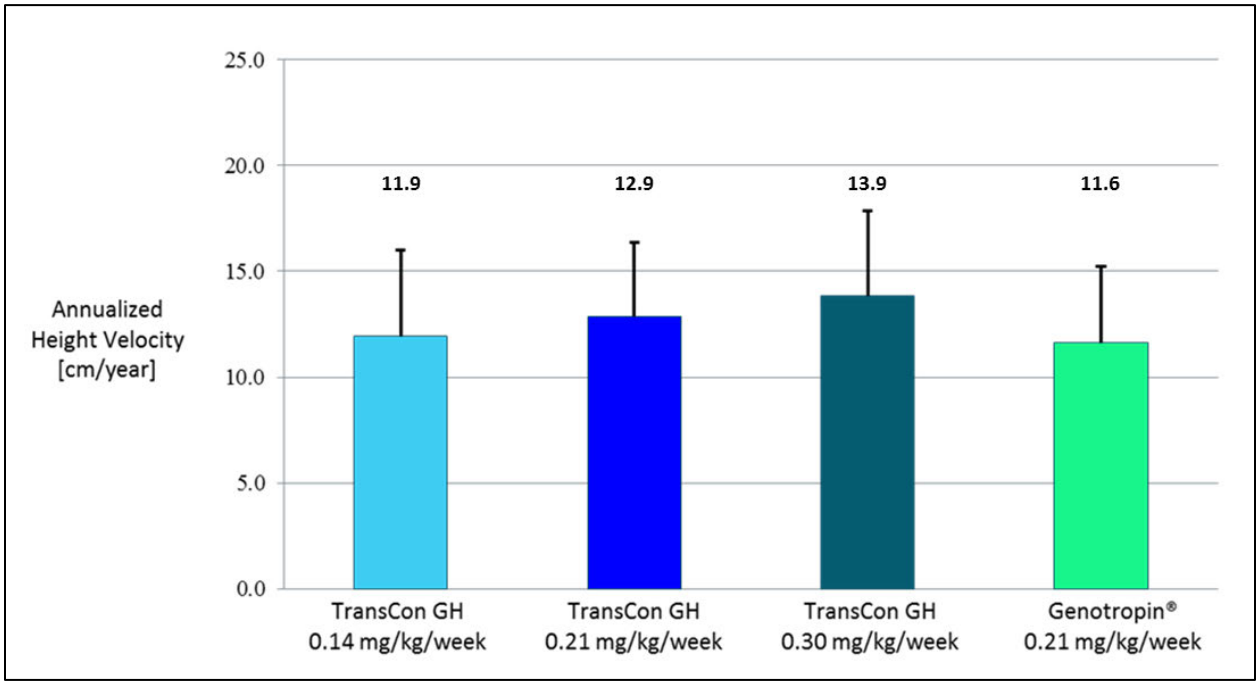
A first phase 1 clinical trial of TransCon hGH (ACP-001) in healthy male volunteers has been conducted as a randomized, double-blind, dose-escalation trial versus placebo and daily hGH (Omnitrope) investigating the safety, tolerability, PK and PD response in 44 healthy male subjects. No negative effects 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. Detailed information is given in the Investigator's Brochure.

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. The PK results showed that dose-linearity was observed for AUC and C_{max} of hGH in 29 subjects. TransCon hGH (ACP-001) slowly released hGH in a sustained, controlled manner and thereby increased the overall exposure of hGH, making it suitable for once-a-week dosing. The PD results showed that ACP-001 elevated IGF-1 over the period of 1 week, with an AUC similar to that provided by daily hGH.

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 study drug (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 2).

Figure 2
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. This subject, treated with the lowest dose of TransCon hGH (0.14 mg hGH/kg/week), demonstrated an annualized HV of 19.0 cm/year compared to the cohort mean of 11.9 cm/year. No neutralizing antibodies were detected. Maximum and average hGH blood concentration were comparable between equivalent weekly doses of TransCon hGH and daily hGH.

A dose-proportional increase in IGF-1 levels into the normal range was observed following dosing of the 3 TransCon hGH dose levels. Consistent with expectations, transient point values of IGF-1 standard deviation score > +2.0 have been observed in a small number of subjects and primarily in the high-dose treatment arm (0.30 mg/kg/week).

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. The single probably related AE was a subject with iron deficiency

anemia, which the investigator attributed to rapid growth. Injection site reactions, mainly mild erythema (phase 2 AGHD) and pain (phase 2 pediatric GHD), occurred across all treatment groups.

TransCon hGH (ACP-011) was found to be bioequivalent to TransCon hGH (ACP-001) in a phase 1 single center, randomized, open-label trial to evaluate the safety, tolerability, PK, and PD of ACP-011 at doses of 0.24, 0.30, and 0.42 mg hGH/kg administered subcutaneously to healthy subjects. There was a crossover portion in the trial to compare the PK and PD parameters of ACP-011 and ACP-001 at the 0.24 mg hGH/kg dose level.

The ratios of the means for C_{max} and AUC for both released hGH and IGF-1 fell within the bioequivalence limits of 80% – 125%. Following a single subcutaneous administration of TransCon hGH (ACP-011), free hGH showed a dose dependent increase in mean serum C_{max} and AUC within the dose range 0.24 to 0.42 mg hGH/kg. Serum concentrations increased rapidly with a median T_{max} of 16.0 to 36.0 hours. Elimination appeared in a mono-phasic manner and the mean terminal half-life ranged from 21.8 to 25.4 hours independent of dose.

Following the switch from ACP-001 to ACP-011 described above, a global phase 3 trial, called the TransCon hGH 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 study 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. Patients 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. Patients completing the trial on study drug may then enroll in the planned phase 3, open-label extension trial, CT-301EXT.

5.4 Trial Rationale

In comparison to the heiGHt trial, the primary objective of this trial is to assess the safety of undergoing the switch from a commercially available daily hGH product to weekly TransCon hGH (ACP-011) in children with GHD (6 months-17 years old, inclusive). Adolescents up to 17 years old who have not completed puberty and infants down to 6 months of age are included to obtain additional safety and tolerability data of TransCon hGH in a broader age range than being evaluated in the heiGHt trial, which is evaluating TransCon hGH in subjects with GHD

age ≥3 to ≤12 years (boys) and ≥3 to ≤11 years (girls), inclusive. Preference and satisfaction for dosing with TransCon hGH or commercially available daily hGH will also be evaluated.

5.5 Summary of Potential Risks and Benefits

TransCon hGH (ACP-011) is a new hGH prodrug product with a proposed once-weekly dosing regimen designed to overcome the inconvenience and suboptimal compliance of daily hGH injections and is anticipated to have a comparable safety and efficacy profile to currently approved daily hGH products, while maintaining exposure (C_{max} and AUC) in the optimal therapeutic range and biodistribution established by 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*).

6. OBJECTIVES

6.1 Primary Objective

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

6.2 Secondary Objectives

- To assess annualized HV in children with GHD at 26 weeks of weekly TransCon hGH treatment
- To assess the proportion of subjects with IGF-1 SDS in the normal range of 0.0 to +2.0 at 26 weeks of weekly TransCon hGH treatment
- To evaluate ΔHSDS in children with GHD at 26 weeks of weekly TransCon hGH treatment
- To determine the incidence of antibodies against TransCon hGH (anti-hGH and anti-PEG) in children with GHD over 26 weeks of weekly TransCon hGH treatment
- To assess the expected C_{max} of TransCon hGH in children with GHD ≥ 6 months to < 3 years old
- To assess the preference for weekly TransCon hGH or commercially available daily hGH treatment
- To assess the treatment satisfaction of weekly TransCon hGH over time

7. TRIAL DESIGN

7.1 Overall Trial Design and Plan

7.1.1 Trial Design

This is a multicenter phase 3, open-label, 26-week trial of weekly TransCon hGH in children 6 months to 17 years old, inclusive, with GHD. Children ≥ 6 months but < 3 years old with GHD may be hGH-treatment naïve or have been treated with daily hGH (≥ 0.20 mg hGH/kg/week) for ≤ 130 weeks. Children 3 to 17 years old, inclusive, must have been treated with daily hGH (≥ 0.20 mg hGH/kg/week) for ≥ 13 weeks but ≤ 130 weeks and be without evidence of closed epiphyses.

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

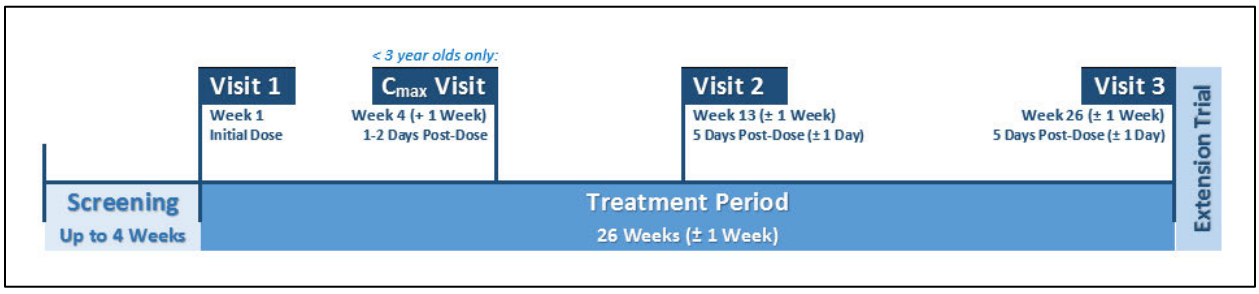
The trial consists of:

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

The total duration of participation for each subject in the trial will therefore be up to approximately 31 weeks (Figure 3).

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

Figure 3
Overall Trial Design



7.1.2 Measures Taken to Minimize Bias

A subject's visits should be performed at approximately the same time of day. Also, assessments should be performed in a similar fashion at each visit. 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, including any subjects who discontinue the study drug early
- The Informed Consent Form (ICF) and Assent Form will include a statement educating subjects and parents/legal guardians about the scientific importance of their data even if the subject discontinues study drug early
- 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
- C_{max} Visit, Visit 2, and Visit 3 have visit windows to allow flexibility for clinic attendance (see Section 10.2.2)
- Fasting is not required to improve attendance at all study visits
- Every effort will be made to contact subjects/parents/legal guardians or other family members to maintain contact with the clinic

7.2 Trial Sites

The trial will be conducted at up to approximately 50 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 study drug and/or 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 study drug

- 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

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

- The site cannot include an adequate number of subjects
- 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 with the investigator
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation

8. SUBJECT POPULATION

Approximately 150 male and female children who at Visit 1 are 3 to 17 years old, inclusive, diagnosed with GHD, weigh no more than 80 kg, have open epiphyses, and have received at least 0.20 mg hGH/kg/week of daily hGH treatment for ≥ 13 weeks but ≤ 130 weeks may enter this trial.

Additionally, children with GHD who at Visit 1 are ≥ 6 months but < 3 years old, weigh at least 5.5 kg, and are either hGH treatment-naïve or have received at least 0.20 mg hGH/kg/week of daily hGH treatment for ≤ 130 weeks may enter this trial.

8.1 Trial Entry Criteria

8.1.1 Inclusion Criteria

1) Investigator-determined GHD diagnosis together with at least one of the following prior to the historical initiation of daily hGH therapy:
   a. 2 GH stimulation test(s) with peak GH level of ≤10 ng/mL
   b. Impaired height defined as at least one of the following:
      i) ≥ 2 SD below the mean height for chronological age and sex when compared to the relevant growth charts:
         (1) 2006 WHO Child Growth Standards for < 2 years old

(2) 2000 CDC Growth Charts for the United States for ≥ 2 years old

ii) ≥ 1.5 SDS below mid-parental height

c. IGF-1 level ≥ 1 SD below the mean IGF-1 level standardized for age and sex according to the local laboratory reference values

d. Bone age x-ray ≥ 6 months less than chronological age

e. Diagnosis of at least one additional pituitary hormone deficiency

f. Congenital hypopituitarism due to congenital hypothalamic-pituitary defect (eg, ectopic posterior pituitary, pituitary hypoplasia, abnormal stalk, septo-optic dyplasia) or genetic defect (eg, GH1, POU1F1, or PROP1)

2) 6 months to 17 years old, inclusive, at Visit 1

a. If 3 to 17 years old, are taking daily hGH at a dose of ≥ 0.20 mg hGH/kg/week for at least 13 weeks but no more than 130 weeks prior to Visit 1

b. If ≥ 6 months but < 3 years old, are either hGH treatment-naïve or are taking daily hGH at a dose of ≥ 0.20mg hGH/kg/week for no more than 130 weeks prior to Visit 1

3) Tanner stage < 5 at Visit 1

4) Open epiphyses (bone age ≤14.0 years for females or ≤16.0 years for males)

5) 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) Weight of < 5.5 kg or > 80 kg at Visit 1

2) Females of child-bearing potential* (until non-clinical developmental toxicity studies have been completed and confirm participation by females of child-bearing potential to be acceptable)
*Although subjects who are of child-bearing potential at the time of enrollment will be exclusionary, subject who begin menses *during* the trial may continue.

3) History of malignant disease

4) Any clinically significant abnormality likely to affect growth or the ability to evaluate growth (eg, chronic diseases or conditions such as renal insufficiency, spinal cord irradiation, hypothyroidism, active celiac disease, malnutrition or psychosocial dwarfism)

5) Poorly-controlled diabetes mellitus (HbA1c >8.0%) or diabetic complications

6) Known neutralizing antibodies against hGH

7) Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids or oral glucocorticoids, with the exception of hormone replacement therapies for hypopituitarism: hypothyroidism (thyroxine), adrenal insufficiency (hydrocortisone), hypogonadism (sex steroids), diabetes insipidus (desmopressin).

   Note: Children with multiple hormonal deficiencies must be on replacement therapy for at least 13 weeks prior to Visit 1. If taking thyroid replacement therapy, child must be considered clinically euthyroid. If taking glucocorticoid replacement therapy, temporary adjustment, as appropriate, is acceptable.

8) Requiring inhaled glucocorticoid therapy (eg, asthma) at doses higher than those listed below for longer than 4 weeks during the 12 months prior to Visit 1.*

   - Budesonide: 400 µg/d
   - Fluticasone: 264 µg/d
   - Beclomethasone: 504 µg/d
   - Flunisolide: 1000 µg/d
   - Mometasone: 211 µg/d
   - Ciclisonide: 264 µg/d

   *Although need for high-dose inhaled glucocorticoid therapy at the time of enrollment into this trial will be exclusionary, subjects who initiate high-dose inhaled glucocorticoid therapy for asthma *during* the trial may continue.

9) Concomitant administration of one of the following:

   - Chronic oral glucocorticoids used for more than 3 months of the 12 months prior to Visit 1, other than as replacement therapy for congenital hypopituitarism
   - Weight-reducing drugs or appetite suppressants, unless used for management of ADHD

10) Major medical conditions, unless approved by Medical Monitor

11) Pregnancy

12) Presence of contraindications to hGH treatment

13) Known or suspected HIV-positive status

14) Known hypersensitivity to the components of the trial medication

15) Likely to be non-compliant with respect to trial conduct (in regards to the subject and/or the parent/legal guardian/caregiver)

16) Participation in any other trial of an investigational agent within 30 days prior to Visit 1

17) Prior exposure to investigational hGH

18) 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. Additionally, the investigator may discontinue the treatment of a subject at any time if considered to be in the subject's best interest. Unless informed consent is withdrawn, any subject who discontinues treatment should be encouraged to remain in the trial and attend all subsequent clinic visits. See Section 7.3.1 for a list of stopping rules governing early termination of subjects from the trial.

In the case of premature discontinuation of a subject's participation in the trial (eg, withdrawal of informed consent), the investigator should schedule an Early Termination Visit to collect data, particularly AE follow-up data (if applicable), and to collect blood for laboratory evaluations. This visit should contain all assessments from Visit 3 (Week 26), and should be documented in the eCRF together with the reason(s) for trial discontinuation. In the case of treatment discontinuation for causes other than withdrawal of informed consent, subjects should be urged to remain in the trial and attend all subsequent trial visits. An Early Termination Visit is not required for subjects who remain in the trial after discontinuing study drug. However, if the subject is not willing to attend all subsequent trial visits, this should be considered a withdrawal from the trial and an Early Termination Visit should be scheduled.

Every effort should be made to observe subjects who have received at least 1 dose of study drug for the entire observation period, even if they discontinued trial treatment. The investigator should make every attempt to contact the subject/parent/legal guardian via phone to arrange the appropriate follow-up assessment(s) for such subjects.

8.3 Subject Replacement Criteria

Subjects who terminate early are not expected to be replaced.

9. TREATMENTS

9.1 Investigational Product

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

- Prefilled syringes with 1 mL sWFI
- Syringes for administration
- Needles for reconstitution and administration

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

9.2 Labeling

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

9.3 Treatment Administered

TransCon hGH will be provided as a lyophilized powder in single-use glass vials to be reconstituted with 1 mL sWFI. Two concentrations will be available, the less concentrated for lighter weight subjects, the more concentrated for higher weight subjects:

- 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.

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 except at Visit 1 where the trial staff may administer the first dose. To minimize local side effects, it is recommended to rotate the 6 injection sites in a subsequent manner (eg, right thigh, right abdomen, right buttock, left thigh, left abdomen, left buttock).

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/mL	0.13	22.0 mg/mL	Contact Medical Monitor
6.7-7.9	11.0 mg/mL	0.16	22.0 mg/mL	Contact Medical Monitor
8.0-9.5	11.0 mg/mL	0.19	22.0 mg/mL	Contact Medical Monitor
9.6-11.4	11.0 mg/mL	0.23	22.0 mg/mL	Contact Medical Monitor
11.5-13.9	11.0 mg/mL	0.27	22.0 mg/mL	Contact Medical Monitor
14.0-16.4	11.0 mg/mL	0.33	22.0 mg/mL	Contact Medical Monitor
16.5-19.9	11.0 mg/mL	0.39	22.0 mg/mL	Contact Medical Monitor
20.0-23.9	11.0 mg/mL	0.47	22.0 mg/mL	Contact Medical Monitor
24.0-28.9	22.0 mg/mL	0.29	11.0 mg/mL	0.57
29.0-34.9	22.0 mg/mL	0.35	11.0 mg/mL	0.69
35.0-41.9	22.0 mg/mL	0.41	11.0 mg/mL	0.83
42.0-50.9	22.0 mg/mL	0.50	11.0 mg/mL	0.50 + 0.50
51.0-60.5	22.0 mg/mL	0.60	11.0 mg/mL	0.60 + 0.61
60.6-73.4	22.0 mg/mL	0.73	11.0 mg/mL	0.73 + 0.73
73.5-87.7	22.0 mg/mL	0.88	11.0 mg/mL	0.88 + 0.88

[a] To be used only when drug availability requires
kg = kilogram; mg = milligram; mL = milliliter

The reason for administering the exact volume as per Table 1 (rather than calculating the exact dose) is as follows. At the conclusion of this 26-week trial, if eligible, subjects may choose to enter the extension trial, CT-301EXT, during which TransCon hGH will initially be administered by syringe and needle. When the 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 auto-injector.

With the auto-injector, TransCon hGH will be provided in single-use dual chamber cartridges (DCCs). Multiple DCC presentations will be available containing 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. The intention within this trial is to mimic dose increments that will eventually be administered via the auto-injector in the CT-301EXT (extension) Trial.

Additionally, dosing based on volumes for weight ranges with 20% bracketing assures that all subjects will receive an average of 0.24 mg/kg/week over the course of the trial.

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 by trial staff and sent home with the subjects/ parents/legal guardians to be stored according to its labeling.

Further details are provided in the trial 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/kg/week dose of TransCon hGH. Treatment guidelines support initiation of hGH at a 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. To align the starting dose across the TransCon hGH program, the same dose has been chosen for the current trial. Given non-compliance rates on daily hGH doses versus the expected increased compliance in this trial, even subjects entering on 0.30 mg hGH/kg/week will likely do well on the lower TransCon hGH dose. Importantly, IGF-1 levels, along with other safety parameters discussed in Section 9.6, will be measured at Visit 2 (and the C_{max} Visit, as applicable) and, if needed, changes in dosing 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 Monitor pre-approval.

At Visit 2, the TransCon hGH dose will be adjusted by the investigator based on weight (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 Monitor). Thus, if the IGF-1 SDS measured at Visit 2 (or the C_{max} Visit, as applicable) is < 0 SDS, and following confirmation of IGF-1 level as < 0 SDS by a second measurement collected 5 days post-dose (±1 day) at an unscheduled visit, the dose may be increased by approximately 20% to the next higher weight bracket by the investigator (See Section 9.3).

9.6.2 Stopping/Dose Reductions

The investigator (with Medical Monitor pre-approval) or Medical Monitor (and, if needed, with the ISC review) may stop or reduce the dose of study drug for an individual subject at any time during the trial 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

  Subjects who are sexually active must use an effective form of contraception
- IGF-1 > +2.0 SDS measured at Visit 2 (or the C_{max} Visit, as applicable) should be confirmed by a second measurement collected 5 days post-dose (±1 day) at an unscheduled visit. If the IGF-1 SDS is still elevated above +2.0, the TransCon hGH dose may be decreased by approximately 20% to the next lower weight bracket, unless a different target is identified in consultation with the Medical Monitor.

  Any re-establishment of the original dose (0.24 mg hGH/kg/week) due to a subsequent sub-optimal IGF-1 response should receive prior approval by the Medical Monitor.
- Substantially reduced IGF-1 and growth response or evidence of a hypersensitivity to TransCon hGH
- Evidence of clinically significant pre-diabetes or diabetes (HbA1c > 6.2% measured at Visit 2 and an absolute increase of 0.5% from Screening HbA1c) should be confirmed by a second measurement at an unscheduled visit. If the repeat values are the same or higher, the TransCon hGH dose may be decreased by approximately 20% to the next lower weight bracket.* If appropriate follow-up monitoring shows progressively worsening glucose intolerance, additional TransCon hGH dose adjustments may be appropriate.

  * If a subject had evidence of borderline glucose intolerance or diabetes prior to starting study drug (eg, fasting plasma glucose (FPG) 98 mg/dL and HbA1c 5.9%), treatment of hyperglycemia should occur prior to study drug treatment adjustment.
- Clinical evidence of benign intracranial hypertension (BIH) based on history and physical exam, including visual changes, headaches, nausea, vomiting, and/or papilledema on fundoscopy should result in discontinuation of TransCon hGH treatment and clinical management

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

- *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 treatment is discontinued, all subsequent visits and assessments should continue as planned. For additional details, refer to Section 8.2.

9.7 Drug Accountability

Trial site staff will be supplied with the study drug and ancillary supplies to distribute as required to subjects/parents/legal guardians. Dedicated site staff will be responsible for study drug and associated procedures, as well as ancillary supplies, exercising accepted medical and pharmaceutical practices. Study drug 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 study drug 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 IWRS will be the only drug accountability documentation by trial sites. Clinical investigators will not be expected to maintain paper source documentation of drug inventory, dispensing, and accountability.

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 study drug and ancillary supplies, along with a copy of the inventory records from the IWRS.

IMPORTANT: Under no circumstances will the investigator allow study drugs 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 will be instructed to return all empty study drug vials at Visit 2 and Visit 3. The completed subject diary, which captures the date, time, person administering study drug, and dose of study drug, should be returned at each site visit. All study drug, used and unused, shall be returned at the end of the subject's participation in the trial or at the visit following study drug stoppage.

9.9 Prior and Concomitant Therapies

9.9.1 Prior Therapy

Prior therapy is considered any therapy given within 4 weeks prior to the Screening Visit and will be recorded on the appropriate eCRF page.

9.9.1.1 Previous hGH Therapies

At Visit 1, subjects ≥ 3 years old must be on current daily hGH (≥ 0.20 mg hGH/kg/week) for ≥ 13 weeks and ≤ 130 weeks, while subjects ≥ 6 months to < 3 years old may be either treatment-naïve or be on current daily hGH (≥ 0.20 mg hGH/kg/week) for ≤ 130 weeks. The current hGH name, dose, injection device type, and start date will be recorded on the appropriate eCRF page. Subjects should remain on a stable dose between Screening and Visit 1.

Subjects are to be instructed to take their regular dose of hGH the evening before Visit 1 but NOT 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 study drug 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 Monitor.

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. Glucocorticoid therapy for indications other than adrenal replacement (eg, asthma) may be administered in a dose equivalent to inhaled budesonide of not more than 400 µg/d.*

   Approximately equivalent doses:

   - fluticasone: 264 µg/d
   - beclomethasone: 504 µg/d
   - flunisolide: 1000 µg/d
   - mometasone: 211 µg/d
   - ciclisonide: 264 µg/d

   *Although need for high-dose glucocorticoid therapy at the time of enrollment into this trial will be exclusionary, subjects who initiate high-dose inhaled glucocorticoid therapy for asthma *during* the trial may continue in this trial.

3. Treatment for diabetes
4. 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

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

10. TRIAL PROCEDURES

10.1 Trial Duration

Each subject's participation is expected to last up to approximately 31 weeks, as follows:

- Screening Period: up to approximately 4 weeks
- Treatment Period: up to 27 weeks of repeat dosing

10.2 Trial Periods and Visits

Following the Screening Period, enrolled subjects will attend a total of 3* morning trial visits:

- **Visit 1:** Week 1, Day 1 (1st week/day of dosing)
- **Visit 2:** Week 13 (±1 week), 5 days (±1 day) after the 12th, 13th or 14th dose
- **Visit 3:** Week 26 (±1 week), 5 days (±1 day) after the 25th, 26th or 27th dose

* All subjects < 3 years old at Visit 1, will also have the following morning visit:

- **C_{max} Visit:** Week 4 (+1 week), **1-2** days after the 4th or 5th dose

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 between visits.

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

For detailed descriptions of assessments refer to Section 11.

10.2.1 Screening (Week -4 to -1, Day -28 to -1)

Prior to any protocol related activities or Screening evaluations, informed consent will be obtained from each potential subject in accordance with GCP and regional regulatory requirements. The format and content of the ICF must be approved by the appropriate institutional review board/independent ethics committee/human research ethics committee (IRB/HREC/IEC) prior to implementation. Release of medical information authorization should also be obtained at the time of informed consent.

The Screening Period will last up to approximately 4 weeks during which clinical data will be collected and investigations will be performed to establish the subject's eligibility for the trial and establish the subject's baseline status. The decision on re-screening will be made on a case by case basis by the Medical Monitor.

The following will be performed during Screening:

1) Medical history
    a. Data supporting a diagnosis of GHD (if available), including dates performed
        i. Height at diagnosis
        ii. Weight at diagnosis
        iii. Prior height measurements over the 52 weeks prior to diagnosis
            - Up to 4 prior height measurements may be provided
            - If more than 4 height measurements are available, only one measurement within any 13 week period should be provided
        iv. Reported or measured biological parental heights
        v. IGF-1 and IGFBP-3 levels at diagnosis, including SDS
        vi. GH stimulation test results
        vii. Karyotype results in females
    b. Pituitary deficiencies
    c. Other relevant diagnoses

d. Prior height measurements over the 52 weeks prior to Screening
   - Up to 4 prior height measurements may be provided
   - If more than 4 height measurements are available, only one measurement within any 13 week period should be provided

e. Prior and current therapies

2) Vital sign measurements
3) Height and weight measurements
4) Limited physical examination
5) Pubertal status assessment (Tanner stage)
6) **Tanner stage 4 only:** Bone age x-ray (if an x-ray performed within the past 52 weeks with a bone age delay of ≥ 6 months is not available)
7) Fundoscopy (to rule out blurred disc margins)
8) Blood collection for the following laboratory assessments*:
   a. IGF-1 and IGFBP-3
   b. 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, hGH and PEG serum levels may be analyzed for the interpretation of immunogenicity titers.
   c. Hormone/glycemic Status (TSH, FT4, FT3, morning cortisol, and HbA1c)
   d. Chemistry
   e. Hematology
   f. Lipid panel
   g. **For female subjects of child-bearing potential only:** hCG

* Banked blood samples may be used for additional characterization of anti-drug antibody responses.

10.2.2 Treatment Period (Weeks 1 to 27, Days 1 to 189)

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

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

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

- Visit 3 will be performed during Week 26 (±1 week), 5 days (±1 day) post-dose
  - If during Week 25, Visit 3 must occur on Days 173 to 175
  - If during Week 26, Visit 3 must occur on Days 180 to 182
  - If during Week 27, Visit 3 must occur on Days 187 to 189

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

- C_{max} Visit to be performed during Week 4 (+1 week), 1-2 days after the 4th or 5th dose
  - If during Week 4, C_{max} Visit must occur on Days 23-24
  - If during Week 5, C_{max} Visit must occur on Days 30-31

Attempts should be made to 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 between the visits.

10.2.2.1 Visit 1 (Week 1, Day 1)

Prior to Visit 1, investigator will review all data collected during Screening Period to determine subject's eligibility.

The following will be performed at Visit 1:

1) Patient-reported outcome questionnaires

   Only completed for subjects treated with daily hGH prior to enrollment:

   a. CSDS-P

   b. **For subject ≥ 9 years old (at Visit 1) only:** CSDS-C

   c. C&OS-P

2) Review changes from baseline status
3) Concomitant medication review
4) Vital sign measurements
5) Height and weight measurements
6) Limited physical examination
7) Pubertal status assessment (Tanner stage)

8) Study drug & subject diary dispensing

9) Study drug preparation/administration 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)
- Includes instructions that administration of study drug should occur at approximately the same time of day on the same day of the week throughout the trial, encouraging evening dosing. Details regarding adjustment of a subject's established dose day/time are provided in the trial manual.

10) Subject diary training

- May be also performed at other visits, as needed
- Includes completion of subject diary with trial staff at time of the first study drug injection and 15 minutes, 1 hour and 2 hour post-dose
- Includes reminder to complete Week 6 questionnaires prior to 6th dose of study drug

11) On-site study drug administration

- Study drug volume calculated based on weight measurement obtained at Visit 1 and the bracketed weight chart for TransCon hGH
- May be administered by either trial staff or subject/parent/legal guardian/caregiver

12) Local tolerability assessment

- Assessed at time of the first study drug injection and 15 minutes, 1 hour and 2 hour post-dose

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 treatment to accommodate home administration of TransCon hGH. Extended support may be offered until subjects/parents/legal guardians are comfortable assuming responsibility for administration of the study drug. See Section 9.3 for details regarding TransCon hGH administration and Section 9.6 for details regarding dose adjustments after Visit 1.

10.2.2.2 C_{max} Visit (Week 4-5, Day 23-24 or Day 30-31)

Only subjects < 3 years old (at Visit 1) will attend the C_{max} Visit at which the following will be performed:

1) Concomitant medications

- Includes review of subject diary

2) AE review
   - Includes review of subject diary, comparison of subject status to baseline status, and examination of injection sites by trial staff
3) Blood collection for the following laboratory assessments:
   a. Expected C_{max} of hGH
   b. IGF-1 and IGFBP-3
   c. Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c)

10.2.2.3 Patient-Reported Outcome Completion within Diary (Week 6)

Immediately prior to the 6th drug administration, the following patient-reported outcome questionnaires will be completed by subjects/parents/legal guardians, as applicable, in the subject diary:

1) PQ-P
   - Only completed for subjects treated with daily hGH prior to enrollment
2) **For subject ≥ 9 years old (at Visit 1) only:** PQ-C
   - Only completed for subjects treated with daily hGH prior to enrollment
3) CSDS-P
4) **For subjects ≥ 9 years old (at Visit 1) only:** CSDS-C
5) C&OS-P

10.2.2.4 Visit 2 (Week 12-14, Day 82-84, 89-91, or 96-98)

The following assessments will be performed at Visit 2:

1) Patient-reported outcome questionnaires
   - Completed prior to subject diary review, AEs review, and concomitant medication review
   - Completed in the order listed below
   a. PQ-P
      - Only completed for subjects treated with daily hGH prior to enrollment
   b. **For subjects ≥ 9 years old (at Visit 1) only:** PQ-C
      - Only completed for subjects treated with daily hGH prior to enrollment
   c. CSDS-P
   d. **For subjects ≥ 9 years old (at Visit 1) only:** CSDS-C
   e. C&OS-P

2) Concomitant medications
   - Includes review of subject diary
3) AE review
   - Includes review of subject diary
4) Study drug compliance calculation
   - Includes review of subject diary and returned study drug
5) Vital sign measurements
6) Height and weight measurements
7) Limited physical examination
8) Pubertal status assessment (Tanner stage)
9) Blood collection for the following laboratory assessments*:
   a. IGF-1 and IGFBP-3
   b. **For subjects < 3 years old (at Visit 1) only:** mPEG
   c. Antibodies against hGH and PEG
      - If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers
   d. Hormone/glycemic Status (TSH, FT4, FT3, morning cortisol, and HbA1c)
   e. Chemistry
   f. Hematology
   g. Lipid panel
   h. **For female subjects of child-bearing potential only:** hCG

   * Banked blood samples may be used for additional characterization of anti-drug antibody responses.
10) Study drug dose adjustment, as needed
11) Study drug & subject diary dispensing

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

10.2.2.5 Visit 3 (Week 25-27, Day 173-175, 180-182, or 187-189)

The following assessments will be performed at Visit 3:

1) Patient-reported outcome questionnaires
   - Completed prior to subject diary review, AEs review, and concomitant medication review

a. CSDS-P

b. **For subjects ≥ 9 years old (at Visit 1) only:** CSDS-C

2) Concomitant medications
   - Includes review of subject diary
3) AE review
   - Includes review of subject diary
4) Study drug compliance calculation
   - Includes review of subject diary and returned study drug
5) Vital sign measurements
6) Height and weight measurements
7) Limited physical examination
8) Pubertal status assessment (Tanner stage)
9) Blood collection for the following laboratory assessments*:
   a. IGF-1 and IGFBP-3
   b. **For subjects < 3 years old (at Visit 1) only:** mPEG
   c. Antibodies against hGH and PEG

      If warranted, TransCon hGH, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers
   d. **For subjects ≥ 9 years old (at Visit 1) only:** TMPD (N1,-N1,-N3-trimethyl-1,3-propane-diamine; a small molecular weight leaving group associated with the linker)
   e. Hormone/glycemic Status (TSH, FT4, FT3, morning cortisol, and HbA1c)
   f. Chemistry
   g. Hematology
   h. Lipid panel
   i. **For female subjects of child-bearing potential only:** hCG

   * Banked blood samples may be used for additional characterization of anti-drug antibody responses.
10) Fundoscopy (to rule out blurred disc margins)

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

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 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 Early Termination Visits

Early Termination Visits are performed for any early termination/withdrawal of a subject from this clinical trial. Early Termination Visits are NOT to be performed for subjects who have terminated study drug but have continued to attend trial visits. The structure and assessments of the Early Termination Visit should be as similar as possible to the final visit (Visit 3).

10.2.5 Follow-up and Extension Phase

All subjects who successfully complete this trial on study drug and who have not completed puberty will be invited to participate in an extension trial, CT-301EXT. If the subject meets the eligibility criteria for the extension trial, Visit 1 for the extension trial should be performed at the same time as Visit 3 for this trial, and data collected at Visit 3 will become the baseline data for the extension trial. The purpose of the extension trial is to assess long-term safety and efficacy of TransCon hGH.

For subjects who do not enter the extension trial and for whom Visit 3 is the final visit, there will be no follow-up visit except as required to follow SAEs that are determined to be related to the study drug (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 with 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 by the same auxologist at approximately the same time of day using the same wall-mounted stadiometer (to minimize bias and reduce variability), the accuracy of which has been verified prior to each visit using a 100 cm 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 height measurements on a 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 horizontal position (Frankfort 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
- 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 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 Limited Physical Examination

A limited physical examination should be performed to include injection site examination to assess for local tolerability. At Screening and 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 trial.

11.5 Fundoscopy

A standard fundoscopy should be performed to rule out blurred disc margins. Additional fundoscopies 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.

11.7 Patient-Reported Outcome Measures

All Patient-Reported Outcomes used in this trial have been assessed for understanding by GHD patients and their parents/legal guardians/caregivers as intended by the Sponsor in a prior Cognitive Debriefing study per the **Guidance for Industry – 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 hGH prior to enrollment in the 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.

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

11.7.2 Child Sheehan Disability Scale

At Visit 1, the Child Sheehan Disability Scale (CSDS) should only be completed for subjects who were treated with daily hGH prior to enrollment. At all other time points, the CSDS should be completed for all subjects.

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. The parent/legal guardian/caregiver will complete the CSDS-P, while the subject, if ≥ 9 years old at Visit 1, will complete the CSDS-C.

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

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

At Visit 1, the Convenience and Overall Satisfaction (C&OS) of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) should only be completed for subjects who were treated with daily hGH prior to enrollment. At all other time points, the C&OS should be completed for all subjects.

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, an abbreviated 9-item TSQM (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 Convenience & Overall Satisfaction domains (C&OS) of the TSQM will be used. Only the parent/legal guardian/caregiver will complete the C&OS of the TSQM-9, thus it has been identified for this trial as the C&OS – Parent (C&OS-P).

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

11.8 Subject Diary

The subject diary will be provided to the subject/parent/legal guardian/caregiver at Visit 1 and should be completed weekly on the day of study drug administration. The data captured within the subject diary includes:

- Date and time of administration
- Dose of study drug
- Person preparing and giving injection
- Location of injection on subject's body
- Assessment of subject pain using the Wong-Baker FACES Pain Rating Scale (see Appendix 2)
- 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 study drug compliance.

11.9 Bone X-Ray

To confirm open epiphyses (bone age ≤14.0 years for females or ≤16.0 years for males), a bone age x-ray must be performed for subjects at Tanner stage 4 only. An x-ray performed within the past 52 weeks with a bone age delay of ≥ 6 months is acceptable. If not available, a bone age x-ray must be performed at Screening and read locally.

11.10 Laboratory Assessments

For subjects > 3 years old at Visit 1, the total blood volume collected throughout the trial will be no more than approximately 44mL.

For subjects ≤ 3 years old at Visit 1, the total blood volume collected throughout the trial will be no more than approximately 54mL.

Further details are provided in the trial manual.

11.10.1 Screening Laboratory Assessments

The following laboratory assessments will be performed on blood collected at Screening:

1. IGF-1 and IGFBP-3
2. 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, hGH and PEG serum levels may be analyzed for the interpretation of immunogenicity titers.
3. Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c)
4. Chemistry
5. Hematology
6. Lipid panel
7. **For female subjects of child-bearing potential only:** hCG

Additionally, banked blood samples may be used for additional characterization of anti-drug antibody responses.

11.10.2 C_{max} Visit Laboratory Assessments

The following laboratory assessments will be performed on blood collected at the C_{max} Visit for subjects < 3 years old (at Visit 1):

1. hGH
2. IGF-1 and IGFBP-3
3. Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c)

11.10.3 Visit 2 Laboratory Assessments

The following laboratory assessments will be performed on blood collected at Visit 2:

1. IGF-1 and IGFBP-3
2. **For subjects < 3 years old (at Visit 1) only:** mPEG
3. Antibodies against hGH and PEG
    - If warranted, TransCon hGH, hGH and PEG serum levels may be analyzed for the interpretation of immunogenicity titers.
4. Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c)
5. Chemistry
6. Hematology
7. Lipid panel
8. **For female subjects of child-bearing potential only:** hCG

Additionally, banked blood samples may be used for additional characterization of anti-drug antibody responses.

11.10.4 Visit 3 Laboratory Assessments

The following laboratory assessments will be performed on blood collected at Visit 3:

1. IGF-1 and IGFBP-3
2. **For subjects < 3 years old (at Visit 1) only:** mPEG
3. Antibodies against hGH and PEG
    - If warranted, TransCon hGH, hGH and PEG serum levels may be analyzed for the interpretation of immunogenicity titers.
4. **For subjects ≥ 9 years (at Visit 1) old only:** TMPD (N1,-N1,-N3-trimethyl-1,3-propane-diamine; a small molecular weight leaving group associated with the linker)
5. Hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c)
6. Chemistry
7. Hematology
8. Lipid panel
9. **For female subjects of child-bearing potential only:** hCG

Additionally, banked blood samples may be used for additional characterization of anti-drug antibody responses.

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).

11.11.1 Local Tolerability Documentation

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

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

At Visit 2 and Visit 3, assessment of local tolerability will be performed by injection site examination by trial staff (documented as part of the limited physical exam), in conjunction with subject diary review.

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

Possible AEs associated with TransCon hGH are listed in the Investigator 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.

Clinically significant treatment-emergent physical examination or laboratory abnormalities and worsening pretreatment conditions should be recorded as AEs.

The Medical Monitor will review all AEs, including SAEs, on an ongoing basis. The key safety data will also be reviewed periodically by an ISC in accordance with its governing charter. Safety assessments will consist of monitoring and recording of all AEs, including SAEs, monitoring of hematology and chemistry parameters, physical examinations, vital sign assessments, and fundoscopies.

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 study drug and the event using the following guideline:

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

- The event follows a reasonable temporal sequence from study drug 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 study drug [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 study drug
- 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 study drug. An AE may be categorized as probably related to the study drug when the event meets the first 3 (or more) of the following criteria:

- The event follows a reasonable temporal sequence from study drug 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 study drug [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 study drug
- 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 study drug. An AE may be categorized as possibly related to the study drug when the event meets the first 2 (or more) of the following criteria:

- The event follows a reasonable temporal sequence from study drug 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 study drug

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

- The event does not follow a reasonable temporal sequence from study drug 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 study drug

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, including SAEs, will be documented through the end of the trial (ie, Visit 3). All AEs ongoing at Visit 3 or Early Termination Visit must be followed until the event is resolved or deemed stable by the investigator. All AEs must be recorded on the appropriate eCRF. 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 AE:

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

Any medical conditions, signs, symptoms, or illnesses active during the Screening Period (ie, up to approximately 4 weeks prior to first study drug administration) will be captured as medical history unless the change is trial procedure-related, in which case it will be reported as a non-treatment-emergent AE. 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 study drug 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 study drug until end of Visit 3 or the Early Termination Visit will be recorded as an AE.

Abnormal laboratory values or test results constitute AEs if they:

- Induce a diagnosis, clinical sign(s), or symptom(s), or
- Are considered clinically significant by the investigator, or
- Require therapy.

Whenever possible, an AE should be recorded as a specific diagnosis or syndrome rather than as a sign, symptom, or abnormal laboratory value. If there is not a diagnosis, the event term should be the clinical sign or symptom. Only if a diagnosis, clinical sign, or symptom is not present should an AE be recorded as the abnormal value itself.

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 study drug administration. At the end of Visit 3 or the Early Termination Visit, all AEs should have a statement regarding resolution.

Any SAE that is determined to be related to the study drug 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 study drug could have serious clinical consequences and/or represent a compliance issue, they should be reported to the Medical Monitor 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
- 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

Additionally, medical events that may jeopardize the subject or may require intervention to prevent one of the outcomes listed above should be considered serious.

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

- Routine treatment or monitoring of the study drug 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 study drug 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

12.2.1.2 Suspected Unexpected Serious Adverse Reaction Definition

A 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.

12.2.1.3 Non-Serious Adverse Events Leading to Discontinuation

If situation permits, non-serious events (including laboratory abnormalities and pregnancies) that may require permanent discontinuation of study drug should be discussed with the Medical Monitor 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 study drug 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

14.1 Trial Endpoints

14.1.1 Safety Endpoints

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

- Incidence of AEs
- Local tolerability, as assessed by the subject/parents/legal guardians/caregivers and the trial staff
- Incidence of antibodies against hGH, including neutralizing antibodies
- Incidence of antibodies against PEG
- Incidence of IGF-1 SDS ≥ 2.0, ≥ 3.0 with confirmation
- Parameters of HbA1c and lipids
- Hormone levels, including thyroid status and morning cortisol
- All other hematology and chemistry parameters
- Vital sign measurements

14.1.2 Efficacy Endpoints

The efficacy endpoints as measured at 26 weeks of weekly TransCon hGH treatment include the following:

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

14.1.3 Pharmacokinetic/Pharmacodynamic Endpoints

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

14.1.4 Other Endpoint

- Preference for TransCon hGH or commercially available daily hGH
- Satisfaction with weekly TransCon hGH

14.2 Sample Size Determination

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

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

14.3 Analysis Populations

The analysis population includes all patients who receive at least one dose of study drug.

14.4 Statistical Analyses

Details of applicable statistical methods will be provided in a statistical analysis plan (SAP).

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 study drug, 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 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, study drug preparation and administration procedures, data collection requirements, and subject eligibility requirements.

15.2 Screen Failures

Subjects who fail to meet the eligibility criteria at any point prior to administration of first study drug dose are defined as Screening Failures. The reason(s) for each Screening Failure will be recorded in the eCRF.

The decision to rescreen will be made on a case by case basis together with the Medical Monitor, including which screening procedures may not need repeating.

15.3 Maintenance of Screening & Enrollment Logs

Procedures for maintenance of Screening and 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 manual.

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 values
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) Study drug 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 blood samples may be used for laboratory 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 needs
3) Trial enrollment and treatment administration should be temporarily suspended pending further data evaluation
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 study drug 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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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 study drugs 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 study drug
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 study drug 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 study drug, 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 study drug 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

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

[1] Subjects <3 years old at Visit 1 will perform the C_{max} Visit. Subjects ≥3 years old at Visit 1 will NOT perform the C_{max} Visit.

[2] An Early Termination Visit should be performed for all subjects exiting the trial and should include all procedures listed for Visit 3. Stopping study drug does NOT require termination from the trial and therefore does NOT require an Early Termination Visit.

[3] Vital sign measurements include heart rate, blood pressure, respiratory rate and body temperature, which should be performed after the subject has rested for at least 5 minutes.

[4] Height should be measured at each visit at approximately the same time of day, preferably by the same auxologist.

[5] Locally read bone age x-ray only required at Screening if subject is at Tanner stage 4 and an x-ray performed within the past 52 weeks with a bone age delay of ≥ 6 months is not available.

[6] Fundoscopy may also be performed at any time, if clinically indicated.

[7] Blood samples collected at Screening will be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. The analyses of antibodies against hGH and PEG may only be conducted after enrollment and are not required for eligibility verification. Data will be used to support evaluation of post-dose antibody detection. Female subjects of child-bearing potential will also have blood samples tested for hCG.

[8] Blood samples collected at the C_{max} Visit will be tested for the following: hGH, IGF-1 and IGFBP-3, and hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c).

[9] Blood samples collected at Visit 2 will be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Subjects < 3 years old at Visit 1 will also have blood samples tested for mPEG. Female subjects of child-bearing potential will also have blood samples tested for hCG.

[10] Blood samples collected at Visit 3 will be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Subjects ≥ 9 years old at Visit 1 will also have blood samples tested for TMPD. Subjects < 3 years old at Visit 1 will also have blood samples tested for mPEG. Female subjects of child-bearing potential will also have blood samples tested for hCG.

[11] At Visit 1, the CSDS-P, CSDS-C, and C&OS-P should only be completed for subjects treated with daily hGH prior to enrollment.

[12] CSDS-P, CSDS-C, C&OS-P, PQ-P, and PQ-C will be completed (as applicable) within the subject diary immediately prior to the 6th dose of study drug and again at Visit 2.

[13] CSDS-C and PQ-C should only be completed by subjects ≥ 9 years old at Visit 1.

[14] Local tolerability assessment at the injection site to be performed at time of injection and 15 minutes, 1 hour, and 2 hour post-dose.

[15] PQ-P and PQ-C should only be completed for subjects treated with daily hGH prior to enrollment.

[16] AE review includes review of subject diary and physical examination of injection sites.

[17] Study drug compliance includes review of subject diary and returned study drug.

[18] Dose adjustments at visits are based on subject weight at visits. However, dose adjustments may occur between visits per Section 9.6.

APPENDICES

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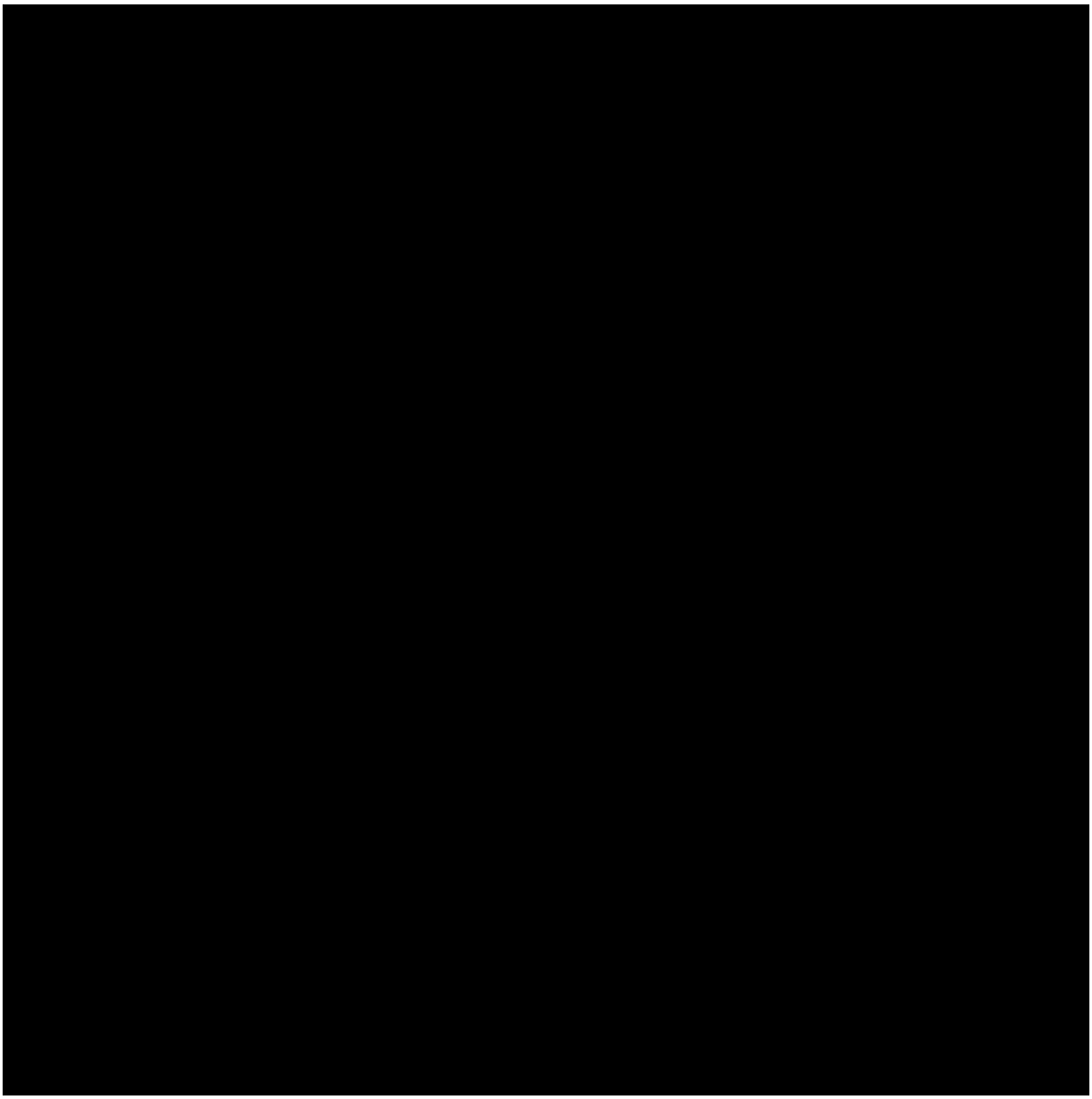

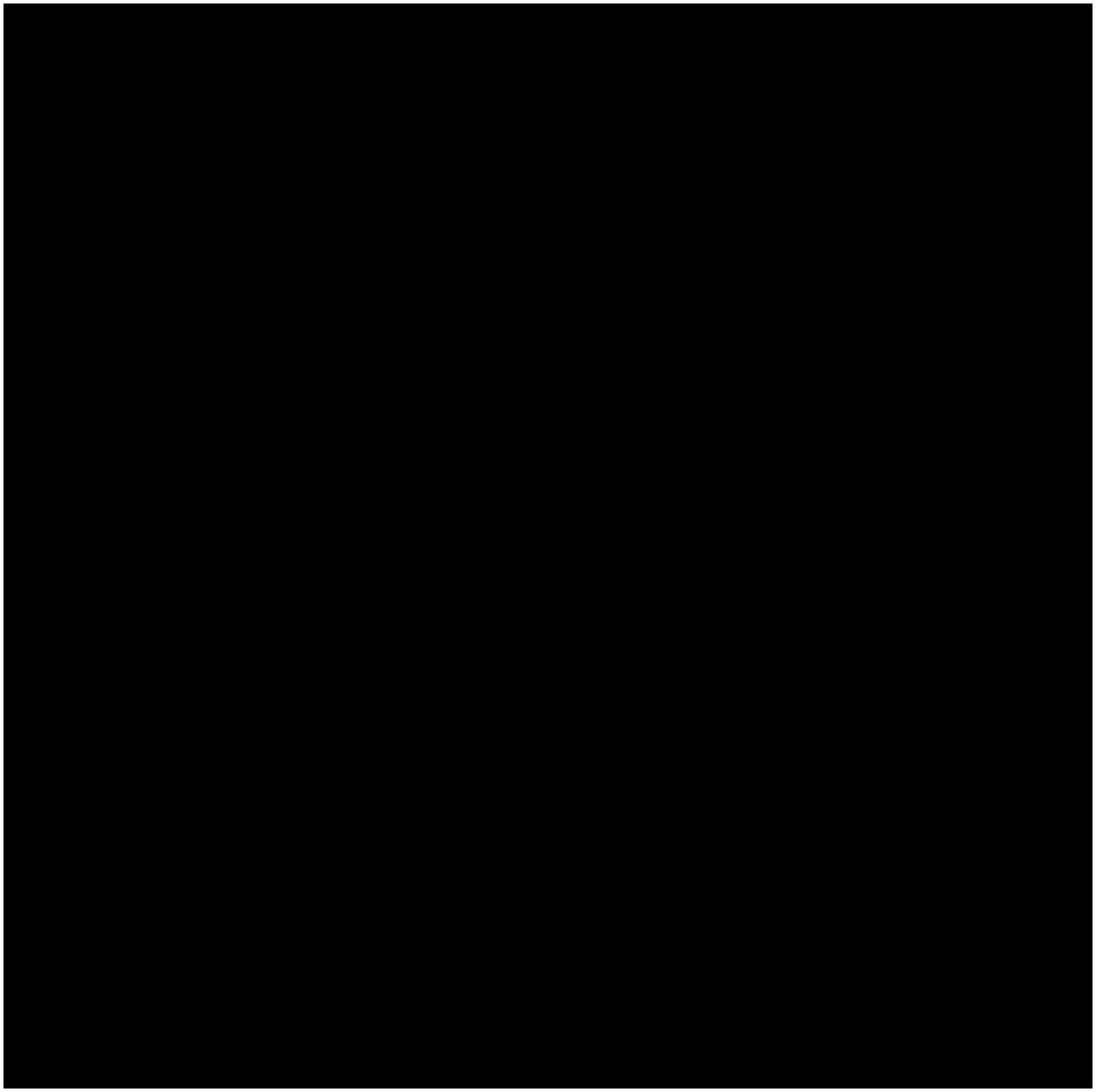

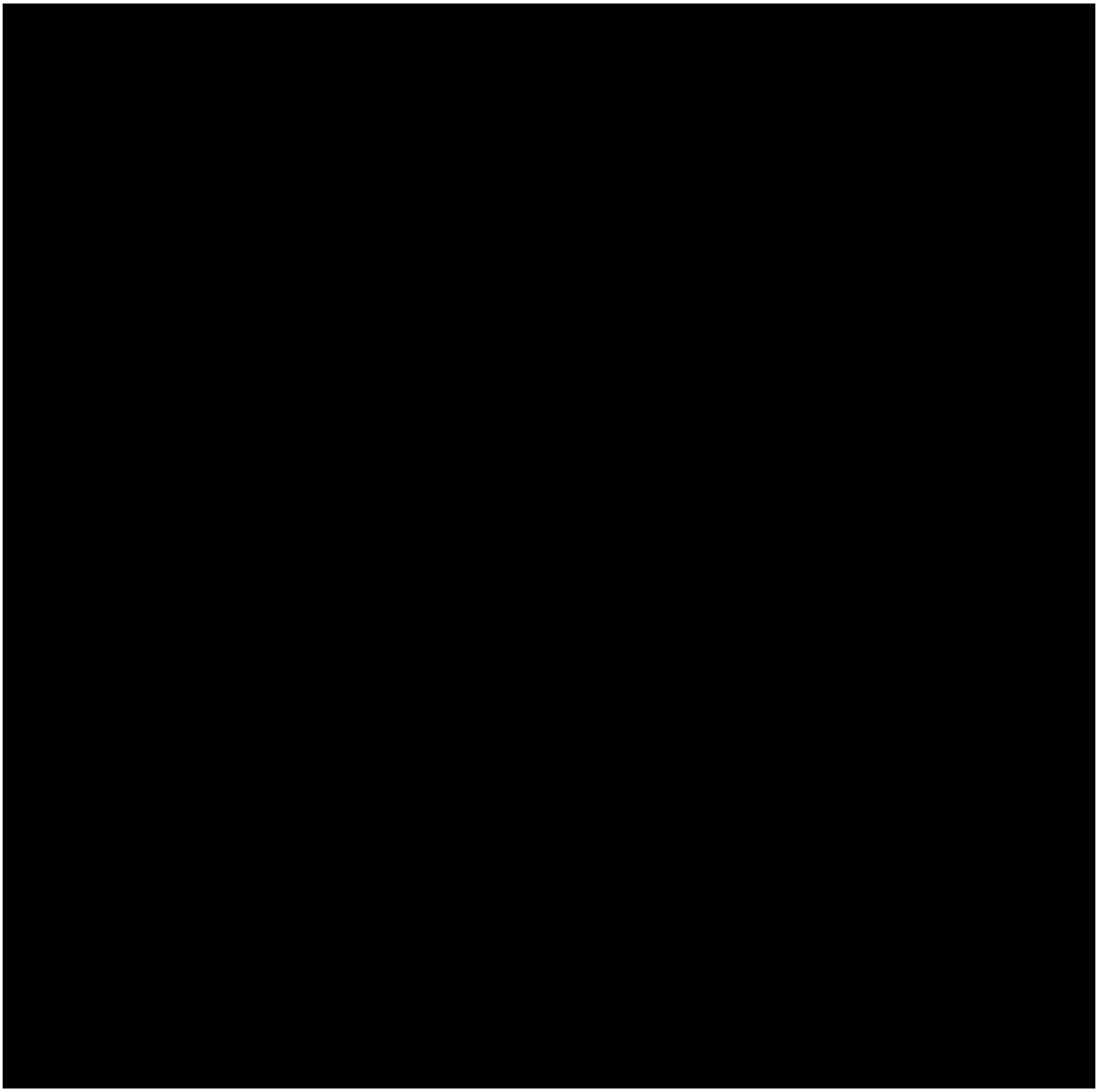

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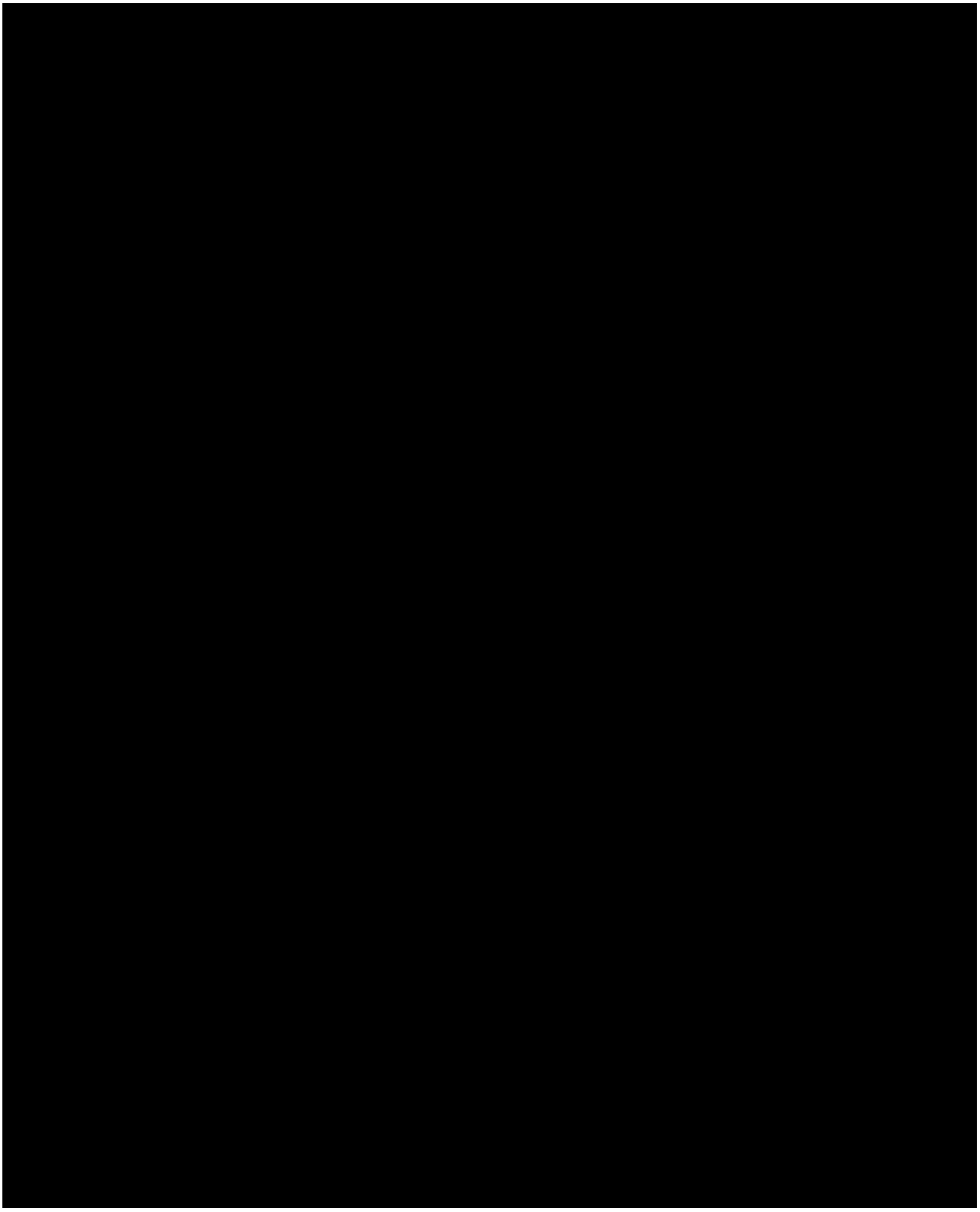

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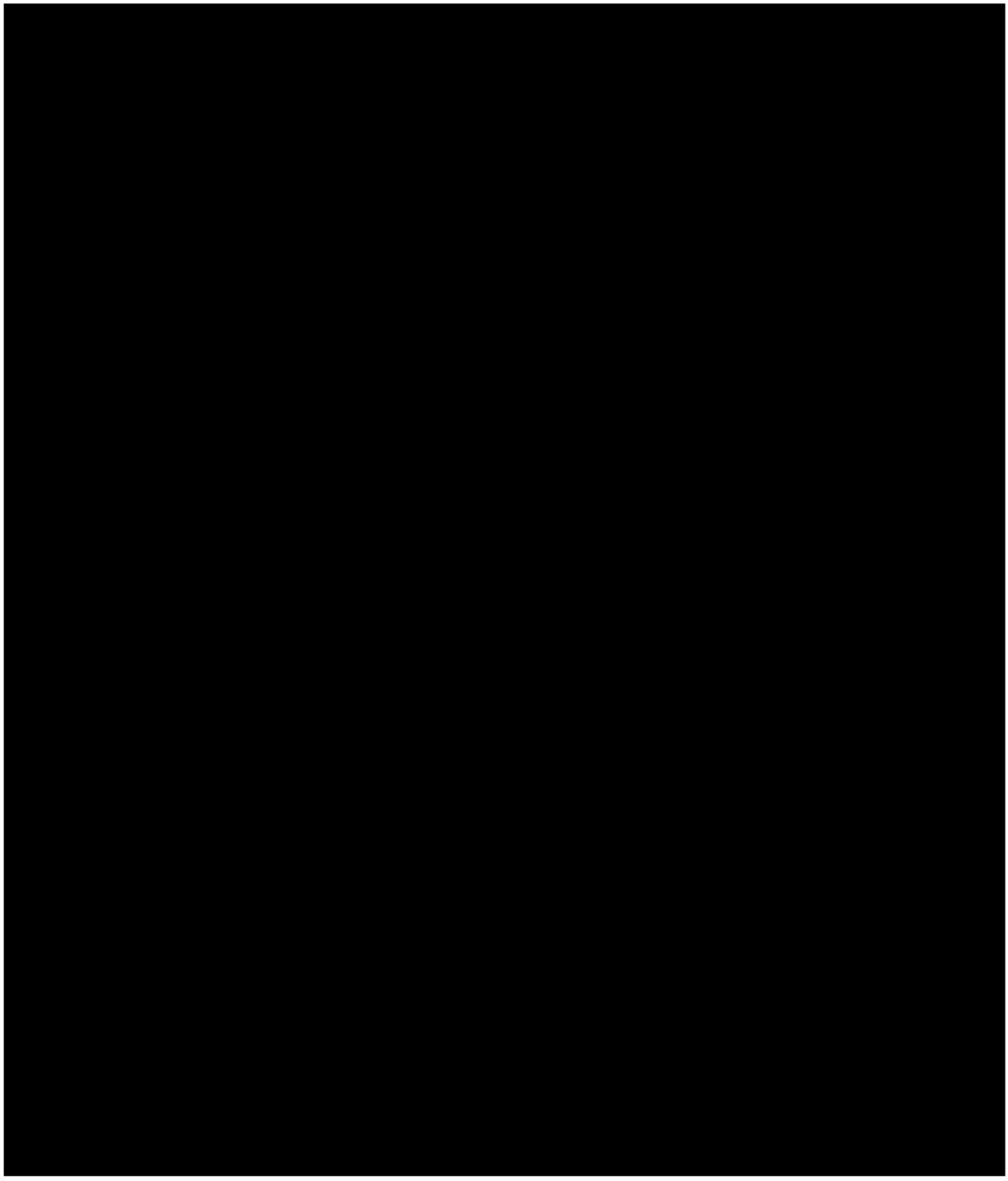

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