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

NCT Number: NCT02781727

Document Date: Protocol Amendment 1: 12 September 2017

PROTOCOL AMENDMENT 1

PRODUCT NAME/NUMBER:	TransCon hGH
PROTOCOL NUMBER:	TransCon hGH CT-301
IND NUMBER:	126053
EUDRACT NUMBER:	2016-001145-11
DEVELOPMENT PHASE:	3
PROTOCOL TITLE:	A multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability, and efficacy of TransCon hGH administered once a week versus standard daily hGH replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency (GHD)
PROTOCOL DATE:	Final v1.0; 04 August 2016 Amendment 1; 12 September 2017
SPONSORED BY:	Ascendis Pharma Endocrinology Division A/S Tuborg Boulevard 5, DK-2900 Hellerup, Denmark
Sponsor Medical Expert/ Medical Monitor:	[redacted]
Sponsor Medical Expert/ Medical Monitor:	[redacted]
CONTRACT RESEARCH ORGANIZATION:	[redacted]

AMENDMENT 1 SUMMARY

Rationale

This amendment to the original protocol is being issued to incorporate feedback from international regulatory agencies and to add pertinent clarifications and administrative edits. This amendment maintains the original intent of the protocol and aligns where possible, with current standard medical practice across various regions globally.

Section(s)	Change	Rationale
Title Page	Align Medical Expert/Medical Monitor removing country region	Administrative change
Global	Updated Medical Monitor to Medical Expert	Administrative change
Signature Pages	Deleted signatures not required	Administrative change - required signatures of Medical Experts are obtained
Global	Updated IGF-I to IGF-1	Administrative change to correct typo
Synopsis - Trial Design	Added (heiGHt trial)	Administrative change as the trial is also referred to as the heiGHt trial
Synopsis - Secondary Objectives, Secondary Efficacy Endpoints; 6.2 Secondary Objectives; 13.1.2 Secondary Efficacy Endpoints; 13.4.4 Efficacy Analysis	Deleted “the change in”	Clarification purposes to the secondary objectives and secondary efficacy endpoints
Synopsis - Trial Design; 7.1.1 Trial Design; 10.2. Trial Duration	Added “approximately” in the screening period. Deleted maximum [max]. Added “recommended period” and “up to”	To allow flexibility in completing screening activities and scheduling for visit 1.
Synopsis - Trial Design; 10.1.1 Screening (Day –42 to –1); 10.2.2 Screening Period	Added “approximately” to 6 week screening period	To allow flexibility to complete screening activities

Section(s)	Change	Rationale
Synopsis - Trial Design - Screening Period; Synopsis - Trial Design - Treatment Period; 10.1.1 Screening (Day –42 to –1); 10.1.2 Treatment Period (Days 1 to 365); 10.3.1 Safety and Efficacy; Appendix 3. Instructions for Obtaining Height Measurements	Added (if possible) in regards to the auxologist being blinded	Clarification as the auxology may be performed by the Investigator or study staff where blinding is not possible
Synopsis - Trial Design - Screening period; 10.1.1 Screening (Day –42 to –1);	Added “and, when available, pre-screening height measurements to assess growth history”	Modification to collect pre-screening height to further characterize the growth history
Synopsis - Trial Design; Synopsis -Trial Entry Criteria - Inclusion Criteria; 8.1.1 Inclusion Criteria; 10.1.1 Screening (Day –42 to –1) 17.2. Schedule of Events (TransCon hGH Subjects); 17.3. Schedule of Events (Genotropin Subjects)	Added “approximately” to 6 month time reference	To allow flexibility in the completion of assessments
Synopsis - Trial Design-Screening Period; 10.1.1 Screening (Day –42 to –1)	Added “unless cortisol measured during an ITT” to the glucagon test and L-Dopa test revised to with “or without” propranolol	Clarification of the cortisol response. L-Dopa test is an approved stimulation test for GHD and some investigators/institutions do not use L-Dopa with propranolol as part of their standard of care GH stimulation protocol for the diagnosis of pituitary insufficiency

Section(s)	Change	Rationale
Synopsis-Trial Design-Screening period; 10.1.1 Screening (Day –42 to –1); Appendix 1. Growth Hormone Stimulation Tests and Other Assessments	Added "approximately" to the last 6 months time reference. Updated language for the stimulation tests. Added Reference to 10.1.1. and Appendix 1 (*Grimberg 2016*)	Tests need not be completed within precisely 6 months. Clarification to reflect recent guidelines, based on the fact that the pituitary somatotrophs are the most susceptible to damage from either radiation or mass lesions, such that all subjects who have deficiency of either ACTH or TSH after cranial radiation, or subjects who are born with absent or deformed pituitary glands and are missing at least 2 hormones in addition to GH all have GH deficiency by definition. See Reference (*Grimberg 2016*)
Synopsis - Trial design - Screening Period; 10.1.1 Screening (Day –42 to –1);	Added "in subjects with idiopathic GHD only" to the 8:00AM cortisol. Deleted "an increase in" with regards to peak cortisol level. Added greater than or equal sign to peak cortisol level value.	Clarification of 8:00AM Cortisol expectation and clarify the peak cortisol level with normal response is greater than or equal to 18 µg/dL
Synopsis - Trial Design-Screening Period; 7.1.2 Measures Taken To Minimize Bias; 10.2.2 Screening Period	Added the greater than sign to age 3 in the minimization rule	Corrected a typo to clarify the age range of greater than or equal to 3
Synopsis - Trial Design-Screening Period; 10.2.2 Screening Period; 14.2. Screen Failures	Added "Individual blood draws may be repeated for the following reasons, but not limited to: eg, ruling out an analytical error, sample handling or shipment issues, conflicting or inconsistent subject data, etc."	Updated language to allow flexibility on when blood draws may be repeated

Section(s)	Change	Rationale
Synopsis - Trial Design - Treatment Period; 10.2.3 Treatment Period	Added "or evening"	To clarify in the Synopsis that TransCon can be given in the evening
Synopsis - Trial Design- Treatment Period; 10.1. Trial Periods and Visits; 10.2.3 Treatment Period	Addition of "approximately" to 168 hours time span	To clarify more accurately the time span for the visit
Synopsis - Trial Design - Treatment Period; 10.3.1 Safety and Efficacy	Added "All samples obtained after Informed Consent will be shipped to a selected central laboratory for analysis. Safety samples may be analyzed locally in case of emergency or if logistics or other unforeseen events do not permit a central analysis"	Addition of language to clarify how blood samples will be assessed
Synopsis - Trial Design - Treatment Period; 10.1.2 Treatment Period (Days 1 to 365); 10.3.1 Safety and Efficacy	Added fasting to V1, V4 and V6	To clarify which visits would require fasting
Synopsis - Trial Design - Treatment Period; 10.1.2 Treatment Period (Days 1 to 365); 10.3.1 Safety and Efficacy	Revised anti-hGH and/or anti-PEG to anti-drug	To more accurately reflect that samples would be used for anti-TransCon hGH antibody characterization as requested by the regulatory authorities
Synopsis - Trial Design - Treatment Period; 10.1.2 Treatment Period (Days 1 to 365); 10.3.1 Safety and Efficacy	Added "predose" to V1 for PEG Samples analyzed in cohort 2	To clarify that anti-PEG antibody would be analyzed from the predose sample at V1
Synopsis -Trial Design - Treatment Period; 9.6. Dose Adjustment Criteria	Added "if deemed to be clinically significant by the investigator"; "and of clinical concern" and the word "may" in the IGF-1 >+2.0 SD	Additional text added to allow clinical assessment by the investigator

Section(s)	Change	Rationale
Synopsis -Trial Design - Treatment Period; 9.6. Dose Adjustment Criteria	Deleted "Fasting insulin level > 14 mIU/L" and added "or appropriate anti-glycemic therapy(ies) may be started" in the glucose parameters	Modified glucose parameters to be consistent with standard medical practice. Added language to clarify the investigator could initiate anti-glycemic therapy as clinically indicated.
Synopsis - Trial Entry Criteria - Inclusion Criterion #2; 8.1.1 Inclusion Criteria	Added "or, after approval by the Medical Expert, at least 1.5 SD below the mid-parental height" to Inclusion Criteria #2. Added References to section 8.1.1 Inclusion Criteria (*Cole 2000, Kriström 2009, Sotos 2014*)	Added language to Inclusion Criteria #2 to align with international regulatory authority recommendations. A number of peer-reviewed GH publications include delta from MPH (1.0 SD or 1.5 SD) as an optimal criteria for short stature in the diagnosis of GHD, acknowledging the fact that one's genetics plays a far more pivotal role in one's stature than does the average height of a population as heterogeneous as that of the US. Using a criterion of height SDS more than 2.0 SD below the mean of the CDC database favors potential enrollment of subjects with shorter-than-average parents who may not not have GHD [as the peak GH level <10.0 ng/ml] clearly does not discriminate between GHD and normal, and by definition 16-17% of the normal population has an IGF-1 SD of < -1.0, and 2.5% of the normal population has a >6 month delay in BA vs CA0,and penalizes subjects with true GHD whose parents are taller than average compared to the US population (eg, of Scandinavaian or German descent). See References (*Cole 2000, Kriström 2009, Sotos 2014*)

Section(s)	Change	Rationale
Synopsis -Trial Entry Criteria - Inclusion Criteria #3; 8.1.1 Inclusion Criteria	Added "or BMI within ±2.0 SD of the mean BMI for bone age and sex" to Inclusion Criteria #3	Added language to Inclusion Criteria #3. GHD kids are often very petite. A 10 year-old kid with a Bone Age of 7 years would not be expected to have the BMI of an average 10-year-old. It is not uncommon for a truly GHD kid with a substantially delayed BA to have a BMI more than 2.0 SD below the mean of the normal, tending-towards-obese US population.
Synopsis -Trial Entry Criteria - Inclusion Criteria #4; 8.1.1 Inclusion Criteria	Added "For subjects with known panhypopituitarism (eg, subjects who are deficient in TSH and/or ACTH post cranial radiation or born with ≥ 2 pituitary hormone deficiencies in addition to GH), GH stimulation tests may not be required" to Inclusion Criteria #4. Added Reference to 8.1.1 Inclusion Criteria (*Grimberg 2016*)	Added language to Inclusion Criteria #4 to reflect recent guidelines, based on the fact that the pituitary somatotrophs are the most susceptible to damage from either radiation or mass lesions, such that all subjects who have deficiency of either ACTH or TSH after cranial radiation, or subjects who are born with absent or deformed pituitary glands and are missing at least 2 hormones in addition to GH all have GH deficiency by definition. See Reference (*Grimberg 2016*)
Synopsis - Trial Entry Criteria - Inclusion Criteria #8; 8.1.1 Inclusion Criteria;	Replaced "at least" with "approximately" in Inclusion Criteria #8	Minor modification to allow flexibility in the replacement therapy

Section(s)	Change	Rationale
Synopsis - Trial Entry Criteria - Exclusion Criteria #4; 8.1.2 Exclusion Criteria	Added "with or without a birth length ≤ -2.0 SD for gestational age" to Exclusion Criteria #4 and deleted "and/or". Added Reference to 8.1.2 Exclusion Criteria (*Mandy 2016*)	Added language to Exclusion Criteria #4 for clarification purposes. SGA is basically a screen for IUGR (intrauterine growth restriction). An infant with IUGR has a GA-based birth weight >2.0 SDS below the mean, but may or may not have a reduced birth length (BL). In contrast, a congenitally GHD infant may have reduced birth length, but less reduced birth weight (BW), if uterine nutrition is adequate. This decreased BW + decreased BL = SGA, and decreased BW alone = SGA, but normal BW with decreased BL does not = SGA. See Reference (*Mandy 2016*)
Synopsis -Trial Entry Criteria - Exclusion Criteria #9; 8.1.2 Exclusion Criteria	Added "children with GHD and clinically cured tumors may be eligible after consultation with the Medical Expert" to Exclusion Criteria #9	Addition of language to Exclusion Criteria #9 for clarification that clinically cured tumors may be eligible after consultation with the Medical Expert
Synopsis - Trial Entry Criteria - Exclusion Criteria #12; 8.1.2 Exclusion Criteria #12	Added "known to impact growth" to Exclusion Criteria #12	Clarification that the intent of this exclusion criteria is to exclude chromosomal abnormalities and syndromes known to impact growth
Synopsis - Planned Trial Sites; 7.1.1 Trial Design; 7.2. Trial Sites	Deleted "South America" from countries list	Modification made as sites are no longer being considered for this region
Synopsis - Statistical Methods; 13.3 Analysis Populations	Added "who have received at least 1 dose of active treatment and have follow-up efficacy data" to ITT subset	To clarify the analysis population

Section(s)	Change	Rationale
Synopsis - Statistical Methods; 13.3. Analysis Populations	Revised Per-protocol Subset text	Revised language in these sections as the statistical methods would be further defined in the SAP
Synopsis - Statistical Methods; 13.4.4 Efficacy Analyses	Added "followed by a test of superiority if non-inferiority is established"; "A mixed model repeated measurement (MMRM) will be the primary analysis to evaluate annualized HV"; "baseline age, peak GH level of the stimulation test, and gender as fixed effects"; and "If the lower confidence bound is > 0, superiority is established"	Revised text for clarification of the analysis methodology
Synopsis - Statistical Methods; 13.4.4 Efficacy Analyses	Added "similar MMRM" and "A test of superiority in proportion of patients within 0-2.0 IGF-1 SDS will be conducted. A procedure to control for familywise type-1 error will be specified in the SAP"	Revised text for clarification of the analysis methodology
Synopsis - Trial and Treatment Duration	Added "approximately" to treatment duration	To allow flexibility in completing screening procedures and the scheduling of subjects
4. LIST OF ABBREVIATIONS	Added "ADHD attention deficit hyperactivity disorder" and "MMRM mixed model repeated measurement". Deleted MM Medical Monitor	Administrative change

Section(s)	Change	Rationale
7.1.2 Measures Taken To Minimize Bias	Added "selected" to sponsor staff and revised examples to (Medical Experts and Statisticians). Deleted Investigator in regards to who would be blinded to treatment	Text revised to clarify which selected sponsor staff would be blinded to treatment and that the Investigator would not be blinded (open label study)
7.3.1 Early Termination of the Subject	Added "Evidence of development of neutralizing antibodies (eg, a blunted IGF-1 response in addition to a positive result in the neutralizing antibody assay)"	Additional information to include evidence of neutralizing antibodies as a potential reason for early termination of a subject in the trial
9.3.1 TransCon hGH	Added "As a result, all subjects in the TransCon hGH group will be treated over the course of the trial at an average dose of 0.24 mg hGH/kg/week"	To clarify TransCon hGH subjects would be treated on 0.24 mg hGH/kg/week over the course of the trial
Section 9.9.2.2 Prohibited Therapies	Added "other than for the treatment of ADHD"	To reflect the intention of the initial protocol to not exclude subjects with GHD and ADHD. Unmodified, this sentence could appear contradictory, in stating that methylphenidate or similar drugs for ADHD are exclusionary or could result in discontinuation.
10.1.5 Follow-up and Extension Phase	Added "and data collected will become the baseline data for the extension trial"	To clarify that data from this trial would be utilized for subjects consented on the extension trial
11.1.2.2 Causality Rating	Replaced "inconvertibly" with "clearly"	For clarification and simplification purposes
11.2.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR) Definition	Deleted "or in Section 11.1.1"	Modification made due to inaccurate citation in regards to identification of an "unexpected" adverse reaction

Section(s)	Change	Rationale
11.2.2 Reporting	Added "the subject ID"	To clarify Subject ID would be part of the minimum information required for reporting an SAE
11.2.2 Reporting	Deleted "approximately" in the reporting of SAE or SUSARs	To align with EU regulatory requirements
13. STATISTICS	Added "The Statistical Analysis Plan (SAP) will provide a detailed description of the planned statistical analyses. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record"	Additional text added to clarify the statistical analysis plan
13.4. Statistical Analyses	Added "Once non-inferiority in annualized HV is established, subsequent hypothesis testing for superiority will be conducted. If TransCon hGH is superior compared to daily hGH in annualized HV, subsequent hypothesis testing for superiority will be conducted in the proportion of patients within 0-2.0 SDS in IGF-1"	Additional text for providing possibility for sequential testing of endpoints

Section(s)	Change	Rationale
17.2. Schedule of Events (TransCon hGH Subjects); 17.3. Schedule of Events (Genotropin Subjects)	Postdose vital signs and Injection site reaction assessment were separated into its own row (in Table for each cohort)	Modified schedule of events tables for both TransCon and Genotropin Subjects to better clarify the postdose vital signs and injection site reaction assessment
17.2 Schedule of Events (TransCon hGH)	Deleted text in footnote 14 "Reanalysis of IGF-1 Screening samples at the PD bioanalytical laboratory may be performed as supportive data for IGF-1 baseline level assessment, in case IGF-1 baseline (V1) results are not available" Added "IGF-1 and PEG will be analyzed at screening and V1 through V6"	For clarification purposes on when the bioanalytical samples would be analyzed
17.3 Schedule of Events (Genotropin)	Revised text in footnote letter I "IGF-1 will be analyzed at Screening and V1 through V6 (excluding V1-2h postdose). hGH and IGFBP-3 will be analyzed at V1 predose through V6; V1-2h postdose sample will only be analyzed for hGH"	For clarification purposes on when the bioanalytical samples would be analyzed

Section(s)	Change	Rationale
[redacted]	[redacted]	[redacted]
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- Good Clinical Practice (GCP) as outlined by the International Conference on Harmonisation (ICH E6) and regional regulations
- Regional required subject data protection laws and regulations
- 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:

- Declaration of Helsinki
- Established principles of GCP (Harmonized)
- With applicable federal, state and/or local laws and regulations in the country where the clinical trial will be conducted
- Clinical trial contractual obligations

CLINICAL TRIAL TITLE:

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

[redacted]

14-SEP-2017
Date

12-SEPT-2017
Date

2. SYNOPSIS

PRODUCT NAME/NUMBER	US: TransCon hGH (ACP-011) for Injection EU: TransCon hGH (ACP-011) Powder for Injection Henceforth referred to as TransCon hGH
PROTOCOL NUMBER	TransCon hGH CT-301
EUDRACT NUMBER/IND NUMBER	2016-001145-11/126053
DEVELOPMENT PHASE	3
PROTOCOL TITLE	A multicenter, phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability, and efficacy of TransCon hGH administered once a week versus standard daily hGH replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency (GHD)
INDICATION	Growth failure in prepubertal children due to growth hormone deficiency
OBJECTIVES	**Primary:** To evaluate and compare the annualized height velocity (HV) of prepubertal children with growth failure due to GHD treated with weekly TransCon hGH to that of a commercially available daily human growth hormone (hGH) formulation at 52 weeks. **Secondary:** • To evaluate the safety of weekly TransCon hGH administered over 52 weeks compared to daily hGH • To evaluate and compare the annualized HV over 52 weeks of weekly TransCon hGH to daily hGH • To evaluate and compare the change in height (HT) standard deviation score (SDS) over 52 weeks of weekly TransCon hGH to daily hGH • To evaluate serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) and IGF-1 SDS and IGFBP-3 SDS; and the normalization of IGF-1 SDS over 52 weeks of weekly TransCon hGH or daily hGH

	• To describe the pharmacokinetic/pharmacodynamic (PK/PD) profile of TransCon hGH, hGH, IGF-1, IGF-1 SDS, IGFBP-3, IGFBP-3 SDS and polyethylene glycol (PEG) administered as a weekly injection (PK/PD subset; TransCon hGH cohort only) • To compare the maximum value of concentration (C_{max}) for hGH of TransCon hGH to the anticipated C_{max} of daily hGH • To determine the incidence of anti-hGH antibodies for both treatments, and treatment emergent anti-PEG antibodies for TransCon hGH over 52 weeks
TRIAL DESIGN	This is a phase 3, randomized, open-label, active-controlled trial of TransCon hGH compared to standard daily growth hormone, over 52 weeks (heiGHt trial). The trial consists of: • Screening period - up to approximately 6 weeks (plus a recommended period of up to 2 weeks until V1) • Treatment period - 52 weeks of dosing • PK/PD profiling and electrocardiogram (ECG) screening bracketing presumed C_{max} of TransCon hGH, hGH, IGF-1 and PEG will be established in a subset of at least 8 TransCon hGH treated subjects (PK/PD subset) **Screening Period** The Screening period will last up to approximately 6 weeks during which clinical data will be collected and investigations will be performed to establish the subject's eligibility for the trial. Prior to any trial specific procedure, a written and signed informed consent will be obtained from the parent(s)/legal guardian(s) and a signed assent from the subject (whenever possible). At sites where the diagnosis of GHD is confirmed prior to consideration for a trial, many of the Screening procedures (which reflect standard of care in the diagnosis of GHD) may be completed prior to signing of informed consent or assent form. These may enable enrollment, based on approval by the Medical Expert. The following assessments will be performed and appropriate data collected: • Data on current anthropometric measurements (auxology), (auxology to be performed at each visit by the same, trained, blinded (if possible) auxologist as far as possible):

	• Absolute HT, measured on a calibrated wall-mounted stadiometer • Body weight • Data on parental height, if available: • Mother's height • Father's height • Complete medical history, including a description of pituitary deficiencies, currently and previously taken relevant medications and, when available, pre-screening height measurements to assess growth history • Overall health status assessment with complete physical examination and vital signs (blood pressure, heart rate, respiratory rate and body temperature) (subjects should rest for at least 5 minutes before vital sign assessment) • Pubertal status assessment (according to Tanner stages) (scant pubic hair is compatible with Tanner Stage 1, absent breast or testicular enlargement) • 12-lead ECG, local reading (subjects should rest for at least 2 minutes before ECG assessment) • Collection of blood for the following laboratory assessments: • Insulin-like Growth Factor-1 (IGF-1) serum levels • Anti-transglutaminase antibodies (results within approximately 6 months prior to Screening may be accepted, the final decision rests with the Medical Expert) • Anti-hGH and anti-PEG binding antibodies (the analysis of the anti-hGH and anti-PEG antibodies may only be conducted after randomization and are not required for eligibility verification. These data will be used to support evaluation of postdose antibody detection) • Routine safety biochemistry and hematology parameters • Other hormone levels: thyroid status (TSH, fT4, and fT3 levels) and morning cortisol • Glucose metabolism: fasting insulin, glucose, HbA1c. In case of suspected glucose intolerance, an oral glucose tolerance test (OGTT) should be performed (glucose metabolism parameters can be assessed locally at any time if there is suspicion of impaired glucose tolerance, which may include an OGTT)

	• Lipid status: Total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) • Stimulation tests: • Two different growth hormone (GH) stimulation tests, chosen from the following: a) insulin tolerance test (with cortisol response to hypoglycemia), b) arginine test, c) clonidine test, d) glucagon test (with or without propranolol, with cortisol response, unless cortisol measured during an intent-to-treat (ITT)), or e) L-dopa test (with or without propranolol) • Sex hormone priming is suggested (but not required) to be performed prior to GH stimulation tests for girls over the age of 10 and boys over the age of 11 • If 1 or both of the stimulation tests have been performed within approximately 6 months prior to Screening and have been well documented (with a proper recording of sample timing and results as well as euthyroid status of the subject) it may be accepted. In accordance with recent Guidelines, in subjects with known panhypopituitarism (eg, subjects who are deficient in TSH and/or ACTH post cranial radiation), GH stimulation tests may not be required in subjects who meet all other inclusion criteria and whose history is consistent with GHD including low growth velocity, low IGF-1 and IGFBP-3 levels, and delayed bone age. Also in children who are born panhypopituitary with deficiency of ≥2 pituitary hormones in addition to GH, do not require stimulation tests. The final decision rests with the Medical Expert • In case the subject was not previously assessed for deficiencies of the hypothalamus-pituitary-adrenal axis (HPA), competence should be demonstrated by an 8:00 AM cortisol > 190 nmol/L (7 µg/dL) in subjects with idiopathic GHD only, or by a peak cortisol level ≥ 500 nmol/L (18 µg/dL) in the context of an insulin tolerance test or glucagon stimulation test. At the discretion of the investigator, or in case Screening results are borderline or not interpretable (eg, from insulin tolerance test) or raising concerns, a Standard Dose or Low Dose Short adrenocorticotropic hormone (ACTH) test should be conducted

	• Karyotype testing to rule out Turner Syndrome will be performed in all female subjects (results obtained prior to Screening may be accepted if well documented; the final decision rests with the Medical Expert) • Sellar magnetic resonance imaging (MRI): contrast dye is recommended (if not conducted within approximately 6 months prior to Screening), performed and read locally • Fundoscopy (to rule out papilledema or signs of intracranial hypertension or mass effect) • Bone age determination – X-ray of the left hand and wrist for determination of bone age (if not performed within approximately 6 months prior to Screening), using a central bone age reader. If conducted within approximately 6 months, the digital or copy of hard film should be sent to the central bone age reader The investigator is recommended to perform the following Screening procedures in a stepwise approach in the order listed: 1) Trial participation should only be offered to subjects and parents/legal guardians thereof with already present suspicion of GHD (based on height measurement and medical history or previously performed diagnostic tests). 2) Non-invasive procedures (demographics, auxology measurements, physical examination, vital sign measurement and pubertal status assessment, review of medical history) are to be performed first. Further procedures should only be undertaken if all results thus far indicate eligibility. 3) Further investigations to be performed: laboratory assessments, GH stimulation tests followed by bone age, MRI, fundoscopy will be performed, also in a stepwise manner. If any Screening procedure during this process demonstrates ineligibility of the subject (see eligibility criteria), the Screening will terminate, and the subject will be classified as a Screening failure. This sequence of events at Screening is suggested to avoid exposure of the subject to unnecessary needle insertions, as well as to enable termination of Screening at any point in case any of the eligibility criteria are not met (such cases will be classified as Screening failures).

All results will be reviewed by the Medical Expert to verify eligibility of each subject prior to randomization. Eligible subjects will be centrally randomized to 1 of the 2 cohorts. Following randomization, it is recommended to start the treatment period (Visit 1) within 2 weeks from the time of randomization.

Prior to randomization subjects will be allocated to strata using the minimization rule according to their age (≥3 to ≤6 and >6 years), peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender.

Re-screening is permitted. Re-screening of subjects with an out of range cortisol and/or thyroid hormone level (inadequate replacement therapy for the insufficiency of other hypothalamo-pituitary axes) may be allowed ≥3 months after replacement treatment adjustment. Individual blood draws may be repeated for the following reasons, but not limited to: eg, ruling out an analytical error, sample handling or shipment issues, conflicting or inconsistent subject data, etc. The decision on re-screening will be made on a case by case basis by the Medical Expert. Re-screened subjects will receive a new Screening number.

Treatment Period

Randomized subjects will receive weekly doses of TransCon hGH or daily doses of Genotropin.

The 2 cohorts will be:

Cohort	Product	Dose Administration
1	TransCon hGH	Once weekly in a dose equivalent to **0.24** mg hGH/kg/week
2	Genotropin	Once daily in a dose equivalent to **0.24** mg hGH/kg/week

Following randomization, it is recommended to start the treatment period (Visit 1) within 2 weeks from the time of randomization. During some clinic visits TransCon hGH (Visits 1 and 2) or Genotropin (Visit 1) may be administered in the morning hours by the trial staff or by subject/parents/legal guardians, although Genotropin will generally be administered daily in the evening hours and TransCon hGH will generally be administered weekly in the morning or evening by subjects/parents/legal guardians (or

	occasionally by the trial staff). Once weekly healthcare services may be offered for the first 4 weeks of treatment to accommodate home administration of TransCon hGH and Genotropin. Extended support might be offered until subjects/parents/legal guardians are comfortable to take over administration of the study drug. Both drugs will be administered subcutaneously (SC) in the left and right buttock, left and right thigh, and left and right abdomen. It is recommended that injection sites are used successively, being rotated by using a different injection site at each subsequent injection. In addition to the Screening visit(s), enrolled TransCon hGH and Genotropin subjects will attend a total of 6 trial visits, all in the morning: V1 (Week 1; Day 1; predose, fasting), V2 (Week 5; predose for TransCon hGH subjects; any day during Week 5 for Genotropin subjects), V3 (Week 13; 48-72 hours postdose for TransCon hGH subjects; any day during Week 13 for Genotropin subjects), V4 (Week 26; 48-72 hours postdose for TransCon hGH subjects, fasting; any day during Week 26 for Genotropin subjects, fasting), V5 (Week 39; 48-72 hours postdose for TransCon hGH subjects; any day during Week 39 for Genotropin subjects) and V6 (Day 365 for TransCon hGH subjects [7 days postdose] and Genotropin subjects, fasting). For the PK/PD subset of TransCon hGH subjects (at least 8 subjects), Visit 3 will span approximately 168 hours following their 13th weekly injection. The 13th and 14th doses will be given at the site. All trial visits will be in the morning hours since the subject is asked to be fasted for Visits 1, 4 and 6, and so that auxology parameters are measured at approximately the same time of day and by the same individual (blinded auxologist), if possible. All attempts will be made to blind the auxologist to treatment assignment. The auxologist will be trained in the trial procedures to gain uniformity of measurement across all sites. Visits 1 and 2 will be scheduled on the day of TransCon hGH administration for Cohort 1, while Visits 3, 4, and 5 will be performed within a window of 48-72h after the weekly administration, to assess the E_{max} for IGF-1. The Genotropin cohort will have Visit 1 on the day of the first Genotropin administration, and Visits 2, 3, 4 and 5 any day during the respective week. Visit 6 will be performed seven days after the last TransCon hGH

	administration for Cohort 1 and the day after the last Genotropin administration in Cohort 2. It is suggested that the site staff follows up with the subject between the visits by eg, phone calls. Safety and efficacy assessments will be performed throughout the trial. All samples obtained after Informed Consent will be shipped to a selected central laboratory for analysis. Safety samples may be analyzed locally in case of emergency or if logistics or other unforeseen events do not permit a central analysis. During visits where study drug administration is planned at the site, these assessments will be performed prior to such administration (predose). While fasting is recommended for all visits, fasting is required at Visits 1, 4, and 6. The following procedures will be performed during V1 through V6 unless otherwise indicated: 1) Physical examination and vital sign measurement (blood pressure, heart rate, body temperature, respiratory rate) (subjects should rest for at least 5 minutes before vital sign assessment) 2) Review of concomitant medication 3) Review of Subject Diary by investigator (V2-V6) 4) Evaluation of Adverse Events (AEs) and local tolerability 5) Safety assessments: • Hormone levels {TSH, fT4, fT3, and morning cortisol; V1 (fasting), V3, V4 (fasting) and V6 (fasting)} • Routine safety biochemistry parameters (sodium, potassium, calcium, phosphate, chloride, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, total protein, creatinine, urea-nitrogen, uric acid, serum iron and transferrin) • Hematology parameters (hemoglobin, leukocytes, differential blood count of leukocytes, platelet count; blood smears will be performed locally for back-up analysis, if needed) • Parameters of glucose metabolism: fasting glucose (when required), insulin, and HbA1c (glucose metabolism parameters can be assessed locally at any time if there is

	suspicion of impaired glucose tolerance, which may include an OGTT) • Parameters of lipid metabolism (cholesterol, LDL and HDL, and triglycerides) 6) Immunogenicity assessment: anti-hGH and anti-PEG antibodies (Cohort 2: anti-PEG antibodies only at Screening and V1 predose, in support of trial specific assay cut-point determination); a subject with observed anti-hGH binding antibodies post dosing (V3-V5) at or close to the C_{max} for TransCon hGH may be brought back for a repeat sample to assess for neutralizing antibodies at a time point deemed appropriate to exclude assay interference. Anti-PEG antibodies will only be analyzed at the end of the individual treatment period once all samples from an individual subject are available. Serum samples collected for immunogenicity assessments will be retained for up to 5 years following trial finalization for possible further characterization of a potential anti-drug antibody response at a specialized laboratory 7) Bioanalytical samples for TransCon hGH (Cohort 1), hGH, PEG, IGF-1 and IGFBP-3 serum levels (for Cohort 2, PEG samples taken only at Screening and V1 predose to assist interpretation of anti-PEG antibody data) 8) Auxology measurements (actual height and body weight), to be performed by the same, trained, blinded (if possible) auxologist at approximately the same time of day (morning) at each visit if possible 9) Fundoscopy (at V4 and V6, and at other visits if clinically indicated) 10) Pubertal status assessment (at V4 and V6) 11) Training on study drug preparation and administration (V1 - during first administration and further as needed) 12) Study drug administration at site at Visit 1 (both cohorts) and Visit 2 (TransCon hGH cohort only) (dose should be adjusted at V3, V4 and V5 according to the subject's weight) - by the trial staff or subject/parent/legal guardian

	13) Vital signs will be assessed over 2 hours at Visit 1, at every clinic visit for all subjects, including over 24 hours postdose at V3 for the Cohort 1 PK/PD subset (subjects should rest for at least 5 minutes before vital sign assessment) 14) ECG at V1 and V4 for all subjects; additionally at V3 only in PK/PD subset at predose and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168h postdose for TransCon hGH subjects (subjects should rest for at least 2 minutes before ECG assessment) 15) Bone age at V6 At least 8 subjects from selected sites and countries in Cohort 1 will be assessed in a PK/PD subset analysis. Subjects may be housed, if needed, for the 13th injection and subsequent procedures. Subjects will stay at the hospital or come back for the scheduled procedures to assess safety and PK/PD profile over 1 week and ECGs intended to bracket presumed C_{max} of hGH, IGF-1, and TransCon hGH prodrug. • Blood sampling for PK (TransCon hGH, hGH, and PEG levels): predose (at -0.5 h) and at 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 hours (h) relative to the 13th TransCon hGH dosing • Blood sampling for PD (IGF-1 and IGFBP-3 levels): predose (at -0.5 h) and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h relative to the 13th TransCon hGH dosing • ECG measurements will be done predose and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h postdose • Vital signs and injection site evaluation will be done at 15 min, 1h, 2h and 24h postdose • The 14th dose will be given in clinic For subjects in the PK/PD subset, all other procedures planned for Visit 3 are also to be performed on the Day 1 of the respective week, prior to dosing. The subject and parents/legal guardians may be offered accommodation until all assessments are completed and the 14th dose given, depending on the agreement of the investigator with the parents/legal guardians, to ensure comfort for the child and reduce unnecessary travel. For all subjects, the absolute (total) dose of TransCon hGH or Genotropin initially administered will be calculated using the weight measurement obtained at Visit 1 (predose). The total dose of TransCon hGH or Genotropin will be adjusted according to the

	subject's weight measurement at Visit 3 (prior to dosing for the PK/PD subset), Visit 4 and Visit 5. Treatment can be discontinued or dose modified at any time during the trial. The following symptoms and laboratory abnormalities are considered to be the main guide for decision making concerning treatment discontinuation or dose modifications:
	• IGF-1 levels
	  • IGF-1 >+2.0 SD at any visit should be confirmed by a second measurement measured as soon as possible if deemed clinically significant by the investigator. Blood samples should be collected 5-7 days postdose (TransCon hGH cohort) or at any day (Genotropin cohort). If the IGF-1 SDS is still elevated above +2.0, and of clinical concern, the hGH dose may be decreased to the next lower dose bracket for TransCon hGH or a 20% decrease in dose (initially to 0.19 mg hGH/kg/week) for subjects on Genotropin. Any re-establishment of the original dose (0.24 mg hGH/kg/week) due to a subsequent sub-optimal IGF-1 response needs to be discussed with the Medical Expert.
	• Glucose parameters:
	  • HbA1c >6.2%
	  • Fasting glucose level >5.5 mmol/L (100 mg/dL)
	  • 2 hour postdose glucose level during OGTT ≥7.8 mmol/L (140 mg/dL)
	For a subject who had evidence of borderline glucose intolerance or diabetes prior to starting hGH therapy (eg, fasting plasma glucose (FPG) level of 98 mg/dL and HbA1c of 5.9%), it might be appropriate to treat for hyperglycemia as needed, without initial study drug treatment adjustment. However, if a subject with no evidence of glucose intolerance reaches the above glucose parameter levels, the FPG and HbA1c should be repeated within 2-4 weeks. If the repeat values are the same or worse, the TransCon hGH dose may be decreased to the next lower dose bracket (~20%; see Pharmacy Manual), and the dose may be reduced by~20% for a subject on Genotropin (eg, to 0.19 mg hGH/kg/week or 0.027 mg hGH/kg/day), or appropriate anti-glycemic therapy(ies) may be started. If appropriate follow-up monitoring shows progressively worsening glucose intolerance, additional hGH dose adjustments may be

	appropriate. If in any case treatment should be discontinued, all subsequent visits and assessments should continue as planned. The Medical Expert will review all AEs on an ongoing basis and all Serious Adverse Event (SAE) reports as received. The key safety data will also be reviewed by an Independent Safety Committee (ISC).
PLANNED NUMBER OF SUBJECTS	Approximately 150
TRIAL POPULATION	Approximately 150 prepubertal, hGH-treatment naïve children (males and females) with GHD will be included. Subjects will be randomized to 1 of 2 treatment groups in a 2:1 ratio: • Two thirds of the 150 subjects (approximately 100 subjects) will receive TransCon hGH treatment to obtain an expected 90 evaluable subjects in this cohort • One third of the 150 subjects (approximately 50 subjects) will receive Genotropin treatment to obtain an expected 45 evaluable subjects in this cohort
TRIAL ENTRY CRITERIA	**Inclusion criteria:** 1) Prepubertal children with GHD (either isolated or as part of a multiple pituitary hormone deficiency) in Tanner stage 1 aged: • Boys: 3-12 years, inclusive • Girls: 3-11 years, inclusive 2) Impaired HT defined as at least 2.0 standard deviations (SD) below the mean height for chronological age and sex (HT SDS ≤-2.0) according to the 2000 CDC Growth Charts for the United States Methods and Development or, after approval by the Medical Expert, at least 1.5 SD below the mid-parental height 3) BMI within ±2.0 SD of the mean BMI for chronological age and sex according to 2000 CDC standards, or BMI within ±2.0 SD of the mean BMI for bone age and sex 4) Diagnosis of GHD confirmed by 2 different GH stimulation tests, defined as a peak GH level of ≤10 ng/mL, determined with a validated assay. One or 2 well documented historical tests (with properly recorded sampling times and results as well as documented euthyroid status of the subject) performed within approximately 6 months prior to Screening can be accepted to replace 1 or both GH stimulation tests. The highest GH level

	determines eligibility. For subjects with known panhypopituitarism (eg, subjects who are deficient in TSH and/or ACTH post cranial radiation or born with ≥ 2 pituitary hormone deficiencies in addition to GH), GH stimulation tests may not be required. 5) Bone age (BA) at least 6 months less than chronological age (X-ray may have been taken within approximately 6 months prior to Screening, the X-ray or digital image should be sent to the central reader). 6) Baseline IGF-1 level of at least 1.0 SD below the mean IGF-1 level standardized for age and sex (IGF-1 SDS ≤-1.0) according to the central laboratory reference values. 7) Normal fundoscopy at Screening (without signs/symptoms of intracranial hypertension). 8) Children with multiple hormonal deficiencies must be on stable replacement therapy (stable dose and normal blood hormone levels) for other hypothalamo-pituitary axes for approximately 3 months. Thyroid replacement therapy for thyroid hormone deficiency must be instituted approximately 6 months (and be stable for approximately 3 months) prior to Screening. Temporary adjustment of glucocorticoid replacement therapy, as appropriate, is acceptable. 9) Normal 46 XX karyotype for girls (results prior to Screening may be accepted). 10) Written, signed informed consent of the parent(s) or legal guardian(s) of the subject and written assent of the subject (if the subject is able to read, understand, and sign). **Exclusion criteria:** 1) Children with a body weight below 12 kg 2) Prior exposure to recombinant hGH or IGF-1 therapy 3) Children with past or present intracranial tumor growth as confirmed by a sellar MRI scan (with contrast dye recommended) at Screening (MRI results from up to approximately 6 months prior to Screening may be accepted) 4) Children born small for gestational age (SGA) (ie, birth weight ≤-2.0 SD for gestational age, with or without a birth length ≤-2.0 SD for gestational age)

	5) Malnutrition, defined as: • Serum albumin level below the lower limit of normal (LLN) according to the reference ranges of the central laboratory, and • Serum iron below the LLN according to the reference ranges of the central laboratory, and • body mass index (BMI) ≤-2.0 SD for age and sex 6) Children with psychosocial dwarfism 7) Children with idiopathic short stature 8) Other causes of short stature such as coeliac disease (confirmed by anti-transglutaminase antibodies test), hypothyroidism, or rickets 9) History or presence of malignant disease; any evidence of present tumor growth; children with GHD and clinically cured tumors may be eligible after consultation with the Medical Expert 10) Any clinically significant abnormality likely to affect growth or the ability to evaluate growth (eg, chronic diseases like renal insufficiency, spinal cord irradiation) 11) Subjects with poorly controlled diabetes mellitus (HbA1c ≥8.0%) or diabetic complications 12) Known chromosomal abnormalities and other named medical syndromes known to impact growth (eg, Turner syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Russell-Silver syndrome, SHOX mutations/deletions and skeletal dysplasias) with the exception of septo-optic dysplasia 13) Closed epiphyses 14) Tanner stage >1 (scant pubic hair alone does not exclude the subject) 15) Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids with the exception of hormone replacement therapies (thyroxine, hydrocortisone, desmopressin) 16) Children requiring glucocorticoid therapy (eg, asthma) who are taking a dose of greater than 400 µg/d of inhaled budesonide or equivalents for longer than 1 month during a calendar year

	(Note: Approximately equivalent doses: fluticasone: 264 µg/d; beclomethasone: 504 µg/d; flunisolide 1,000 µg/d; triamcinolone: 1,000 µg/d; mometasone: 211 µg/d; ciclesonide 264 µg/d) 17) Major medical conditions and/or presence of contraindication to hGH treatment 18) Known or suspected HIV-positive subject 19) Known hypersensitivity to the components of the study drug 20) The subject and/or the parent/legal guardian are likely to be non-compliant with respect to trial conduct 21) Participation in any other trial of an investigational agent within 3 months prior to Screening 22) 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 TransCon hGH is a hGH (human Growth Hormone) prodrug that liberates somatropin as the active ingredient through controlled autohydrolysis resulting in sustained release of unmodified somatropin. TransCon hGH consists of recombinant hGH which is transiently conjugated to a PEG molecule through a (TransCon) linker. This conjugation inactivates hGH, thereby creating the TransCon hGH prodrug. After injection of TransCon hGH, autohydrolysis of the linker occurs in a controlled pH- and temperature-dependent manner whereby unmodified, fully active somatropin is released. TransCon hGH will be provided in glass vials and requires reconstitution with 1 mL sterile water for injection, and will be administered by syringe and needle.
REFERENCE PRODUCT(S)	Name: Genotropin (somatropin [rDNA origin] for injection)
TREATMENT REGIMENS	**TransCon hGH** TransCon hGH will be administered as once weekly SC injections of 0.24 mg hGH/kg/week. The administration will preferably be in the morning hours, by the trial staff or by the subjects/parents/legal guardians (under supervision by the trial staff at visits where drug administration is

	foreseen). Only if preferred by a parent/guardian/subject, TransCon hGH administration at home may be once weekly in the evening. **Genotropin** Genotropin (somatropin [rDNA origin] for injection) will be administered as daily SC injections in a standard dose of 0.24 mg hGH/kg/week. The total weekly dose will be equally split into 7 daily doses of 0.034 mg hGH/kg/day. A commercially approved injection device will be used for administration of the drug. With the exception of Visit 1 where the injection will be performed in the morning by the trial staff or by the subjects/parents/legal guardians (under supervision by the trial staff), daily administration of Genotropin will preferably be in the evening hours by the parents/legal guardians or subjects. Only if preferred by a parent/guardian/subject, Genotropin administration at home may be once daily in the morning. At some trial visits, trial staff will supervise injections.
PLANNED TRIAL SITES	Approximately 100 trial sites in approximately 20 countries in North America, Europe, Middle East and North Africa, and Oceania
CRITERIA FOR EVALUATION	**Efficacy endpoints:** Primary efficacy endpoint: Annualized HV at 52 weeks for weekly TransCon hGH and daily hGH treatment groups Secondary efficacy endpoints: • Annualized HV for the TransCon hGH and the daily hGH treatment group over 52 weeks • Change in HT SDS over 52 weeks for the TransCon hGH and the daily hGH treatment group • Serum IGF-1 and IGFBP-3 levels and IGF-1 SDS and IGFBP-3 SDS; and normalization of IGF-1 SDS over 52 weeks for the TransCon hGH and the daily hGH treatment group **Safety endpoints:** • Incidence of AEs • Local tolerability (assessed by the subject, the parents/legal guardians and the investigator)

	• Incidence of anti-hGH antibodies including neutralizing antibodies as needed (both cohorts) and incidence of treatment-emergent anti-PEG antibody formation (in TransCon hGH subjects) • IGF-1 levels and IGF-1 SDS • Parameters of glucose metabolism (fasting glucose and insulin level, HbA1c) and lipid parameters • Hormone levels: thyroid status and morning cortisol • All other hematology and biochemistry blood parameters • ECG • Results of the physical examinations, vital sign measurements • Bone age at 52 weeks **Pharmacokinetic and pharmacodynamic endpoints:** Subset of at least 8 TransCon hGH treated subjects after 13 weeks of treatment: • PK profile of TransCon hGH over 1 week • PK profile of hGH over 1 week • PK profile of PEG over 1 week • PD profile of IGF-1 and IGFBP-3 over 1 week • PD profile of IGF-1 SDS and IGFBP-3 SDS over 1 week • C_{max} for hGH of TransCon hGH
STATISTICAL METHODS	<u>Analysis Populations</u> The following data subsets will be analyzed: **Safety Analysis Subset** – The safety analysis set will include all randomized subjects who have received at least 1 dose of active treatment. **Intent-to-treat Subset** – The ITT subset will include all randomized subjects who have received at least 1 dose of active treatment and have follow-up efficacy data. **Per-protocol Subset** – The basis of Per-protocol (PP) subset is the ITT set. Subjects with major protocol deviations will be excluded from the Per-protocol (PP) analysis. Major protocol deviations excluding subjects from the PP analysis set will be defined in the Statistical Analysis Plan (SAP).

	PK/PD Population – The PK/PD population includes a subset of subjects from the TransCon hGH cohort who attended Visit 3 as planned and from whom blood sampling was performed at time points predose, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 168 hours postdose. Efficacy Analysis The primary endpoint, annualized height velocity at Week 52, will be compared between TransCon hGH treatment and daily hGH treatment, by a non-inferiority comparison with a non-inferiority margin of 2.0 cm/year, followed by a test of superiority if non-inferiority is established. A mixed model repeated measurement (MMRM) will be the primary analysis to evaluate annualized HV at week 52. The model will include baseline age, peak GH level of the stimulation test, and gender as fixed effects. Least square means will be derived and presented together with 95%-confidence intervals by treatment group. For the primary efficacy analysis, a 2-sided 95% confidence interval will be calculated for the difference in least square means between the 2 treatment groups [TransCon hGH treatment minus daily hGH] at Week 52. If the lower confidence bound is >-2.0 cm, non-inferiority is demonstrated in terms of effectiveness. If the lower confidence bound is > 0, superiority is established. All observed data including post-discontinuation data will be used for the primary analysis. Missing values will be imputed as follows for subjects who prematurely discontinued: From all subjects in the same treatment group who also prematurely discontinued treatment but had a height measurement at Week 52, annualized height change from the last measurement before discontinuation to Week 52 will be calculated. Missing height values at Week 52 will then be imputed by adding the mean change (standardized to the corresponding period between last height measurement and Week 52) to the last height measurement obtained. Based on the imputed height value at Week 52 the corresponding imputed annualized height velocity will be calculated. The primary efficacy analysis will be performed in the Intent-to-treat set. A sensitivity analysis will be provided for the Per-protocol set.

	For the continuous secondary efficacy endpoints (height velocity at further visits, change in height SDS, serum IGF-1 levels and IGFBP-3 levels, IGF-1 SDS, IGFBP-3 SDS), similar MMRM models will be used. Two sided 95% confidence intervals will be calculated for the difference in least square means between the 2 treatment groups. The rate of subjects achieving normalization of serum IGF-1 SDS will be calculated by treatment group and visit. A test of superiority in proportion of patients within 0-2.0 IGF-1 SDS will be conducted. A procedure to control for familywise type-1 error of multiple hypothesis testing will be specified in the SAP. In general, for secondary endpoints, missing values will be imputed by a method fully described in the SAP. Moreover, sensitivity analyses concerning missing values for the primary endpoint will be described in the SAP. All efficacy endpoints will be summarized descriptively by treatment group. Additional descriptive summaries may be added by treatment group and randomization stratum, separately for all 3 randomization strata. Figures will be created to display the time course of continuous efficacy endpoints by treatment group.
SAMPLE SIZE DETERMINATION	This is a pivotal clinical trial intended to support market approval. Based on the phase 2 trial (Protocol ACP-001_CT-004) and similar growth hormone studies published in the literature, and assuming a SD of 3.5 cm/year with a non-inferiority margin of 2.0 cm, a sample size of 147 subjects in the ITT population will be needed to show non-inferiority of TransCon hGH treatment compared to daily hGH with a power of 90%. This sample size calculation is based on a 2:1 randomization and a 1-sided alpha level of 0.025. A sample size of 150 subjects randomized has been chosen to account for slight imbalances in the randomization due to stratification of randomization. For 150 enrolled subjects, approximately 450 subjects may need to be screened in the trial.

TRIAL AND TREATMENT DURATION	The total duration of the trial for a subject is expected to be 60 weeks, with up to approximately 6 weeks of Screening and a 52-week active treatment period (plus approximately 2 weeks between randomization and V1). Subjects will be invited to participate in an extension trial after the completion of the initial 52 week treatment period. The intended purpose of the extension period is to assess long-term safety and efficacy. Subjects on Genotropin treatment (Cohort 2) will be switched to TransCon hGH treatment for this extension trial.

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°C	degrees Celsius
ACTH	adrenocorticotropic hormone (corticotropin)
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AGHD	adult growth hormone deficiency
ALT	alanine-aminotransferase
AM	ante meridiem
AST	aspartate-aminotransferase
AUC	area under the curve
BA	bone age
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cm	centimeter
C_{max}	maximum value of concentration
CRO	contract research organization
d	day
DCC	dual chamber cartridge
dL	deciliter
DMP	data management plan
DNA	desoxyribonucleic acid
eCDMS	electronic clinical data management system
ECG	electrocardiogram
E coli	*escherichia coli*
eCRF	electronic case report form
E_{max}	maximum effect observed
EOT	end of treatment
EU	European Union
FAS	full analysis subset
FDA	Food and Drug Administration
FPG	fasting plasma glucose
fT3	free triiodothyronine
fT4	free thyroxin
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone releasing hormone
GMP	Good Manufacturing Practice

h	hour
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
hGH	human growth hormone
HIV	human immunodeficiency virus
HPA	hypothalamus-pituitary-adrenal axis
HREC	human research ethics committee
HT	height
HV	height velocity
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IM	intramuscular
IND	Investigational New Drug
IRB	institutional review board
ISC	Independent Safety Committee
ITT	intent-to-treat
IU	international units
IV	intravenously
kDa	kilodalton
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
m	meter
m^2	square meter
mL	milliliter
mg	milligram
µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
min	minutes
mmol	millimole
MMRM	mixed model repeated measurement
mPEG	methoxypolyethylene glycol
MRI	magnetic resonance imaging
ng	nanogram
nmol	nanomole

OGTT	oral glucose tolerance test
PD	pharmacodynamic(s)
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PO	per os
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis subset
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
SHOX	short stature homeobox
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to maximum concentration is attained
TSH	thyroid-stimulating hormone
US	United States
V	visit
WFI	water for injection
WHO	World Health Organization
WHO-DRL	WHO Drug Reference List

5. INTRODUCTION

5.1. Background and Rationale

GH; somatropin) is a product of endocrine secretion of the pituitary gland which targets many 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 GH is pulsatile in nature; the major secretory pulses (up to 70% of daily secretion) occur with the first episode of slow-wave sleep. During childhood GH levels are relatively stable until puberty, when the GH pulse amplitude is elevated with no change in the frequency of pulses; afterwards GH pulse levels gradually decline through adulthood. GH production and secretion are regulated by multiple factors; growth hormone-releasing hormone (GHRH) and ghrelin are the most significant stimulators, while somatostatin has the strongest inhibitory action.

The human GH gene cluster is located on human chromosome 17q22-24, encoding a 191 amino-acid protein of 22 kDa and a less abundant 20 kDa GH molecule, as well as related proteins. GH 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 GH. IGF-1 is also produced by the growth cartilage in response to GH, where it acts locally as a paracrine-autocrine growth factor. IGF-1 is found in association with specific IGF-binding proteins, whose main functions are to extend the IGF-1 half-life in the circulation, to transport IGF-1 to the target cells, and to modulate its biological actions.

The most important and obvious function of GH is the promotion of growth in children. Through its IGF-1 mediated, 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, GH has important metabolic functions: it exerts potent anti-insulin effects resulting in decreased glucose utilization (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 GH which can appear at any time point in life and is due to various known and unknown factors. Childhood GHD can be:

- Congenital (organic causes such as pituitary aplasia, primary empty sella syndrome etc. or genetic causes including various mutations);
- Acquired (tumors of the hypothalamic-pituitary region, most commonly craniopharyngioma, head trauma, infection etc.); or
- Idiopathic (no clear etiology).

The etiology of childhood GHD is most commonly of hypothalamic origin with impaired GHRH secretion, the most common diagnosis being isolated idiopathic GHD.

Isolated GHD in children is characterized by short stature, low height velocity, and a propensity to hypoglycemia because of the relatively unopposed insulin action. Average adult height for untreated patients with severe isolated growth hormone deficiency is 143 cm in men and 130 cm in women (*Kemp 2014*). GHD children have normal body proportions, but small hands and feet and a small mid-face; they have excess of subcutaneous truncal fat, decreased muscle mass, thin hair and nails, a high-pitched voice, delayed puberty as well as an overall delay in bone and dental maturation. Hypoglycemic episodes are found in approximately 5% of GHD pediatric subjects and resolve with growth hormone therapy (*Kemp 2014*). GHD can also influence cognitive functions and the overall sense of well-being. When accompanied by other pituitary deficiencies other clinical manifestations may also be present.

GHD is a well-recognized clinical entity in the adult as well. It causes abnormalities in body composition, lipid metabolism, and physical and psychosocial function, all of which improve with GH replacement therapy. Body composition changes are common and include reduced lean body mass, increased fat mass with selective deposition of intraabdominal visceral fat, and increased waist-to-hip ratio. Hyperlipidemia and atherosclerosis, left ventricular dysfunction, hypertension, and increased plasma fibrinogen levels may also be present, causing a risk for cardiovascular and cerebrovascular events in these patients. Patients may experience a lack of energy, poor concentration, as well as social isolation and depression. GHD is also associated with relative insulin insensitivity and an increased prevalence of impaired glucose tolerance and diabetes mellitus.

It is now over 50 years since the human pituitary GH extract was purified and the first GHD patient was successfully treated. Contamination with infectious agents (Creutzfeld-Jakob prions) led to discontinuation of its use. A recombinant human GH (hGH; somatropin) was then produced by introducing the human DNA sequence into *Escherichia coli* (*E coli*) that became commercially available in 1985. The product is identical to the natural human growth hormone 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, SHOX deficiency, Noonan syndrome, idiopathic short stature, and children born SGA. The safety and efficacy profile of daily hGH preparations in pediatric and adult populations is well established and has invariably been deemed satisfactory. However, the requirement of daily subcutaneous administrations for pediatric GH therapy causes a significant burden and interruption of normal daily life to children and their legal guardians as well as compliance issues. Therefore, a product with less frequent dosing, comparable efficacy and an adequate safety profile may provide considerable improvement over currently available

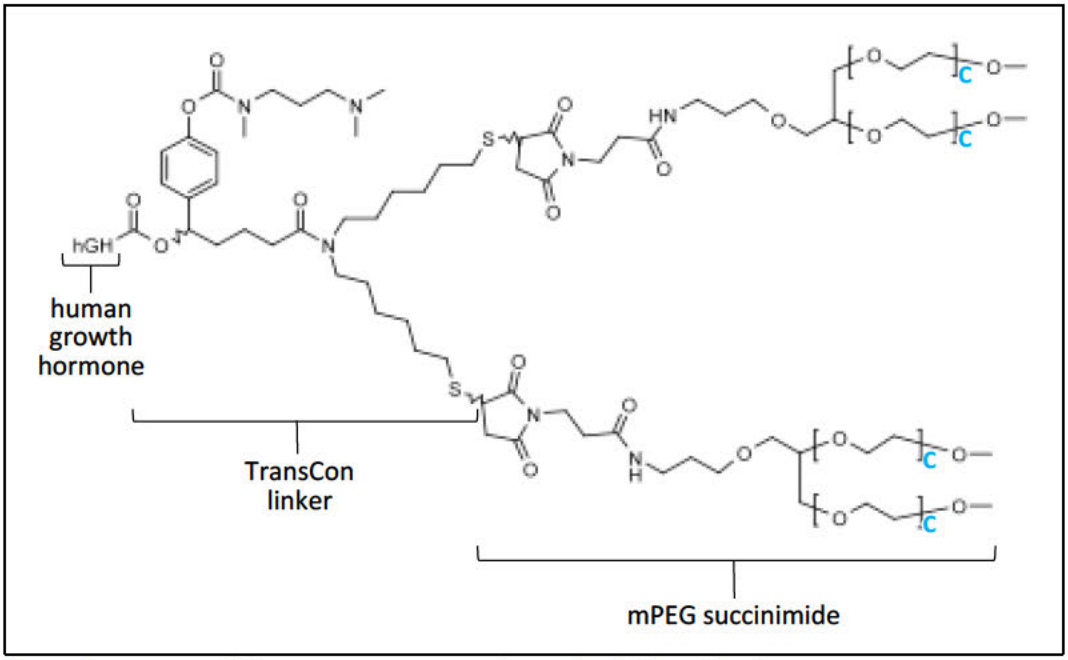
conventional GH replacement therapy regimens. At the present time there are no commercially available sustained-release or long-acting GH preparations.

The Sponsor is developing new proprietary drugs using TransConjugation (ie, attaching proteins or small molecules to a carrier), thereby creating an inactive prodrug. The prodrug is stable during storage, but after subcutaneous injection the TransCon hGH prodrug enters the bloodstream where the active ingredient (somatropin) 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:

- Improved efficacy/safety profiles
- Extended in vivo half-life over traditional conjugation methods

TransCon hGH is an hGH prodrug that liberates somatropin as the active pharmaceutical ingredient through controlled auto-hydrolysis resulting in sustained release. TransCon hGH consists of hGH that is conjugated to a methoxypolyethylene glycol (mPEG) molecule through a (TransCon) linker (Figure 1). This conjugation effectively inactivates hGH, thereby creating the TransCon hGH prodrug. After injection of TransCon hGH and entry into the bloodstream, autohydrolysis of the linker occurs in a controlled pH- and temperature-dependent manner whereby fully active somatropin is released.

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 1st order kinetics, whereby unmodified, fully active hGH is released. As the released hGH is completely unmodified, it has the same mode of action and volume of distribution as endogenous growth hormone. This is important for optimal efficacy, as a substantial portion of hGH activity is mediated by local hGH effects in target tissue. 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 remains intact following release of hGH and is cleared from the body through renal clearance as known for other high molecular weight molecules.

The hGH contained in TransCon hGH is synthesized by recombinant technology, using a strain of E. coli modified by the introduction of the human gene for growth hormone, the amino acid sequence is therefore identical to that of human origin.

The Sponsor initiated the TransCon hGH development program with TransCon PEG80 hGH (ACP-001), in which the carrier was 80 kDa mPEG, for which 4 clinical trials were conducted: 2 phase 1 trials in healthy adults, 1 phase 2 trial in adult growth hormone deficiency, and 1 phase 2 trial in pediatric growth hormone deficiency. Acceptable safety, PK, and PD were shown in these trials. Importantly, safety and efficacy comparable to Genotropin were shown in the phase 2 pediatric growth hormone deficiency trial.

Upon completion of the TransCon hGH (ACP-001) 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 somatropin or the inactive nature of the parent TransCon hGH product. The linker component and somatropin are identical between TransCon hGH (ACP-001) and TransCon hGH (ACP-011); the only change is to reduce the size of the mPEG carrier. This change resulted in TransCon hGH (ACP-011), a drug product with lower viscosity and higher product concentration that enables smaller injection volumes and use of a small-gauge needle. Additionally, the PEG exposure is reduced by ≥50%.

5.2. Relevant Findings from Nonclinical Studies

TransCon PEG40 hGH

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 rabbit, 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 or on standard pharmacology end points assessed following repeat dosing in cynomolgus monkeys. Expected pharmacological effects included a minimal increased body weight gain at dose levels 20-fold above the expected therapeutic dose following weekly repeat dosing of up to 26 weeks in the cynomolgus monkey at doses up to and including 4.8 mg hGH/kg. Test article-related microscopic findings, interpreted as exaggerated pharmacology and non-adverse, were limited to the mammary glands in both male and female animals. The findings included small amounts of exudate, ductal dilation (galactocele), mononuclear cell infiltrate, and vacuolation primarily seen at the top dose of 4.8 mg hGH/kg. These are recognized effects of high growth hormone doses in monkeys, presumably reflecting cross-reactivity with the prolactin receptor. Systemic exposure to TransCon hGH (ACP-011), with the associated hGH mediated increases in the PD biomarker, IGF-1, was observed in all of these studies. 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.

One 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 doses) over 4 weeks. A total of 37 subjects were randomized. The pharmacokinetic results showed that dose-linearity was observed for area under the curve (AUC) and C_{max} of hGH in 29 subjects given increasing doses of ACP-001. Reversible PEGylation of 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 pharmacodynamic results

showed that ACP-001 demonstrated a consistent elevation of IGF-1 over the period of 1 week, indicating it is as potent as daily hGH with regards to IGF-1 elevation based on hGH equivalents.

One 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 doses) over 26 weeks. There were 55 subjects who 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 height velocities among the 3 dose levels administered weekly ranged from 11.9 cm for the 0.14 mg/hGH/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. No reports of drug-related serious or unexpected AEs were observed. Adverse events 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) was consistent with published data for daily growth hormone. No neutralizing antibodies were detected. Maximum hGH blood concentration was comparable between equivalent weekly doses of TransCon Growth Hormone 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 have been observed in a small number of subjects and primarily in the high-dose treatment arm.

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. Injection site reactions, mainly mild erythema (phase 2 AGHD) and pain (phase 2 pediatric GHD), occurred across all treatment groups.

Literature data indicate that the PEG associated with a biological molecule should provide no extra concern because 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 does not represent an unacceptable additional risk to humans (*Webster 2007*). Detailed information is given in the Investigator's Brochure.

5.3.1 Pharmacokinetics of hGH Following Administration of TransCon hGH (ACP-001) and TransCon hGH (ACP-011)

This was a phase 1 single center, randomized, open label trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics 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 to the trial to compare the PD parameters of ACP-011 and ACP-001 at the 0.24 mg hGH/kg dose level.

TransCon hGH (ACP-011) was found to be bioequivalent to TransCon hGH (ACP-001), with the ratios of the means for C_{max} and AUC for both released hGH and IGF-1 falling 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 time to maximum concentration is attained (T_{max}) of 16.0 to 36.0 hours, indicative of release of hGH from TransCon hGH in both the subcutaneous tissue and the systemic circulation. Elimination appeared in a mono-phasic manner and the mean terminal half-life ranged from 21.8 to 25.4 hours independent of dose. TransCon hGH (ACP-001) dosed at 0.24 mg hGH/kg exhibited comparable T_{max}, C_{max} and $AUC_{0\text{-}168h}$ for hGH and IGF-1 to the equivalent dose of TransCon hGH (ACP-011).

5.4. Summary of Potential Risks and Benefits

Currently somatropin is available only in daily injection formulations, causing a significant burden and interruption of normal daily life to children and their parents as well as compliance issues. Decreased compliance with somatropin is known to result in sub-optimal efficacy (height velocity). Therefore, a product with less frequent dosing, comparable efficacy and safety may provide considerable improvement over currently available conventional GH replacement therapy regimens. TransCon hGH (ACP-011) is a new hGH prodrug product with a proposed once weekly dosing regimen designed to overcome the inconvenience of daily hGH injections and is anticipated to have a comparable safety profile to currently approved daily hGH products. Due to their depot formulations, other long-acting growth hormone products have been associated with lipoatrophy, resulting from prolonged local tissue exposure to growth hormone activity. Because of the fast absorption of the inactive prodrug into the blood stream, followed by sustained release of hGH in the peripheral circulation, it is expected that lipoatrophy at the injection site, which has been observed with permanently PEGylated growth hormones and polymer encapsulated hGH depots, will be avoided with TransCon hGH. Obviating the need for daily injections should increase compliance and therefore efficacy, which would be of great benefit to both pediatric and adult patients with GHD and other disorders with associated growth impairment and need for hGH supplementation (*European Union 2008*).

6. OBJECTIVES

6.1. Primary Objective

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

6.2. Secondary Objectives

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

7. TRIAL DESIGN

7.1. Overall Trial Design and Plan

7.1.1 Trial Design

This is a phase 3, randomized, open-label, active-controlled trial of TransCon hGH as compared to standard daily growth hormone, over 52 weeks (Figure 2). The trial will be conducted at approximately 100 sites in approximately 20 countries in North America, Europe, Middle East and North Africa, and Oceania. All centers will be specialized treatment centers in the management of pediatric GHD.

The trial consists of:

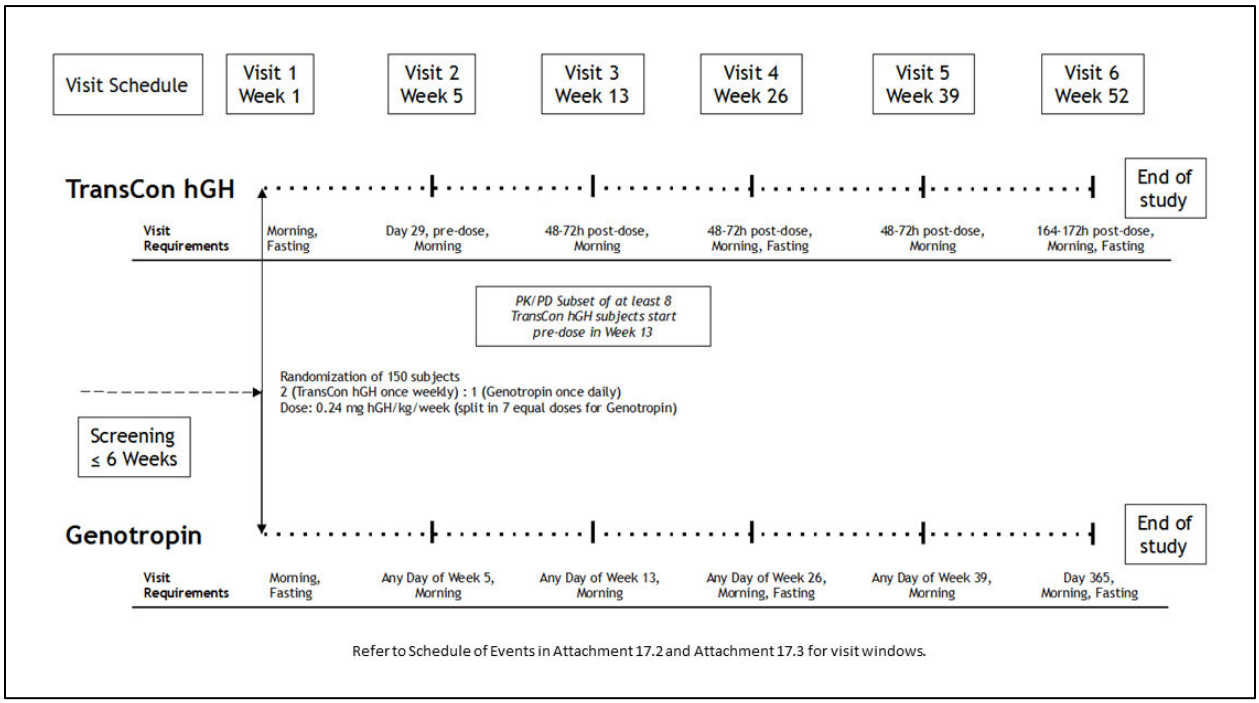
- Screening period - up to approximately 6 weeks (plus a recommended period of up to 2 weeks until V1)
- Treatment period - 52 weeks of dosing

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

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

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

Figure 2
Overall Trial Design



h = hour; hGH = human growth hormone; kg = kilogram; mg = milligram; PD = pharmacodynamics; PK = pharmacokinetic

7.1.2 Measures Taken To Minimize Bias

Once all results determining the eligibility of the subject are available and reviewed by the Medical Expert, the subject will be centrally randomized to 1 of 2 cohorts: either TransCon hGH or Genotropin, in a 2:1 ratio, and allocated to strata using the minimization rule according to their age (≥3 to ≤6 and >6 years), peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender. For the stratum peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), the stratum will be allocated based on the highest GH value of the 2 stimulation tests. The subject will be assigned a unique randomization number along with the cohort allocation.

The trial auxologists will be trained and kept blinded to treatment allocation as far as possible at each site.

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

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

This is an open-label trial. Due to different dose frequencies and dosing techniques, it is not deemed suitable to employ blinding methods between TransCon hGH and Genotropin treatment assignment. However, attempts will be made to keep selected Sponsor staff (Medical Experts and Statisticians) blinded to treatment.

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

7.2. Trial Sites

The trial will be conducted at approximately 100 sites in approximately 20 countries in North America, Europe, Middle East and North Africa, and Oceania. All centers will be specialized treatment centers in the management of pediatric GHD.

7.3. Stopping Rules

7.3.1 Early Termination of Subjects

Valid reasons for which a subject's participation in the clinical trial may be discontinued are considered to constitute one of the following:

- Withdrawal of consent by the subject or parent/legal guardian;
- AE:
    - Occurrence of a malignancy during the course of trial
        - Development of benign intracranial hypertension

  - Occurrence of AEs that result in the investigator's or parent's/legal guardian's wish to discontinue treatment (such as, but not limited to, serious intercurrent critical illness, slipped capital femoral epiphysis, scoliosis, avascular necrosis, development of lipoatrophy, etc.)
  - Abnormal laboratory values that affect the subject's safety, if discontinuation is considered necessary by the investigator or the Medical Expert
  - A severe adverse drug reaction, if discontinuation of study drug is desired by the subject/parent/legal guardian or considered necessary by the investigator or the Medical Expert
  - Evidence of development of neutralizing antibodies (eg, a blunted IGF-1 response in addition to a positive result in the neutralizing antibody assay)
- Use of prohibited concomitant medication (refer to Section 9.9.2.2)
- If the investigator and/or Sponsor considers that withdrawal from the trial is necessary (lack of subject compliance, serious protocol deviation)
- Subject is lost-to-follow-up
- Note: In the event of premature discontinuation of study drug treatment for any of the above reasons, every effort should be made to encourage and enable the subject to attend all remaining study visits. Additionally, the reasons for study drug or study early discontinuation or any missed visits will be captured in the database.

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 in respect of their nature, severity and duration or the unexpected incidence of known AEs
- 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
- Careless or premeditated false documentation in the electronic case report form (eCRF)
- Inadequate co-operation with the investigator
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation

8. SUBJECT POPULATION

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

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

See Section 8.1 for eligibility criteria.

8.1. Trial Entry Criteria

8.1.1 Inclusion Criteria

Inclusion criteria for this trial are as follows:

1) Prepubertal children with GHD (either isolated or as part of a multiple pituitary hormone deficiency) in Tanner stage 1 aged (*Tanner 1976*):
   - Boys: 3 -12 years, inclusive
   - Girls: 3 -11 years, inclusive
2) Impaired HT defined as at least 2.0 SD below the mean height for chronological age and sex (HT SDS ≤-2.0) according to the 2000 CDC Growth Charts for the United States Methods and Development (www.cdc.gov/growthcharts, *Kuczmarski 2002*) or, after approval by the Medical Expert, at least 1.5 SD below the mid-parental height (*Cole 2000*, *Kriström 2009*, *Sotos 2014*).
3) BMI within ±2.0 SD of the mean BMI for chronological age and sex according to 2000 CDC standards, or BMI within ±2.0 SD of the mean BMI for bone age and sex
4) Diagnosis of GHD confirmed by 2 different GH stimulation tests, defined as a peak GH level of ≤10 ng/mL, determined with a validated assay. One or 2 well documented historical tests (with properly recorded sampling times and results as well as documented euthyroid status of the subject) performed within approximately 6 months prior to Screening can be accepted to replace 1 or both GH stimulation tests. The highest GH level determines eligibility. For subjects with known panhypopituitarism (eg, subjects who are deficient in TSH and/or ACTH post cranial radiation or born with ≥ 2 pituitary hormone deficiencies in addition to GH), GH stimulation tests may not be required (*Grimberg 2016*).
5) Bone age (BA) at least 6 months less than the chronological age (X-ray may have been taken within approximately 6 months prior to Screening, the X-ray or digital image should be sent to the central reader)
6) Baseline IGF-1 level of at least 1.0 SD below the mean IGF-1 level standardized for age and sex (IGF-1 SDS ≤-1.0) according to the central laboratory reference values
7) Normal fundoscopy at Screening (without signs/symptoms of intracranial hypertension)

8) Children with multiple hormonal deficiencies must be on stable replacement therapy (stable dose and normal blood hormone levels) for other hypothalamo-pituitary axes for approximately 3 months. Thyroid replacement therapy for thyroid hormone deficiency must be instituted approximately 6 months (and be stable for approximately 3 months) prior to Screening. Temporary adjustment of glucocorticoid replacement therapy, as appropriate, is acceptable.
9) Normal 46 XX karyotype for girls (results prior to Screening may be accepted)
10) Written, signed informed consent of the parent(s) or legal guardian(s) of the subject and written assent of the subject (if the subject is able to read, understand, and sign)

8.1.2 Exclusion Criteria

Exclusion criteria for this trial are as follows:

1) Children with a body weight below 12 kg
2) Prior exposure to recombinant hGH or IGF-1 therapy
3) Children with past or present intracranial tumor growth as confirmed by a sellar MRI scan (with contrast dye recommended) at Screening (MRI results from up to approximately 6 months prior to Screening may be accepted)
4) Children born SGA (ie, birth weight ≤-2.0 SD for gestational age, with or without a birth length ≤-2.0 SD for gestational age) (*Mandy 2016*)
5) Malnutrition, defined as:
   - Serum albumin level below the LLN according to the reference ranges of the central laboratory, and
   - Serum iron below the LLN according to the reference ranges of the central laboratory, and
   - BMI ≤-2.0 SD for age and sex
6) Children with psychosocial dwarfism
7) Children with idiopathic short stature
8) Other causes of short stature such as coeliac disease (confirmed by anti-transglutaminase antibodies test), hypothyroidism, or rickets
9) History or presence of malignant disease; any evidence of present tumor growth; children with GHD and clinically cured tumors may be eligible after consultation with the Medical Expert
10) Any clinically significant abnormality likely to affect growth or the ability to evaluate growth (eg, chronic diseases like renal insufficiency, spinal cord irradiation)
11) Subjects with poorly controlled diabetes mellitus (HbA1c ≥8.0%) or diabetic complications

12) Known chromosomal abnormalities and other named medical syndromes known to impact growth (eg, Turner syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Russell-Silver syndrome, SHOX mutations/deletions and skeletal dysplasias) with the exception of septo-optic dysplasia
13) Closed epiphyses
14) Tanner stage >1 (scant pubic hair alone does not exclude the subject)
15) Concomitant administration of other treatments that may have an effect on growth such as anabolic steroids with the exception of hormone replacement therapies (thyroxine, hydrocortisone, desmopressin)
16) Children requiring glucocorticoid therapy (eg, asthma) who are taking a dose of greater than 400 µg/d of inhaled budesonide or equivalents for longer than 1 month during a calendar year

    (Note: Approximately equivalent doses: fluticasone: 264 µg/d; beclomethasone: 504 µg/d; flunisolide 1,000 µg/d; triamcinolone: 1,000 µg/d; mometasone: 211 µg/d; ciclesonide 264 µg/d)
17) Major medical conditions and/or presence of contraindication to hGH treatment
18) Known or suspected HIV-positive subject
19) Known hypersensitivity to the components of the study drug
20) The subject and/or the parent/legal guardian are likely to be non-compliant with respect to trial conduct
21) Participation in any other trial of an investigational agent within 3 months prior to Screening
22) 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 (discontinuation of treatment) 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 he/she considers it to be in the subject's best interest. If significant safety issues arise, dosing may be discontinued but unless informed consent is withdrawn any subject who discontinues treatment with either TransCon hGH or Genotropin should be encouraged to remain in the trial and attend all clinic visits. The final decision for treatment discontinuation will be made by the Medical Expert and investigator. See Section 7.3 for a list of stopping rules governing early termination of subjects from trial.

In the case of premature discontinuation of a subject's participation in the trial (eg, withdrawal of informed consent), the investigator should schedule a trial discontinuation visit to collect data, particularly AE follow-up data (if applicable) and to collect samples for laboratory evaluations. This visit should contain assessments from the End of Trial Visit (Visit 6, Day 365), and should

be documented in the eCRF together with the reason for trial discontinuation. In case of treatment discontinuation for other causes than withdrawal of the informed consent, subjects should be asked to remain in the trial and attend all subsequent trial visits.

Every effort should be made to observe subjects who have been randomized and received at least 1 dose of study drug until the scheduled end of their observation, even if they discontinued the trial treatment. The investigator should make every attempt to contact the subject/parent/legal guardian via phone to arrange the appropriate follow-up assessment for such subjects and document the course of the subject's condition.

8.3. Subject Replacement Criteria

Subjects withdrawn from the trial may be replaced if the number of evaluable subjects drops below 90 in Cohort 1 or 45 in Cohort 2.

9. TREATMENTS

9.1. Identification of Investigational Product(s)

TransCon hGH will be provided as single-use glass vials and supplied to the sites in cartons. Most materials needed for study drug reconstitution and administration will be provided to the investigational sites and distributed by the investigator to the subject, including: prefilled syringes with 1 mL water for injection and/or vials containing water for injection; 1 mL syringes for administration; and needles for reconstitution and administration.

Genotropin will be provided as a 2-chamber cartridge with a commercially approved device. In some countries Genotropin may be provided by prescription from a local pharmacy with reimbursement by the Sponsor. Most additional materials needed for study drug administration will be provided to the investigational sites and distributed by the investigational site to the subject, including: injection device and needles for administration with the injection device (other than in countries were Genotropin along with injection device and needles are provided by prescription from a local pharmacy with reimbursement by the Sponsor).

Both TransCon hGH and Genotropin will be dispensed to parents/legal guardians in sufficient amounts to provide the subject with enough supply of study drug until the next visit.

9.2. Labeling

All study drug will be labeled according to Good Manufacturing Practice (GMP) and local requirements. Parents/legal guardians will be provided with dosing and storage instructions. Study drug labels will comply with the regulatory requirements of each country and will be printed in local language; the storage conditions will be contained on the carton label.

9.3. Treatments Administered

9.3.1 TransCon hGH

TransCon hGH will be provided as a lyophilized powder, in single-use glass vials, to be reconstituted with 1 mL sterile water for injection. For the composition and characteristics of TransCon hGH, refer to the Investigator's Brochure.

TransCon hGH will be injected SC into the left and right buttock, left and right thigh, and left and right abdomen in the morning hours by the trial staff or by the subject/parent/legal guardian. To minimize local side effects it is recommended to rotate the 6 injection sites in a subsequent manner (eg, right buttock, right abdomen, right thigh, left thigh, left abdomen, left buttock).

During the extension trial planned at the conclusion of this 52-week randomized trial, the plan is to switch from TransCon hGH (ACP-011) in vials to TransCon hGH (ACP-011) in dual chamber cartridges (DCC's), in which TransCon hGH will be supplied as a single dose in a DCC for administration by an Auto-Injector. The DCC presentations will use the 2 compounded solution concentrations also used for the vials in the randomized portion of this trial, 12.1 mg hGH/vial (11.0 mg hGH/mL when reconstituted) and 24.2 mg hGH/vial (22.0 mg hGH/mL when reconstituted), and will be filled with different volumes of the 2 solutions to provide nine presentations with dose increments of approximately 20%. Doses from 3.0 mg hGH to 13.3 mg hGH will be available. When the subjects are dosed with 0.24 ± 0.02 mg hGH/kg/week the associated volumes for injection for each weight range are shown in the table below (Table 1).

For the trial to support the use of the Auto-Injector during the extension phase, the aim is to mimic the dose increments and the associated weight ranges both with respect to injection volume and mg hGH. Therefore, 2 vial presentations will be manufactured; a 12.1 mg hGH/vial (11.0 mg hGH/mL when reconstituted) and 24.2 mg hGH/vial (22.0 mg hGH/mL when reconstituted). Only the drug product at 12.1 mg hGH/vial will be available at start of phase 3. The consequence is that subjects ≥24 kg will initially be dosed with a somewhat higher volume, and subjects ≥42 kg will initially need 2 injections on the same day using 2 different injection site locations until the 24.2 mg hGH/vial is available during resupply of study drug.

Table 1 shows the dose volumes to be used for each weight range, both when only the 12.1 mg hGH/vial (11.0 mg hGH/mL when reconstituted) is available early in the phase 3 trial, and the dose volumes that will be used when both the 12.1 and 24.2 mg hGH/vials (11.0 and 22.0 mg hGH/mL when reconstituted) are available. All of these dose volumes provide an average dose of 0.24 ± 0.02 mg hGH/kg/week within each weight range. As a result, all subjects in the TransCon hGH group will be treated over the course of the trial at an average dose of 0.24 mg hGH/kg/week.

Table 1
Drug Concentration After Reconstitution With 1 mL Water for Injection, Dosing Brackets and Volumes to be Administered

Only 12.1 mg hGH/vial available			12.1 mg hGH/vial and 24.2 mg hGH/vial available		
Drug Concentration in Vial	**Subject Weight Range (kg)**	**Volume Dosed (mL)**	**Drug Concentration in Vial**	**Subject Weight Range (kg)**	**Volume Dosed (mL)**
11.0 mg hGH/mL	11.5-13.9	0.27	11.0 mg hGH/mL	11.5-13.9	0.27
11.0 mg hGH/mL	14.0-16.4	0.33	11.0 mg hGH/mL	14.0-16.4	0.33
11.0 mg hGH/mL	16.5-19.9	0.39	11.0 mg hGH/mL	16.5-19.9	0.39
11.0 mg hGH/mL	20.0-23.9	0.47	11.0 mg hGH/mL	20.0-23.9	0.47
11.0 mg hGH/mL	24.0-28.9	0.57	22.0 mg hGH/mL	24.0-28.9	0.29
11.0 mg hGH/mL	29.0-34.9	0.69	22.0 mg hGH/mL	29.0-34.9	0.35
11.0 mg hGH/mL	35.0-41.9	0.83	22.0 mg hGH/mL	35.0-41.9	0.41
11.0 mg hGH/mL	42.0-50.9	0.50 x 2	22.0 mg hGH/mL	42.0-50.9	0.50
11.0 mg hGH/mL	51.0-60.5	0.60 + 0.61	22.0 mg hGH/mL	51.0-60.5	0.60

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

Once the 24.2 mg hGH/vial is available, all subjects will be treated with a single injection per week.

9.3.2 Genotropin

Genotropin is a lyophilized powder dispensed in a 2-chamber cartridge. For the composition and characteristics of Genotropin, refer to the Summary of Product Characteristics.

Genotropin will be administered as daily SC injections in a standard dose equivalent to 0.24 mg hGH/kg/week. The total weekly dose will be equally split into 7 daily doses of 0.034 mg hGH/kg/day. Genotropin will be administered with an injection device for SC use into the left and right buttock, left and right thigh, and left and right abdomen, recommended in the evening hours (at bedtime), by the subject/parent/legal guardian. Administration will be done at the trial site during the first visit in the morning hours. To minimize local side effects it is recommended to rotate the injection sites in the same manner as TransCon hGH (see Section 9.3.1).

For specific dosing instructions for both treatment cohorts, please refer to the Pharmacy Manual.

9.4. Dispensing and Storage

While at the site, TransCon hGH and Genotropin must be kept in a locked area with access limited to designated trial staff and must be stored at +2°C to +8°C. Water for injection should be stored at 2 to 30°C. All products will be temperature monitored, as appropriate. Genotropin will be dispensed by the trial staff or sent home to the parents/legal guardians in cool boxes in a transportation bag (eg, trolley case and/or backpack) and should be stored in a refrigerator at +2°C to +8°C as soon as possible, out of reach of children. TransCon hGH will be dispensed by trial staff or sent home to the parents/legal guardians in cool boxes in a transportation bag and should be stored below 30°C at home, and only moved to cold storage (+2°C to +8°C) if the

ambient temperature is above 30°C. The storage conditions will be carefully described to the subject/parent/legal guardian.

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

9.5. Selection of Doses in the Trial

TransCon hGH (ACP-011) is an inactive prodrug. The phase 2 pediatric GHD trial with TransCon hGH (ACP-001) demonstrated that a dose of 0.21 mg hGH/kg/week provided comparable PK, PD (IGF-1 SDS), efficacy (annualized height velocity) and safety/tolerability compared to the equivalent weekly dose of Genotropin divided into 7 daily doses. The Bridging Trial demonstrated that ACP-011 has comparable PK (hGH) and PD (IGF-1) to ACP-001, meeting the formal definition of bioequivalence. The smaller PEG in ACP-011 resulted in less than half the PEG exposure compared to ACP-001. As somatropin is recommended at a dose of 0.025-0.05 mg hGH/kg/day (0.175-0.35 mg hGH/kg/week) and Genotropin is approved up to a dose of 0.245 mg hGH/kg/week for pediatric GHD, a dose of 0.24 mg hGH/kg/week for both TransCon hGH and Genotropin appears to be justified and appropriate. The nonclinical and clinical data supports once weekly dosing with TransCon hGH. The randomized treatment period of 52 weeks is consistent with current regulatory recommendations, and the extension trial will provide longer-term safety and efficacy data.

9.6. Dose Adjustment Criteria

Treatment can be discontinued or dose modified at any time during the trial. The following symptoms and laboratory abnormalities are considered to be the main guide for decision making concerning treatment discontinuation or dose modification:

- IGF-1 levels
  - IGF-1 >+2.0 SD at any visit should be confirmed by a second measurement measured as soon as possible if deemed to be clinically significant by the investigator. Blood samples should be collected 5-7 days postdose (TransCon hGH cohort) or at any day (Genotropin cohort). If the IGF-1 SDS is still elevated above +2.0, and of clinical concern, the hGH dose may be decreased to the next lower dose bracket for TransCon hGH (see Pharmacy Manual and Section 9.3) or a 20% decrease in dose (initially to 0.19 mg hGH/kg/week) for subjects on Genotropin. Any re-establishment of the original dose (0.24 mg hGH/kg/week) due to a subsequent sub-optimal IGF-1 response needs to be discussed with the Medical Expert.
- Glucose parameters
  - HbA1c > 6.2%
  - Fasting glucose level > 5.5 mmol/L (100 mg/dL)
  - 2 hour postdose glucose level during OGTT ≥ 7.8 mmol/L (140 mg/dL)

For a subject who had evidence of borderline glucose intolerance or diabetes prior to starting hGH therapy (eg, FPG 98 mg/dL and HbA1c 5.9%), it might be appropriate to treat for hyperglycemia as needed, without initial study drug treatment adjustment. However, if a subject with no evidence of glucose intolerance reaches the above glucose parameter levels, the FPG and HbA1c should be repeated within 2-4 weeks. If the repeat values are the same or worse, the TransCon hGH dose may be decreased to the next lower dose bracket (~20%; see Pharmacy Manual), and the dose may be reduced by ~20% for a subject on Genotropin (eg, to 0.19 mg hGH/kg/week or 0.027 mg hGH/kg/day), or appropriate anti-glycemic therapy(ies) may be started. If appropriate follow-up monitoring shows progressively worsening glucose intolerance, additional hGH dose adjustments may be appropriate. If in any case treatment should be discontinued, all subsequent visits and assessments should continue as planned.

If a subject develops any of the above listed criteria or develops a severe GH-related AE at any time during the course of the trial (eg, peripheral edema, severe headache, intracranial hypertension or other adverse drug reaction and/or abnormal laboratory values), the investigator or Medical Expert/Sponsor (and ISC if needed) may propose a dose modification.

9.7. Drug Accountability

Sites will be supplied with the study drug to distribute as required to subjects. Dedicated site staff will be responsible for all procedures concerning the study drug.

The investigational medicinal products will be delivered to trial sites and dispensed to the subjects/subjects' parents/legal guardians according to the relevant storage conditions for each product. In some countries the Genotropin comparator and injection device may be provided by prescription, with reimbursement by the Sponsor. Centrally supplied study drug must be kept in an appropriate, secure area at the trial site and stored according to the conditions specified on the study drug labels at the trial site (refrigerator) and subject's home.

Study drug inventory accounting should be completed to record the receipt and distribution. Any study drug delivery must be confirmed including date, quantity, batch number, and subject identification number. An accurate record of the date and amount of study drug dispensed to each subject must be recorded and be available for inspection at any time.

An appointed trial monitor will review the accountability and inventory forms on a regular basis.

Clinical trial supplies include, but are not limited to, lab supplies and study drugs. The Sponsor will be responsible for the supply, administration, inventory, and applicable accountability of clinical trial supplies, exercising accepted medical and pharmaceutical practices, except in the case of pharmacy-provided Genotropin in some countries. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the trial, the investigator will keep the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned until further notice.

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

9.8. Treatment Compliance

Treatment compliance will be assessed during the treatment period and will be based on drug accountability and review of the Subject Diary and Instructions for Use. Parents/legal guardians will be instructed to return to the site all used study drug at each visit. The completed Subject Diary where the date, time and the dose of study drug administration will be recorded along with any noted local injection site reactions or other adverse events and concomitant medications should be returned at each visit. All study drug, used and unused, shall be returned at the end of the trial.

All drug accountability records will be kept secure by the trial staff and will be verified by the trial monitor.

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.

9.9.2 Permitted and Prohibited Therapies

Concomitant therapy is considered any medication other than the investigational or reference product that is administered from the first day of study drug administration up until the end of the trial. Any change in documented, permitted concomitant medication being taken at the beginning of the clinical trial must be recorded in the eCRF, noting the type of medication, the dose, duration, 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 in collaboration with the Medical Expert and Sponsor.

9.9.2.1 Permitted Therapies

- Replacement therapy for pituitary deficiencies of other axes. As growth hormone may enhance the transformation of hydrocortisone to cortisone, the investigator may increase the dose of hydrocortisone replacement therapy if needed (eg, for anticipated stress).
- Glucocorticoid therapy for indications other than adrenal replacement (eg, asthma) may be administered in a dose equivalent to inhaled budesonide of not more than 400 µg/d for a maximum of approximately 1 month during 1 calendar year (approximate equivalent doses: fluticasone: 264 µg/d; beclomethasone: 504 µg/d; flunisolide 1,000 µg/d; triamcinolone: 1,000 µg/d; mometasone: 211 µg/d; ciclesonide 264 µg/d).
- Treatment for diabetes

- Over-the-counter vitamins, minerals or other dietary supplements only if their use is agreed to by the investigator.

9.9.2.2 Prohibited Therapies

- Estrogen
- Anabolic steroids; systemic corticosteroids other than in the doses indicated above
- Weight-reducing drugs or appetite suppressants other than for the treatment of attention deficit hyperactivity disorder (ADHD)

10. TRIAL PROCEDURES

Prior to any protocol related activities or Screening evaluations (see the Schedule of Events), 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/IEC/HREC) prior to implementation. Release of medical information authorization should also be obtained at the time of informed consent.

10.1. Trial Periods and Visits

In addition to the Screening visit(s), enrolled TransCon hGH and Genotropin subjects will attend a total of 6 trial visits, all in the morning: V1 (Week 1; Day 1; predose, fasting), V2 (Week 5; predose for TransCon hGH subjects; any day during Week 5 for Genotropin subjects), V3 (Week 13; 48-72 hours postdose for TransCon hGH subjects; any day during Week 13 for Genotropin subjects), V4 (Week 26; 48-72 hours postdose for TransCon hGH subjects, fasting; any day during Week 26 for Genotropin subjects, fasting), V5 (Week 39; 48-72 hours postdose for TransCon hGH subjects; any day during Week 39 for Genotropin subjects) and V6 (Day 365 for TransCon hGH subjects [7 days postdose] and Genotropin subjects, fasting).

For the PK/PD subset of TransCon hGH subjects (at least 8 subjects), Visit 3 will span approximately 168 hours following their 13th weekly injection. The 13th and 14th injections will be given at the site.

An overview of all visits is provided in the Schedules of Events (Attachments 17.2 and 17.3).

10.1.1 Screening (Day –42 to –1)

The Screening period will last up to approximately 6 weeks during which clinical data will be collected and investigations will be performed to establish the subject's eligibility for the trial. The following assessments will be performed and appropriate data collected.

1) Data on current anthropometric measurements (auxology), (auxology to be performed at each visit by the same, trained, blinded auxologist as far as possible):
   - Absolute HT, measured on a calibrated wall-mounted stadiometer

- Body weight

2) Data on parental height, if available:
   - Mother's height
   - Father's height
3) Complete medical history, including a description of pituitary deficiencies, currently and previously taken relevant medications and, when available, pre-screening height measurements to assess growth history
4) Overall health status assessment with complete physical examination and vital signs (blood pressure, heart rate, respiratory rate and body temperature) (subjects should rest for at least 5 minutes before vital sign assessment)
5) Pubertal status assessment (according to Tanner stages) (*Tanner 1976*) (scant pubic hair is compatible with Tanner Stage 1, absent breast or testicular enlargement)
6) 12-lead ECG, local reading (subjects should rest for at least 2 minutes before ECG assessment)
7) Collection of blood for the following laboratory assessments:
   - IGF-1 serum levels
   - Anti-transglutaminase antibodies (results within approximately 6 months prior to Screening may be accepted, the final decision rests with the Medical Expert)
   - Anti-hGH and anti-PEG binding antibodies (the analysis of the anti-hGH and anti-PEG antibodies may only be conducted after randomization and are not required for eligibility verification. These data will be used to support evaluation of postdose antibody detection)
   - Routine safety biochemistry and hematology parameters
   - Other hormone levels: thyroid status (TSH, fT4, and fT3 levels) and morning cortisol
   - Glucose metabolism: fasting insulin, glucose, HbA1c. In case of suspected glucose intolerance, an OGTT should be performed (glucose metabolism parameters can be assessed locally at any time if there is suspicion of impaired glucose tolerance, which may include an OGTT)
   - Lipid status: Total cholesterol, triglycerides, HDL and LDL
8) Stimulation tests:
   - Two different GH stimulation tests, chosen from the following: a) insulin tolerance test (with cortisol response to hypoglycemia), b) arginine test, c) clonidine test, d) glucagon test (with or without propranolol, with cortisol response unless cortisol measured during an ITT), or e) L-dopa test (with or without propranolol)
   - Sex hormone priming is suggested (but not required) to be performed prior to GH stimulation tests for girls over the age of 10 and boys over the age of 11

- If 1 or both of the stimulation tests have been performed within approximately 6 months prior to Screening and have been well documented (with a proper recording of sample timing and results as well as euthyroid status of the subject) it may be accepted. In accordance with recent Guidelines, in subjects with known panhypopituitarism (eg, subjects who are deficient in TSH and/or ACTH post cranial radiation), GH stimulation tests may not be required in subjects who meet all other inclusion criteria and whose history is consistent with GHD including low growth velocity, low IGF-1 and IGFBP-3 levels, and delayed bone age (*Grimberg 2016*). Also in children who are born panhypopituitary with deficiency of ≥2 pituitary hormones in addition to GH, do not require stimulation tests. The final decision rests with the Medical Expert
- In case the subject was not previously assessed for deficiencies of the HPA, competence should be demonstrated by an 8:00 AM cortisol > 190 nmol/L (7 µg/dL) in subjects with idiopathic GHD only, or by a peak cortisol level ≥ 500 nmol/L (18 µg/dL) in the context of an insulin tolerance test or glucagon stimulation test. At the discretion of the investigator, or in case Screening results are borderline or not interpretable (eg, from insulin tolerance test) or raising concerns, a Standard Dose or Low Dose Short ACTH test should be conducted

9) Karyotype testing to rule out Turner Syndrome will be performed in all female subjects (results obtained prior to Screening may be accepted if well documented; the final decision rests with the Medical Expert)
10) Sellar MRI: contrast dye is recommended (if not conducted within approximately 6 months prior to Screening); performed and read locally
11) Fundoscopy (to rule out papilledema or signs of intracranial hypertension or mass effect)
12) Bone age determination – X-ray of the left hand and wrist for determination of bone age (if not performed within approximately 6 months prior to Screening), using a central bone age reader. If conducted within approximately 6 months, the digital or copy of hard film should be sent to the central bone age reader.

The investigator is recommended to follow a stepwise approach in the order listed:

- Trial participation should only be offered to subjects and parents/legal guardians thereof with already present suspicion of GHD (based on height measurement and medical history or previously performed diagnostic tests).
- Non-invasive procedures (demographics, auxology measurements, physical examination, vital sign measurement and pubertal status assessment, review of medical history) are to be performed first. Further procedures should only be undertaken if all results thus far indicate eligibility.

- Further investigations to be performed: laboratory assessments, GH stimulation tests followed by bone age, MRI, fundoscopy will be performed, also in a stepwise manner. If any Screening procedure during this process demonstrates ineligibility of the subject (see eligibility criteria), the Screening will terminate and the subject will be classified as a Screening failure.

This sequence of events at Screening is suggested to avoid exposure of the subject to unnecessary needle insertions, as well as to enable termination of Screening at any point in case any of the eligibility criteria are not met (such cases will be classified as Screening failures).

All results will be reviewed by the Medical Expert to verify eligibility of each subject prior to randomization. Eligible subjects will be centrally randomized to 1 of the 2 cohorts. Following randomization, it is recommended to start the treatment period (Visit 1) within 2 weeks from the time of randomization.

10.1.2 Treatment Period (Days 1 to 365)

For all cohorts, the following procedures will be performed during Visit 1 through Visit 6, unless otherwise indicated:

1) Physical examination and vital sign measurement (blood pressure, heart rate, body temperature, respiratory rate) (subjects should rest for at least 5 minutes before vital sign assessment)
2) Review of concomitant medication
3) Review of Subject Diary by investigator (V2 – V6)
4) Evaluation of Adverse Events (AEs) and local tolerability
5) Safety assessments:
    - Hormone levels {TSH, fT4, fT3, and morning cortisol; V1 (fasting), V3, V4 (fasting), and V6 (fasting)}
    - Routine safety biochemistry parameters (sodium, potassium, calcium, phosphate, chloride, total bilirubin, alkaline phosphatase, LDH, AST, ALT, GGT, albumin, total protein, creatinine, urea-nitrogen, uric acid, serum iron and transferrin)
    - Hematology parameters (hemoglobin, leukocytes, differential blood count of leukocytes, platelet count; blood smears will be performed locally for back-up analysis, if needed)
    - Parameters of glucose metabolism: fasting glucose (when required), insulin, and HbA1c (glucose metabolism parameters can be assessed locally at any time if there is suspicion of impaired glucose tolerance, which may include OGTT)
    - Parameters of lipid metabolism (cholesterol, LDL and HDL, and triglycerides)

6) Immunogenicity assessment: anti-hGH and anti-PEG antibodies (for Cohort 2, anti-PEG antibodies only at Screening and V1 predose in support of trial specific assay cut-point determination); a subject with observed anti-hGH binding antibodies post dosing (V3-V5) at or close to the C_{max} for TransCon hGH may be brought back for a repeat sample to assess for neutralizing antibodies at a time point deemed appropriate to exclude assay interference. Anti-PEG antibodies will only be analyzed at the end of the individual treatment period once all samples from an individual subject are available.

   Serum samples collected for immunogenicity assessments will be retained for up to 5 years following trial finalization for possible further characterization of a potential anti-drug antibody response at a specialized laboratory

7) Bioanalytical samples for TransCon hGH (Cohort 1), hGH, PEG, IGF-1 and IGFBP-3 serum levels; (for Cohort 2, PEG samples taken only at Screening and V1 predose to assist interpretation of anti-PEG antibody data) (see Table 2)
8) Auxology measurements (actual height and body weight), to be performed by the same, trained, blinded (if possible) auxologist at approximately the same time of day (morning) at each visit if possible
9) Fundoscopy (at V4 and V6, and at other visits if clinically indicated)
10) Pubertal status assessment (at V4 and V6)
11) Training on study drug preparation and administration (V1 - during first administration and further as needed)
12) Study drug administration at site at Visit 1 (both cohorts) and Visit 2 (TransCon hGH cohort only) (dose should be adjusted at V3, V4 and V5 according to the subject's weight) – by the trial staff or subject/parent/legal guardian
13) Vital signs will be assessed over 2 hours at Visit 1, at every clinic visit for all subjects, including over 24 hours postdose at V3 for the Cohort 1 PK/PD subset (subjects should rest for at least 5 minutes before vital sign assessment)
14) ECG at V1 and V4 for all subjects; additionally at V3 only in PK/PD subset at predose and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168h postdose for TransCon hGH subjects (subjects should rest for at least 2 minutes before ECG assessment)
15) Bone age at V6

The dose of TransCon hGH or Genotropin initially administered will be calculated using the weight measurement obtained at Visit 1 (predose). The dose of TransCon hGH or Genotropin will be adjusted according to the subject's weight measurement at Visit 3 (prior to dosing for the PK/PD subset), Visit 4, and Visit 5.

At each visit the parents/legal guardians will be given enough study drug for treatment until the next visit. Subject Diary availability will be ensured to record the date and time of injection, any local reactions or other Adverse Events and concomitant medication.

It is suggested that the site staff follows up with the subject between the visits by eg, phone calls.

Table 2
Bioanalytical Samples at Visits 1 to 6

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

h=hours; hGH = human growth hormone

10.1.2.1 TransCon hGH Cohort (Cohort 1)

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

All attempts should be made to adhere to the planned visit schedule. However, in case the subject is not able to attend Visits 3, 4, 5 and 6 during Week 13, 26, 39 or 52, respectively, these visits can be performed with a + 2 week window for Visit 3, meaning either Week 14 or 15, if Week 13 is not achievable; and a ± 1 week window for Visits 4, and 5, meaning either Week 25 or 27, if Week 26 is not achievable or Week 38 or 40, if Week 39 is not achievable; and a + 1 week visit window for Visit 6, meaning Week 53, if Week 52 is not achievable. Bioanalytical sampling will follow in accordance with the Schedule of Events (Attachment 17.2). All visits should be in the morning for consistency of auxology measurements, and because subjects should be fasting for Visits 1, 4, and 6.

10.1.2.2 Genotropin Cohort (Cohort 2)

- At Visit 1, subjects will be dosed in the morning at the clinic.
- All subjects in the Genotropin cohort will attend Visit 1 fasting with administration of the dose at the investigational site and predose sampling, and will have an additional postdose sampling for hGH at 2 hours.

- Visits 2, 3, 4 and 5 will be performed on any day during Weeks 5, 13, 26 and 39, respectively. Preferably, all clinic visits will be in the morning for consistency of auxology measurements. Visit 4 needs to be conducted in the morning hours, since the subject is requested to be fasting. Visit 6 will be performed 1 day after the last dosing (Day 365) in the morning hours, since the subject is requested to be fasting.

All attempts should be made to adhere to the planned visit schedule. However, in case the subject is not able to attend Visit 3, 4, 5 and 6 during Week 13, 26, 39, or 52, respectively, these visits can be performed with a + 2 week window for Visit 3, meaning either Week 14 or Week 15, if Week 13 is not achievable; and a ± 1 week visit window for Visits 4 and 5, meaning either Week 25 or 27, if Week 26 is not achievable or Week 38 or 40, if Week 39 is not achievable; and a + 1 week visit window for Visit 6, meaning Week 53, if Week 52 is not achievable. Visit assessments can occur on any day during the concerned Weeks 5, 13, 26, 39, and 52 in accordance with the Schedule of Events (Attachment 17.3).

10.1.2.3 Pharmacokinetic/Pharmacodynamic Subset

At least 8 subjects from selected sites and countries in Cohort 1 will be assessed in a PK/PD subset analysis. Subjects will attend Visit 3 on Day 1 of Week 13 (Day 85). Visit 3 may be performed within a window of + 2 weeks, starting on Day 1 of either Week 13, 14 or 15. Subjects will stay at the hospital or come back for the scheduled procedures to assess safety and PK/PD profile over 1 week and ECGs intended to bracket presumed C_{max} of hGH, IGF-1, and TransCon hGH prodrug:

- Blood sampling for PK (TransCon hGH, hGH, and PEG levels): predose (at -0.5h) and at 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 hours (h) relative to the 13th TransCon hGH dosing
- Blood sampling for PD (IGF-1 and IGFBP-3 levels): predose (at -0.5h) and 8, 12, 16, 24, 36, 48, 72, 96, 120, and 168 h relative to the 13th TransCon hGH dosing
- ECG measurements will be done predose and at 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h postdose
- Vital signs and injection site evaluations will be done at 15 min, 1h, 2h, and 24h postdose
- The 14th dose injection will be given at the clinic

For subjects in the PK/PD subset, all other procedures planned for Visit 3 are also to be performed on the Day 1 of the respective week, prior to dosing. The subject and parents/legal guardians may be offered accommodation until all assessments are completed and the 14th dose given, depending on the agreement of the investigator with the parents/legal guardians, to ensure comfort for the child and reduce unnecessary travel.

Each PK/PD blood sample will require 2 mL of blood (details in Appendix 5).

The collection, processing, storage, and shipment of samples are described in the Laboratory Manual.

10.1.3 Unscheduled Visits

Unscheduled visits are those visits that occur between regularly scheduled visits and are performed to assess a previously noted Adverse Event, abnormal/alarming laboratory values, and/or clinical findings. In such cases, the subject's parent/legal guardian will be contacted via telephone to arrange an unscheduled visit to assess the noticed abnormalities. Only focused assessments (guided by the reason for the visit) are foreseen for these visits.

10.1.4 Early Termination Visits

Early termination visits are performed for any early termination/withdrawal of a subject from this clinical trial. This does not apply to subjects who have discontinued study drug but agreed to continue trial visits. The structure and assessments of the early termination visit should be as much as possible similar to the last visit (V6).

10.1.5 Follow-up and Extension Phase

All subjects who successfully complete this 52 week trial are invited to participate in an extension trial, for whom Visit 6 represents the first visit for the extension trial and data collected will become the baseline data for the extension trial. This extension trial is to assess long-term safety and efficacy. Subjects on Genotropin treatment (Cohort 2) will switch over to TransCon hGH treatment.

There is no follow up visit for subjects who do not enter the extension trial for whom Visit 6 is the final trial visit.

10.2. Trial Duration

Each subject's participation is expected to last about 60 weeks, as follows:

- Screening period: up to approximately 6 weeks (plus a recommended period of up to 2 weeks until V1)
- Treatment period: 52 weeks of repeated dosing

10.2.1 Overall Trial Schedule

10.2.2 Screening Period

The Screening period will last up to approximately 6 weeks during which clinical data will be collected and investigations will be performed to establish the subject's eligibility for the trial. Prior to any trial specific procedure, a written and signed informed consent will be obtained from the parent(s)/legal guardian(s) and a signed assent from the subject (whenever possible). At sites where the diagnosis of GHD is confirmed prior to consideration for a trial, many of the Screening procedures (which reflect standard of care in the diagnosis of GHD) may be completed prior to signing of informed consent or assent form. These may enable enrollment, based on approval by the Medical Expert. For the assessments that will be performed during the

Screening period refer to Section 10.1.1 and the Schedules of Events (Attachments 17.2 and 17.3).

All results determining the eligibility of the subject will be reviewed by the Medical Expert prior to randomization of each subject. Eligible subjects will be centrally randomized to 1 of 2 cohorts: TransCon hGH or Genotropin, in a 2:1 ratio. Prior to randomization subjects will be allocated to strata using the minimization rule according to their age (≥3 to ≤6 and >6 years), peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender.

Re-screening is permitted. Re-screening of subjects with an out of range cortisol and/or thyroid hormone level (inadequate replacement therapy for the insufficiency of other hypothalamo-pituitary axes) may be allowed ≥3 months after replacement treatment adjustment. Individual blood draws may be repeated for the following reasons, but not limited to: eg, ruling out an analytical error, sample handling or shipment issues, conflicting or inconsistent subject data, etc. The decision on re-screening will be made on a case by case basis by the Medical Expert. Re-screened subjects will receive a new Screening number.

10.2.3 Treatment Period

Randomized subjects will receive weekly doses of TransCon hGH or daily doses of Genotropin. The 2 cohorts will be as shown in Table 3.

Table 3
Dose Cohorts

Cohort	Product	Dose Administration
1	TransCon hGH	Once weekly in a dose equivalent to **0.24** mg hGH/kg/week
2	Genotropin	Once daily in a dose equivalent to **0.24** mg hGH/kg/week

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

Following randomization, it is recommended to start the treatment period (Visit 1) within 2 weeks from the time of randomization. During some clinic visits TransCon hGH (Visits 1 and 2) or Genotropin (Visit 1) may be administered in the morning hours by the trial staff or by subject/parents/legal guardians, although Genotropin will generally be administered daily in the evening hours and TransCon hGH will generally be administered weekly in the morning or evening by subjects/parents/legal guardians (or occasionally by the trial staff). Once weekly healthcare services may be offered for the first 4 weeks of treatment to accommodate home administration of TransCon hGH and Genotropin. Extended support may be offered until subjects/parents/legal guardians are comfortable to take over administration of the study drug. Both drugs will be administered SC in the left and right buttock, left and right thigh, and left and right abdomen. It is recommended that injection sites are used successively, being rotated by using a different injection site at each subsequent injection.

In addition to the Screening visit(s), enrolled TransCon hGH and Genotropin subjects will attend a total of 6 trial visits, all in the morning: V1 (Week 1; Day 1; predose, fasting), V2 (Week 5; predose for TransCon hGH subjects; any day during Week 5 for Genotropin subjects), V3 (Week 13; 48-72 hours postdose for TransCon hGH subjects; any day during Week 13 for Genotropin subjects), V4 (Week 26; 48-72 hours postdose for TransCon hGH subjects, fasting; any day during Week 26 for Genotropin subjects, fasting), V5 (Week 39; 48-72 hours postdose for TransCon hGH subjects; any day during Week 39 for Genotropin subjects) and V6 (Day 365 for TransCon hGH subjects [7 days postdose] and Genotropin subjects, fasting).

For the PK/PD subset of TransCon hGH subjects (at least 8 subjects), Visit 3 will span approximately168 hours following their 13th weekly injection as follows: 1, 2, 3, 4, 5, 6 and 8 days after the dose of that week. The 13th and 14th doses will be given in the clinic.

TransCon hGH and Genotropin will be administered at the site at the first trial visit. The administration at the trial site will be done by the trial staff or by the subject/parent/legal guardian. Bioanalytical samples for the assessment of TransCon hGH and PEG (TransCon hGH treated subjects; for Cohort 2, PEG samples taken only at Visit 1 to assist interpretation of anti-PEG antibody data), and hGH and IGF-1/IGFBP-3 levels (all subjects) will be performed at all visits at selected time points. For a detailed visit schedule refer to Section 10.1.2 and the Schedule of Events in Attachments 17.2 and 17.3.

The dose of TransCon hGH or Genotropin will be calculated using the weight measurement obtained at Visit 1 (predose). The dose of TransCon hGH or Genotropin will be adjusted according to the subject's weight measurement at Visit 3 (prior to dosing for the PK/PD subset), Visit 4 and Visit 5. The dose may be decreased for safety reasons at any time during the trial course, according to the predefined dose-adjustment criteria (Section 9.6).

It is suggested that the site staff follows up with the subject between the visits by eg, phone calls.

10.3. Assessments

10.3.1 Safety and Efficacy

Safety and efficacy assessments will be performed throughout the trial. All samples obtained after Informed Consent will be shipped to a selected central laboratory for analysis. Safety samples may be analyzed locally in case of emergency or if logistics or other unforeseen events do not permit a central analysis. During visits where study drug administration is planned at the site, these assessments will be performed prior to such administration (predose). While fasting is recommended for all visits, fasting is required at Visits 1, 4, and 6. The following procedures will be performed during V1 through V6 unless otherwise indicated:

1) Physical examination and vital sign measurement (blood pressure, heart rate, body temperature, respiratory rate) (subjects should rest for at least 5 minutes before vital sign assessment)

2) Review of concomitant medication
3) Review of Subject Diary by investigator (V2-V6)
4) Evaluation of AEs and local tolerability
5) Safety assessments:
   - Hormone levels {TSH, fT4, fT3, and morning cortisol; V1 (fasting), V3, V4 (fasting) and V6 (fasting)}
   - Routine safety biochemistry parameters (sodium, potassium, calcium, phosphate, chloride, total bilirubin, alkaline phosphatase, LDH, AST, ALT, GGT, albumin, total protein, creatinine, urea-nitrogen, uric acid, serum iron and transferrin)
   - Hematology parameters (hemoglobin, leukocytes, differential blood count of leukocytes, platelet count; blood smears will be performed locally for back-up analysis, if needed)
   - Parameters of glucose metabolism: fasting glucose (when required), insulin, and HbA1c (glucose metabolism parameters can be assessed locally at any time if there is suspicion of impaired glucose tolerance, which may include an OGTT)
   - Parameters of lipid metabolism (cholesterol, LDL and HDL, and triglycerides)
6) Immunogenicity assessment: anti-hGH and anti-PEG antibodies (Cohort 2: anti-PEG antibodies only at Screening and V1 predose, in support of trial specific assay cut-point determination); a subject with observed anti-hGH binding antibodies post dosing (V3-V5) at or close to the C_{max} for TransCon hGH may be brought back for a repeat sample to assess for neutralizing antibodies at a time point deemed appropriate to exclude assay interference. Anti-PEG antibodies will only be analyzed at the end of the individual treatment period once all samples from an individual subject are available.
7) Serum samples collected for immunogenicity assessments will be retained for up to 5 years following trial finalization for possible further characterization of a potential anti-drug antibody response at a specialized laboratory
8) Bioanalytical samples for TransCon hGH (Cohort 1), hGH, PEG, IGF-1 and IGFBP-3 serum levels (for Cohort 2, PEG samples taken only at Screening and V1 predose to assist interpretation of anti-PEG antibody data)
9) Auxology measurements (actual height and body weight), to be performed by the same, trained, blinded (if possible) auxologist at approximately the same time of day (morning) at each visit if possible
10) Fundoscopy (at V4 and V6, and at other visits if clinically indicated)
11) Pubertal status assessment (at V4 and V6)
12) Training on study drug preparation and administration (V1 - during first administration and further as needed)

13) Study drug administration at site at Visit 1 (both cohorts) and Visit 2 (TransCon hGH cohort only) (dose should be adjusted at V3, V4 and V5 according to the subject's weight) - by the trial staff or subject/parent/legal guardian
14) Vital signs will be assessed over 2 hours at Visit 1, at every clinic visit for all subjects, including over 24 hours postdose at V3 for the Cohort 1 PK/PD subset (subjects should rest for at least 5 minutes before vital sign assessment)
15) ECG at V1 and V4 for all subjects; additionally at V3 only in PK/PD subset at predose and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168h postdose for TransCon hGH subjects (subjects should rest for at least 2 minutes before ECG assessment)
16) Bone age at V6

10.3.2 Pharmacokinetic and Pharmacodynamic

At least 8 subjects from selected sites and countries in Cohort 1 will be assessed in a PK/PD subset analysis. Subjects will attend Visit 3 on Day 1 of Week 13 (Day 85). Visit 3 may be performed within a window of + 2 weeks, starting on Day 1 of either Week 13, 14 or 15. Subjects will stay at the hospital or come back for the scheduled procedures to assess safety and the PK/PD profile over 1 week and ECGs intended to bracket the presumed C_{max} of hGH, IGF-1, and TransCon hGH prodrug:

- Blood sampling for PK (TransCon hGH, hGH, and PEG levels): predose (at -0.5 h) and at 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h relative to the 13th TransCon hGH dosing
- Blood sampling for PD (IGF-1 and IGFBP-3 levels): predose (at -0.5 h) and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h relative to the 13th TransCon hGH dosing
- ECG measurements will be done predose and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h postdose
- Vital signs and injection site evaluation will be done at 15 min, 1 h, 2 h and 24 h postdose
- The 14th dose will be given in clinic

For subjects in the PK/PD subset, all other procedures planned for Visit 3 are also to be performed on the Day 1 of the respective week, prior to dosing. The subject and parents/legal guardians may be offered accommodation until all assessments are completed and the 14th dose given, depending on the agreement of the investigator with the parents/legal guardians, to ensure comfort for the child and reduce unnecessary travel.

11. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING

11.1. Adverse Events

11.1.1 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 this 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, use in combination with another drug), route of administration, formulation, or dose, including an overdose (ICH E6, 21 CFR Part 312.32).

Risks to trial subjects MAY include rare events of the types listed below. Some of these risks are due to taking the investigational drug TransCon hGH, but most are known or thought to be associated with approved hGH therapies such as Genotropin. In view of the investigational nature of TransCon hGH, possible risks are not necessarily limited to those listed:

- Headaches
- Muscle pain
- Joint stiffness
- High blood sugar (hyperglycemia)
- Sugar in the urine (glycosuria)
- Intracranial hypertension with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products
- Edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias
- Hypothyroidism - In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment.
- Slipped Capital Femoral Epiphysis – these may occur more frequently in patients with endocrine disorders (including GHD or in patients undergoing rapid growth). Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.
- Progression of Pre-existing Scoliosis - progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis.
- Skin atrophy

- When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site [see Dosage and Administration].
- Allergic reaction - As with any protein, local (skin reactions, such as rash or swelling) or systemic allergic reactions (including rare generalized hypersensitivity reactions) may occur. Parents/legal guardians/subjects should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.
- Pancreatitis - Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Pancreatitis should be considered in any somatropin-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 Expert will review all AEs on an ongoing basis and all Serious Adverse Event (SAE) reports as received. The key safety data will also be reviewed periodically by an ISC. Safety assessments will consist of monitoring and recording of all AEs, including SAEs, regular monitoring of hematology and blood chemistry parameters, regular physical examination, vital sign assessment, fundoscopy, and ECGs.

11.1.2 Severity, Causality and Outcome Assessment

11.1.2.1 Severity Rating

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

Mild – The subject is aware of the sign or symptom, but finds it easily tolerated. 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 subject has enough discomfort to cause interference with or change in some of their usual activities. The event is of some concern 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 was at immediate risk of death from the event as it occurred.

11.1.2.2 Causality Rating

The principal investigator will assess the causal relationship of the study drug to the event, using the following guideline:

Definite – This category applies to those adverse experiences which the investigator feels are clearly related to the study medication. An adverse experience may be assigned as definitely related when the event meets the first 4 or more of the following criteria:

- It follows a reasonable temporal sequence from administration of the trial product
- It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
- It disappears or decreases on cessation of the study drug. [There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (eg, [1] bone marrow suppression, [2] tardive dyskinesias)
- It follows a known pattern of response to the suspected drug
- It reappears upon re-challenge (if applicable)

Probable – This category applies to those adverse events that are considered, with a high degree of certainty, to be related to the study drug. The relationship of the adverse event to the study drug may be considered probable when the event meets the first 3 or more of the following criteria:

- It follows a reasonable temporal sequence from administration of the trial product
- It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
- It disappears or decreases on cessation of the study drug. [There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (eg, [1] bone marrow suppression, [2] tardive dyskinesias)]
- It follows a known pattern of response to the suspected drug
- It reappears upon re-challenge (if applicable)

Possible – This category applies to those experiences in which the connection with the study drug administration is reasonable, although not probable, and is not likely to be due to anything else. An adverse event may be considered possible if or when the first 2 or more of the following criteria apply:

- It follows a reasonable temporal sequence from administration of the trial product
- It is possible but unlikely that it may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
- It follows a known pattern of response to the suspected drug

Unlikely/Remote – In general, this category is applicable to an adverse event that meets the first 2 or more of the following criteria:

- It does not follow a reasonable temporal sequence from administration of the trial product
- It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
- It does not follow a known pattern of response to the suspected drug
- It does not appear to worsen when the drug is re-administered (if applicable)

Unrelated/Not Related – This category is applicable to those adverse events, which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under Probable, Possible, or Unlikely, as noted above.

11.1.2.3 Adverse Event Outcome

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

Resolved – The subject has fully recovered from the event with no residual effects observable or returned to baseline status.

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

Ongoing – Effects of the event are still present, regardless of whether the effect is changing or stable and persistent.

Death Due to this Event

Death Due to Other Event

Lost to Follow-up

11.1.3 Reporting Procedures for All Adverse Events

All adverse events will be collected in response to a general question about the subject's well-being and any possible changes from the previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific adverse event.

AEs, including any serious adverse events, will be collected through the end of trial (ie, the Week 52 Visit 6). AEs ongoing at Visit 6 or the time of premature trial discontinuation must be followed until the event is resolved or deemed stable by the investigator. All AEs must be recorded on the "Adverse Events" case report form. AEs either observed by the investigator or reported by the subject must be recorded regardless of causality.

The following attributes must be assigned to each event:

- Description
- Dates of onset and resolution
- Started or worsened prior or after first dose of study drug on Day 1
- Severity
- Assessment of relationship to study drug
- Outcome
- Action taken
- Determination of "serious" (or not)

Any medical history condition, signs, symptoms, and illnesses active during the Screening phase (ie, total of approximately 6 weeks prior to start of randomized trial treatment) will be captured as baseline (pre-existing) events, if appropriate, to assure that any change(s) in these experiences during the trial also are recorded as an AE and a complete safety profile is obtained. See Section 11.2.2 for additional reporting procedures for serious adverse events.

An event that occurs after signing of ICF but prior to first study drug administration will be documented as medical history unless the event is trial procedure–related, in which case it will be reported as a non–treatment-emergent AE. Any new or worsening pretreatment event that occurs from the time of the first study drug administration until the end of treatment (EOT) Visit will be recorded as an AE. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy; these should be recorded on the AE eCRF page under the signs, symptoms, or diagnosis associated with them.

Whenever possible, an AE should be recorded as a specific diagnosis or syndrome rather than as a sign or symptom. If no specific diagnosis or syndrome can be identified, the AE should be recorded as a separate and individual event. 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 reported at the maximum intensity experienced. If a previously recorded AE or pretreatment condition 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 pretreatment condition, returned to baseline status recorded prior to study drug administration. At the time of the final trial evaluation, all AEs should have a statement regarding resolution. Any SAE that is determined to be related to study drug will be followed until resolution or stabilization.

An accidental overdose is not an AE if there are no signs or symptoms. Any undesirable medical occurrence resulting from an accidental overdose is an AE, and should be recorded and reported on the appropriate eCRF page. The investigator should document any case of overdose and monitor the subject. Since accidental overdoses with the study drug could have serious clinical consequences and/or represent a compliance issue, they should be reported immediately to the Medical Expert and evaluated by the Sponsor.

11.2. Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

11.2.1 Definitions

11.2.1.1 Serious Adverse Event (SAE) Definition

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

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (**Note:** the term "life-threatening" in the definition of "serious" 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 (hospitalization for an elective procedure or a routinely scheduled treatment, or hospitalization scheduled in advance of trial participation, is not a SAE by this criterion)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect. (This serious criterion applies if a subject exposed to an investigational product gives birth to a child with a congenital anomaly or birth defect)

Medical and scientific judgment should be exercised in deciding whether classification of an adverse event as serious is appropriate in other situations, such as important medical events that may not result in death, be immediately life-threatening or require hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in the definition above. These events should also usually be considered serious.

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

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- Treatment that was elective or preplanned for a pre-existing condition that is unrelated to the indication under the trial and did not worsen
- Admission to a hospital or other institution 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

11.2.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR) 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 if it is not listed at the specificity or severity that has been observed. Expectedness will be determined by the Sponsor.

11.2.1.3 Non-serious AE Leading to Discontinuation

If situation permits, non-serious events (including laboratory abnormalities) that may require permanent discontinuation of study drug should be discussed with the Medical Expert prior to making any final decision, and if discontinued, should be entered on the eCRF within 3 working days.

11.2.2 Reporting

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

In addition to telephone notification (discussed above), serious adverse event data must be entered on the Serious Adverse Event Report form and transmitted within 48 hours.

It is the responsibility of the Sponsor to assess expectedness. Premier Research's responsibility is to report SUSARs to investigators, central IECs/IRBs/HRECs, national ethics committees if applicable, and appropriate Regulatory Authorities within the time frames required by applicable regulations. It is the investigator's responsibility to notify the regional ethical or institutional review boards of SAEs and any new and significant safety information. At minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

11.3. Event of Special Interest: Local Tolerability

An abnormal injection site reaction is defined as:

- An injection site reaction which is observed at the time of visit and is moderate to severe in intensity

- An injection site reaction between the previous and present visit, or remaining at the time of visit, which requires medical attention
- Any other injection site reaction deemed abnormal (eg, intensity and/or duration) to the investigator's judgment, other than those ordinarily observed in subcutaneous injections

Assessment of local tolerability will be performed by examining the injection sites (by the investigator if a reaction is present at the time of a visit) and on the basis of anamnestic data and records in the Subject Diary. At first study drug administration at Visit 1, local tolerability assessments will be done at 15 min, 1h and 2h postdose.

Observations will be recorded on appropriate eCRF pages. If an injection site reaction meets the criteria defined for an "abnormal result" it will be considered an AE.

11.3.1 Injection Site Pain

Injection site pain will be evaluated by the investigator or designated staff if the injection is given at the clinical site and by the parent/legal guardian if the injection is given at home. The pain will be evaluated using the Wong-Baker FACES Pain Rating Scale (see Appendix 2). In addition, each subject and parent/legal guardian will be queried during visits regarding possible injection site pain.

11.3.2 Injection Site Status

Injection site status will be evaluated by the investigator or designated staff using the Injection Site Assessment Scale (Appendix 2). In addition, each subject and parent/legal guardian will be guided to record possible reactions in the Subject Diary and will be queried during visits.

The following information will be captured:

- Description of the reaction
- Location: left thigh/right thigh/left buttock/right buttock/left part of abdomen/right part of abdomen
- Duration: onset, end date
- Intensity: grading according to the scales provided in appendices (the investigator should assess the subjects/subject's parents/legal guardians description)
- Action taken: action(s) taken by subjects, medical intervention or medication
- Comments

12. SAFETY MONITORING

The Sponsor will conduct an ongoing review of all trial data, with particular attention given to laboratory findings, AEs, and concomitant medication data. Any significant trends in safety observations or other findings of significance that are considered related to 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:

- Are serious in nature and not commonly seen in the absence of exposure to somatropin
- Occur at a greater frequency or at greater severity than described in the current Investigator's Brochure for TransCon hGH for Injection

Any AE that occurs in the course of the clinical trial must be monitored and followed up until:

- It has receded
- Pathological laboratory findings have returned to normal
- Steady state has been achieved
- It has been shown to be unrelated to the study drug and/or trial related procedures

It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

13. STATISTICS

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

13.1. Trial Endpoints

13.1.1 Primary Efficacy Endpoint

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

13.1.2 Secondary Efficacy Endpoints

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

13.1.3 Safety Endpoints

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

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

13.1.4 Pharmacokinetic and Pharmacodynamic Endpoints

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

- PK profile of TransCon hGH over 1 week
- PK profile of hGH over 1 week
- PK profile of PEG over 1 week
- PD profile of IGF-1 and IGFBP-3 over 1 week
- PD profile of IGF-1 SDS and IGFBP-3 SDS over 1 week
- C_{max} for hGH of TransCon hGH

13.2. Sample Size Determination

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

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

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

13.3. Analysis Populations

The following data subsets will be analyzed:

Safety Analysis Subset – The safety analysis set will include all randomized subjects who have received at least 1 dose of active treatment.

Intent-to-treat Subset – The ITT subset will include all randomized subjects who have received at least 1 dose of active treatment and have follow-up efficacy data.

Per-protocol Subset – The basis of PP subset is the ITT set. Subjects with major protocol deviations will be excluded from the PP analysis. Major protocol deviations excluding subjects from the Per-protocol analysis set will be defined in the SAP.

PK/PD Population – The PK/PD population includes a subset of subjects from the TransCon hGH cohort who attended Visit 3 as planned and from whom blood sampling was performed at time points predose, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 168 hours postdose.

13.4. Statistical Analyses

Details of applicable statistical methods will be given in a SAP. Annualized height velocity at Week 52 of TransCon hGH will be compared to that of daily hGH, by a non-inferiority comparison with a margin of 2.0 cm. Once non-inferiority in annualized HV is established, subsequent hypothesis testing for superiority will be conducted. If TransCon hGH is superior compared to daily hGH in annualized HV, subsequent hypothesis testing for superiority will be conducted in the proportion of patients within 0-2.0 SDS in IGF-1.

Summary statistics (including but not limited to: arithmetic mean, standard deviation, standard error of the mean, minimum value, median, maximum value, number of non-missing values) will be presented for continuous variables (absolute values at each time point and changes from baseline if applicable). Frequency statistics (counts and percentages) will be presented for categorical variables. Where appropriate, the presentation of results will include shift tables, plots or confidence intervals.

Data from all clinical assessments will be listed and, where appropriate, summarized by cohort using descriptive statistics.

If any deviation to the planned statistical analysis occurs, it will be addressed and described in the clinical study report.

13.4.1 Trial Subjects and Demographics

13.4.1.1 Background and Demographic Characteristics

Assessments made at Screening and baseline visits will be summarized by treatment group. These assessments will include demographic characteristics and other relevant parameters, as well as the stratification factors: age (≥3 to ≤6 and >6 years), peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender (male/female). By-treatment summaries will serve to identify imbalances between the treatment groups at baseline. Summary tables will be provided for the full analysis subset (FAS), the PP analysis set and for the safety analysis subset (SAS) by means of descriptive statistics and frequency tables, where appropriate.

13.4.2 Exposure and Compliance

For each subject, the individual extent of exposure will be calculated in terms of:

- Total duration of treatment
- Total dose
- Total dose adjusted to body weight

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

Study drug compliance will be calculated as specified in the SAP. It will be listed by subject and presented for the SAS set by means of summary statistics by treatment group.

13.4.3 Previous and Concomitant Therapy

Previous and current medication will be summarized by counts and percentages, overall and per WHO-DRL category. This table will include those medications reported on the "Previous and concomitant medication" eCRF page, which have a stop date prior to the date of the first administration of the study drug.

Previous and current non-medicinal therapy will be handled and tabulated in the same way as specified above for previous and current medication.

13.4.4 Efficacy Analyses

The efficacy endpoints are listed in Sections 13.1.1 and 13.1.2. The primary endpoint, annualized height velocity at Week 52, will be compared between TransCon hGH treatment and daily hGH treatment, by a non-inferiority comparison with a non-inferiority margin of 2.0 cm/year, followed by a test of superiority if non-inferiority is established.

A MMRM will be the primary analysis to evaluate annualized HV at week 52. The model will include baseline age, peak GH level of the stimulation test, and gender as fixed effects. Least square means will be derived and presented together with 95%-confidence intervals by treatment group.

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

All observed data including post-discontinuation data will be used for the primary analysis. Missing values will be imputed as follows for subjects who prematurely discontinued: From all subjects in the same treatment group who also prematurely discontinued treatment but had a height measurement at Week 52, annualized height change from the last measurement before discontinuation to Week 52 will be calculated. Missing height values at Week 52 will then be

imputed by adding the mean change (standardized to the corresponding period between last height measurement and Week 52) to the last height measurement obtained. Based on the imputed height value at Week 52 the corresponding imputed annualized height velocity will be calculated.

The primary efficacy analysis will be performed in the Intent-to-treat set. A sensitivity analysis will be provided for the Per-protocol set.

For the continuous secondary efficacy endpoints (height velocity at further visits, change in height SDS, serum IGF-1 levels and IGFBP-3 levels, IGF-1 SDS, IGFBP-3 SDS), similar MMRM models will be used. Two sided 95% confidence intervals will be calculated for the difference in least square means between the 2 treatment groups.

The rate of subjects achieving normalization of serum IGF-1 SDS will be calculated by treatment group and visit. A test of superiority in proportion of patients within 0-2.0 IGF-1 SDS will be conducted. A procedure to control for familywise type-1 error of multiple hypothesis testing will be specified in the SAP.

In general, for secondary endpoints, missing values will be imputed by a method fully described in the SAP. Moreover, sensitivity analyses concerning missing values for the primary endpoint will be described in the SAP.

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

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

13.4.4.1 Pharmacokinetics/Pharmacodynamics

The PK/PD endpoints are listed in Section 13.1.4.

PK/PD parameters will be calculated for all subjects in the PK/PD subset, using WinNonlin Enterprise Float, Kinetica or SAS.

PK parameters will be derived from a PK/PD subset of TransCon hGH subjects from TransCon hGH, hGH and PEG levels versus time profiles.

PD parameters will be derived from a PK/PD subset of TransCon hGH subjects from IGF-1 and IGFBP-3 levels versus time profiles both on untransformed and baseline corrected data. Calculation of IGF-1 SDS and IGFBP-3 SDS parameters, will be performed as applicable (untransformed and baseline corrected).

Details concerning calculations to be performed and PK/PD parameters to be estimated will be described in the SAP.

Assessment of serum exposure of TransCon hGH (Cohort 1), hGH (both Cohorts) and PEG (Cohort 1, V1-V6; Cohort 2, V1), as well as IGF-1 and IGFBP-3 (both Cohorts) at single time points during Visits 1 through to Visit 6 will be performed, and detailed in the SAP.

13.4.5 Safety Analyses

The safety endpoints of the trial are listed in Section 13.1.3. The assessment of safety will be based mainly on the frequency of AEs, frequency of antibody development, serum IGF-1 levels and the number of laboratory values that fall outside of laboratory specified reference ranges. Other safety data (eg, vital signs, special tests, etc.) will be considered as appropriate.

Safety endpoints will be summarized using descriptive statistics. AEs will be listed by cohort and subject number. AEs will be tabulated by cohort, body system, severity and the relationship to the study drug. Changes in laboratory variables will be displayed on shift tables and through the tabulation of summary statistics for each variable. Other information collected (eg, severity or relatedness to the study drug) will be listed as appropriate.

If appropriate, laboratory and/or ECG data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post baseline value), by presenting summary statistics of raw data (means, medians, standard deviations, ranges) and change from baseline values and by flagging of notable values in data listings.

Data from other tests (eg, blood pressure or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Summary statistics will be given where appropriate.

In addition, the number and percentage of subjects developing anti-hGH binding and neutralizing antibodies and developing or increasing anti-PEG antibodies (TransCon hGH cohort only) will be summarized by cohort.

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

The safety analysis will be based upon the SAS subset.

13.4.6 Interim Analysis

No interim analysis is planned.

14. TRIAL CONDUCT

14.1. 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 an initiation visit or Investigator Meeting. Training must take place before any subjects are

enrolled at that site. Initiation visits and Investigator Meetings will include but may not be limited to review of GCP guidelines, study drug preparation and administration procedures, data collection requirements, and subject eligibility requirements.

14.2. Screen Failures

Subjects who fail to meet the eligibility criteria at any point during the Screening period are defined as Screening failures. The reasons (may be multiple) for each Screening failure will be recorded in the appropriate eCRF page.

Re-screening is permitted. Re-screening of subjects with an out of range cortisol and/or thyroid hormone level (inadequate replacement therapy for the insufficiency of other hypothalamo-pituitary axes) may be allowed ≥3 months after replacement treatment adjustment. Individual blood draws may be repeated for the following reasons, but not limited to: eg, ruling out an analytical error, sample handling or shipment issues, conflicting or inconsistent subject data, etc. The decision on re-screening will be made on a case by case basis by the Medical Expert. All Screening procedures may be repeated. Re-screened subjects will receive a new Screening number.

14.3. Maintenance of Screening Logs

Procedures for maintenance of screening logs are discussed in the Trial Manual.

14.4. Data Handling and Record Keeping

14.4.1 Data Management

14.4.1.1 Collection of Data

Data will be collected by means of eCRFs. The eCRF is an integral part of the trial and subsequent reports. The eCRF must be used to capture all the data collected, and must be kept current to reflect the subject status during the course of the trial. Only a subject identification number and subject initials will be used to identify the subject. The investigator must keep a separate log of subject names and medical record numbers (or other personal identifiers).

The trial will use an Internet-based remote data entry system to collect the clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 Good Clinical Practice. 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 Good Clinical Practice) 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 CRO, 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.

14.4.1.2 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.

14.4.2 Source Data Documents

Clinical data will be collected by the Sponsor and/or its representative through an electronic clinical data management system (eCDMS) that is 21 CFR Part 11 compliant and supports remote monitoring. The handling of data, including data quality assurance, will comply with regulatory guidelines and will be defined in the trial-specific data management plan.

14.4.3 Data Handling

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

14.4.4 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/IEC/HREC review, and regulatory inspection.

14.4.5 Record Keeping

The investigator is responsible for maintaining adequate records to fully document the conduct of the trial, including but not limited to the following:

- All versions of the Investigator's Brochure and the signed protocol and amendments in effect during the conduct of the trial
- Signed ICFs
- Source documents including adequate case histories
- Signed, dated, and completed CRFs or data collection forms and documentation of data corrections
- Notification of SAEs and related reports
- Investigational product accountability logs and documentation of return of unused and used investigational product vials

- Dated and documented regional ethical or institutional review board approvals and approval of regulatory authorities
- Normal laboratory test values and laboratory certifications
- Curricula vitae of all clinical investigators
- Completed Forms FDA 1572
- Trial Initiation Visit documentation
- Delegation of Authority Log
- Signed Signature of Agreement for Protocol and Amendment and agreements between involved parties
- Relevant communication, including that related to monitor site visits (eg, letters, meeting notes, notes from telephone calls)
- Interim, annual, or final reports to regional ethical or institutional review board and regulatory authorities
- Subject screening log, subject identification code list, and subject enrollment log
- Audit certificate if applicable

14.5. Data Quality Control

14.5.1 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.

14.5.2 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 Premier Research's standard operating procedures (SOPs). A comprehensive data management plan (DMP) will be developed including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, 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.

14.5.3 Auditing Procedures

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance audit may be initiated by the Sponsor. The investigator has to ensure that the subjects/subject's parents/legal guardians are aware of and consent that personal information may be reviewed during the data verification process as a part of monitoring/auditing by the Sponsor, properly authorized agents of the Sponsor or subject to inspection by competent authorities. In addition, participation and personal information is treated as strictly confidential to the extent the applicable law permits and 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, 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.

14.6. 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 local and central laboratories. Some blood samples may be used for laboratory test validation.

The laboratories will provide a list of the 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 be notified promptly to the Sponsor. The laboratories may also be audited by the Sponsor or by competent authorities.

14.7. Trial Termination or Completion

The investigator should notify the IEC/IRB/HREC in writing of the completion or early termination of the trial. On 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.

14.8. 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 IEC/IRB/HREC before the amendment is implemented. However, in the event of apparent immediate hazard to a subject, a

deviation from the protocol may be implemented 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 IEC/IRB/HREC 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 IEC/IRB/HREC, as required by regional regulations. The investigator must send a copy of the documented approval to the Sponsor and/or its representative.

14.9. 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.

14.10. 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 relative 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. It is not permitted to publish any data of this trial without prior Sponsor approval.

15. 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
- Regional required subject data protection laws and regulations
- Applicable regional regulations

15.1. 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 the accumulating safety data. After each meeting it will advise the Sponsor on the continuing safety of current subjects in the trial 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 Charter agreed to by all members. The Charter will define data content, format 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:

- The trial should continue without modification
- The trial should continue but with modification to the Protocol or with additional data presentation needs
- The trial should be temporarily suspended to further enrollment and treatment administration, pending further evaluation of data
- 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.

15.2. Informed Consent

The draft ICF must be reviewed by the Sponsor and/or its representative prior to submission to a regional IEC/IRB/HREC 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 document 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 in the subject's file at the trial site and a copy of each provided to the subject.

15.3. IEC/IRB/HREC Approvals

The Principal Investigator at each site is responsible for obtaining approval from the appropriate regional IEC/IRB/HREC 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 IEC/IRB/HREC.

- Obtaining review board approval for any protocol amendments and ICF revisions before implementing the changes
- Providing the review board with any required information before or during the trial
- 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 reapprovals and relevant communication to the Sponsor and/or its representative

- 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
- Notifying the review board at the end of the trial, in accordance with regional guidelines and regulations

15.4. Subject Compensation for Adverse Effects on Health

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

15.5. Finance and Insurance

Will be described in trial documents.

16. REFERENCES

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17. ATTACHMENTS

17.1. Signature of Agreement

In signing this protocol, the investigator agrees to:

- 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
- Comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice plus appropriate regional regulatory laws and requirements
- Personally conduct or supervise the described investigation
- Inform any subjects or persons used as controls that the study drugs are being used for investigational purposes
- Ensure requirements relating to obtaining informed consent and regional ethical or institutional review board approval have been met
- Report to the Sponsor or its representative any AEs that occur in the course of the investigations, as specified in Section 11.1.3
- Read and understand the Investigator's Brochure, including potential risks and side effects of the drug
- Ensure all associates, colleagues, and employees assisting in the conduct of the trial are informed of their obligations in meeting their commitments
- 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
- 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
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements
- 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 investigational medicinal product, and agree to personally conduct or supervise the described investigation(s) in accordance with the relevant, current protocol(s) and will deviate from the protocol only after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to inform all subjects that the investigational medicinal product is being used for experimental purposes, and I will ensure that the requirements relating to obtaining informed consent are met. I agree to report to the Sponsor any adverse experiences that occur in the course of the investigation(s).

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.

Additionally, I will not make any changes in the research without IEC/IRB/HREC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

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: _____

17.2. Schedule of Events (TransCon hGH Subjects)

Visit	Screening[1] (-6-0 weeks)	1[1] (Week 1)	2 (Week 5)	3 (Week 13)	4 (Week 26)	5 (Week 39)	6 (Week 52)
Trial Day (TransCon hGH subjects)		**1** (Predose, Morning)	**29** (Predose, Morning)	**87-88[2]** (48-72 h post-dose, Morning)	**178-179** (48-72 h post-dose, Morning)	**269-270** (48-72 h post-dose, Morning)	**365** (164-172 h post-dose, Morning)
Visit Window (weeks)				**+2**	**±1**	**±1**	**+1**
Informed consent	x						
Medical history	x						
Concomitant medication and adverse events		x	x	x	x	x	x
Review of subject diary			x	x	x	x	x
Height and weight measurement	x	x	x	x	x	x	x
Physical examination and vital signs[3]	x	x	x	x	x	x	x
Pubertal status	x				x		x
GH-stimulation test(s)[4,5]	x						
Assessment of adrenal status[6,7]	x						
Karyotype testing[8]	x						
12-lead ECG[9]	x	x		x[10]	x		
X-ray of left hand and wrist[4]	x						x
Sellar MRI[4]	x						
Fundoscopy[11]	x				x		x
Safety laboratory parameters[12]	x	x	x	x	x	x	x
Fasting required	x	x			x		x
Hormone status[13]	x	x		x	x		x
Bioanalytical samples[14]	x	x	x	x	x	x	x
Anti-transglutaminase antibodies[4]	x						
Anti-hGH and anti-PEG antibodies	x[15]	x	x	x	x	x	x
PK/PD Sampling (PK/PD subset)[16]				x[10]			
Drug administration training[17]		x					
Adjustment of dose to body weight				x	x	x	
Study drug administration at site[17]		x	x	x[16]			
Postdose vital signs[3]		x[18]		x[19]			
Injection site reaction assessment		x[18]	x	x	x	x	x

Abbreviations: ECG = electrocardiogram; h = hour; hGH = human growth hormone; MRI = magnetic resonance imaging; PEG = polyethylene glycol; PD = pharmacodynamic; PK = pharmacokinetic

[1] Following randomization, it is recommended to start V1 within 2 weeks from the time of randomization.

[2] TransCon hGH PK/PD subset subjects will start Visit 3 predose on Day 85.

[3] Vital signs: Heart rate, blood pressure, respiratory rate and body temperature. Subjects should rest for at least 5 minutes before vital sign assessment.

[4] These diagnostic assessments may be performed prior to Screening within approximately 6 months with proper documentation and approval by the Medical Expert.

[5] Sex hormone priming suggested (but not required) to be performed in girls over the age of 10 and boys over the age of 11.

[6] 8:00 AM cortisol (eg, baseline for GH stimulation test) < 7 µg/dL requires an ACTH stimulation test. 8:00 AM cortisol ≥ 7 µg/dL satisfies inclusion. This assessment may be performed prior to Screening within approximately 3 months with proper documentation and approval by the Medical Expert.

[7] These assessments may be performed prior to Screening within approximately 3 months with proper documentation and approval by the Medical Expert.

[8] Karyotype evaluation in girls. Results prior to Screening may be accepted if well documented; the final decision rests with the Medical Expert.

[9] Subjects should rest for at least 2 minutes before ECG assessment. Screening ECG is locally read; all other ECGs to be read centrally.

[10] At predose and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h postdose for TransCon hGH PK/PD subset subjects.

[11] Should be performed at any time if clinically indicated.

[12] Hematology (blood smears will be performed locally for back-up analysis), blood chemistry, lipid and glucose metabolism (fasting glucose, insulin, HbA1c, and OGTT can be assessed locally at any time in case of suspicion of glucose intolerance).

[13] Hormone status: TSH, fT3, fT4, and morning cortisol.

[14] Bioanalytical samples for TransCon hGH, hGH, PEG, IGF-1 and IGFBP-3: IGF-1 and PEG will be analyzed at screening and V1 through V6. TransCon hGH, hGH, and IGFBP-3 analysis only at V1 to V6. Screening PEG levels only to be analyzed after randomization.

[15] The analysis of the anti-hGH and anti-PEG antibodies may only be conducted after randomization and are not required for eligibility verification.

[16] Only for TransCon hGH PK/PD subset subjects.

[17] Training on study drug preparation and administration (V1 - during first administration and further as needed).

[18] At 15 min, 1 h and 2 h postdose.

[19] At 15 min, 1 h, 2 h and 24 h postdose for TransCon hGH PK/PD subset subjects; time point for other subjects as they attend to site.

17.3. Schedule of Events (Genotropin Subjects)

Visit	**Screening[a] (-6-0 weeks)**	**1[a] (Week 1)**	**2 (Week 5)**	**3 (Week 13)**	**4 (Week 26)**	**5 (Week 39)**	**6 (Week 52)**
Trial Day (Genotropin subjects)		**1 (Predose, Morning)**	**29-35 (Morning)**	**85-91 (Morning)**	**176-182 (Morning)**	**267-273 (Morning)**	**365 (Morning)**
Visit Window (weeks)				**+2**	**±1**	**±1**	**+1**
Informed consent	x						
Medical history	x						
Concomitant medication and adverse events		x	x	x	x	x	x
Review of Subject Diary			x	x	x	x	x
Height and weight measurement	x	x	x	x	x	x	x
Physical examination and vital signs[b]	x	x	x	x	x	x	x
Pubertal status	x				x		x
GH-stimulation test(s)[c,d]	x						
Assessment of adrenal status[e,f]	x						
Karyotype testing[g]	x						
12-lead ECG[h]	x	x			x		
X-ray of left hand and wrist[c]	x						x
Sellar MRI[c]	x						
Fundoscopy[i]	x				x		x
Safety laboratory parameters[j]	x	x	x	x	x	x	x
Fasting required	x	x			x		x
Hormone status[k]	x	x		x	x		x
Bioanalytical samples[l]	x	x[m]	x	x	x	x	x
Anti-transglutaminase antibodies[c]	x						
Anti-hGH and anti-PEG antibodies	x[n,o]	x[o]	x[o]	x[o]	x[o]	x[o]	x[o]
Drug administration training[p]		x					
Adjustment of dose to body weight				x	x	x	
Study drug administration at site[p]		x[q]					
Postdose vital signs[b]		x[r]					
Injection site reaction assessment		x[r]	x	x	x	x	x

Abbreviations: ECG = electrocardiogram; h = hour; hGH = human growth hormone; MRI = magnetic resonance imaging; PEG = polyethylene glycol; PD = pharmacodynamic; PK = pharmacokinetic

[a] Following randomization, it is recommended to start V1 within 2 weeks from the time of randomization.

[b] Vital signs: Heart rate, blood pressure, respiratory rate and body temperature. Subjects should rest for at least 5 minutes before vital sign assessment.

[c] These diagnostic assessments may be performed prior to Screening within approximately 6 months with proper documentation and approval by the Medical Expert.

[d] Sex hormone priming suggested (but not required) to be performed in girls over the age of 10 and boys over the age of 11.

[e] 8:00 AM cortisol (eg, baseline for GH stimulation test) < 7 µg/dL requires an ACTH stimulation test. 8:00 AM cortisol ≥ 7 µg/dL satisfies inclusion. This assessment may be performed prior to Screening within approximately 3 months with proper documentation and approval by the Medical Expert.

[f] These assessments may be performed prior to Screening within approximately 3 months with proper documentation and approval by the Medical Expert.

[g] Karyotype evaluation in girls. Results prior to Screening may be accepted if well documented; the final decision rests with the Medical Expert.

[h] Subjects should rest for at least 2 minutes before ECG assessment. Screening ECG is locally read; all other ECGs to be read centrally.

[i] Should be performed at any time if clinically indicated.

[j] Hematology (blood smears will be performed locally for back-up analysis), blood chemistry, lipid and glucose metabolism (fasting glucose, insulin, HbA1c, and OGTT can be assessed locally at any time in case of suspicion of glucose intolerance).

[k] Hormone status: TSH, fT3, fT4, and morning cortisol.

[l] Bioanalytical samples for hGH, PEG, IGF-1 and IGFBP-3. IGF-1 will be analyzed at Screening and V1 through V6 (excluding V1-2h postdose). hGH and IGFBP-3 will be analyzed at V1 predose through V6; V1-2h postdose sample will only be analyzed for hGH. PEG samples are taken at Screening and V1 predose only, to assist interpretation of anti-PEG antibody data.

[m] V1: predose and 2 h postdose sample.

[n] The analysis of the anti-hGH and anti-PEG antibodies may only be conducted after randomization and are not required for eligibility verification.

[o] Analysis for anti-PEG antibodies will only be performed at Screening and V1 (predose) in support of assessment of a trial specific assay cut-point.

[p] Training on study drug preparation and administration (V1 - during first administration and further as needed).

[q] Dosing for Genotropin subjects allowed in the morning.

[r] At 15 min, 1 h, and 2 h postdose.

17.4. PK/PD Sampling and Assessment Schedule for PK/PD subset at Visit 3

	Time Relative to Dosing							
Cohort 1 (TransCon hGH)	**Days**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Blood sampling	Hours	–0.5, 8, 12, 16	24, 36	48	72	96	120	168
ECG	Hours	–0.5, 8, 12, 16	24, 36	48	72	96	120	168
Injection Site Tolerability	Hours	15 min, 1, 2	24					
Vital Signs	Hours	15 min, 1, 2	24					

Abbreviations: ECG = electrocardiogram; hGH = human growth hormone

APPENDICES

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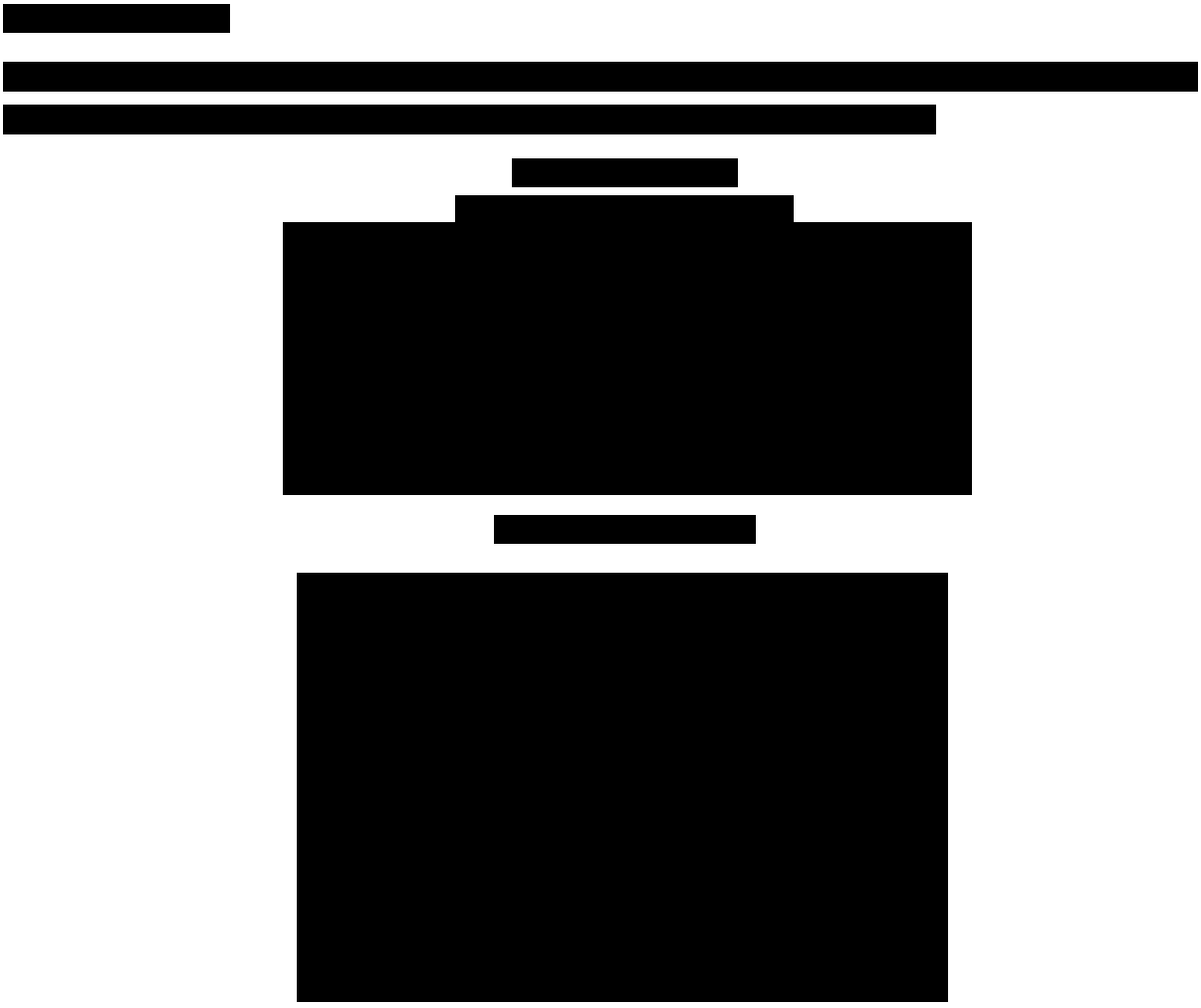

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