A PHASE 3, RANDOMIZED, MULTICENTER, OPEN-LABEL, CROSSOVER STUDY ASSESSING SUBJECT PERCEPTION OF TREATMENT BURDEN WITH USE OF WEEKLY GROWTH HORMONE (SOMATROGON) VERSUS DAILY GROWTH HORMONE (GENOTROPIN®) INJECTIONS IN CHILDREN WITH GROWTH HORMONE DEFICIENCY

Investigational Product Number:	PF-06836922
Investigational Product Name:	Somatrogon
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2018-000918-38
Protocol Number:	C0311002
Phase:	Phase 3

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	26 August 2019	Section 4.1. Inclusion Criterion #2 modified to allow patients using HumatroPen® (USA only) and Omnitrope® Pen (USA only) to participate in the study. Section 4.2. Exclusion Criterion #7 modified to reflect the inclusion of patients using HumatroPen® (USA only) and Omnitrope® Pen (USA only). Sections 5 & 5.5. Modified to reflect the inclusion of patients using HumatroPen® (USA only) and Omnitrope® Pen (USA only). Section 6.1.1. Modified to reflect the inclusion of patients using HumatroPen® (USA only) and Omnitrope® Pen (USA only). Other typographical or administrative edits to improve readability and consistency.
Amendment 4	03 May 2019	Section 4.2. Addition of children with closed epiphyses to the Exclusion Criteria to address the request of EU Health Authorities. Section 4.2. Exclusion criteria regarding allowable injectable medications clarified. Sections 5.5, 6.1.1, 6.2.3, & 6.2.4. Dosing windows expanded for Genotropin (36 hours ±24 hours) and somatrogon (7 days ±72 hours) prior to Visits 1 and 4 providing increased flexibility in dosing for subjects/caregivers prior to visits. Section 5.8.1. Allowable injectable concomitant medications clarified. Section 6. Clarified that labs performed at Screening Visit are also fasting. Section 7.2.1.2. Table 1. Correction made to lab name (Leukocytes changed to Leukocyte

Document	Version Date	Summary of Changes and Rationale
		Esterase). Other typographical or administrative edits to improve readability and consistency.
Amendment 3	08 Nov 2018	Added free thyroxine (FT4) testing at Screening and at Visits 4 and 7 at the request of the MHRA. Section 8.5. Correction made to the process for recording device complaints. Language simplified to capture all device complaints. Modified Section 13, definition of end of trial to be last subject last visit (LSLV) at the request of the MHRA.
Amendment 2	28 Aug 2018	Schedule of Activities. Anti-rhGH antibodies (and neutralizing antibodies) added at Screening, and Visits 4 and 7 at the request of the FDA. Section 2 and Protocol Summary. Detection of anti-rhGH antibodies (and neutralizing antibodies) added to align with FDA request. Section 5.4. Arm included as an allowable injection site for Genotropin; its prior omission was in error. Sections 6.1.1, 6.2.4, & 6.2.7. Anti-rhGH antibodies (and neutralizing antibodies) added to Study Procedures to align with Schedule of Activities. Section 7.2.5.1 and Table 1. Heading changed to Anti-somatrogon Antibodies, Anti-rhGH Antibodies, and Neutralizing Antibodies (NAb) to reflect the addition of anti-rhGH antibodies to the assessments. Section 9.4. Anti-rhGH antibodies (and neutralizing Ab) added to Safety Analysis to align with Schedule of Activities Other typographical or administrative edits to

Document	Version Date	Summary of Changes and Rationale
		improve readability and consistency.
Amendment 1	18 July 2018	Schedule of Activities. Medication dispensation added for Genotropin at Visits 3 and 6. Schedule of Activities. DYAD Questionnaire (completed by Clinical Site Staff) added at Visits 1, 4 and 7. Section 2. 'Child/Caregiver Dyad' changed to 'Subject/Caregiver Dyad' for consistency. Section 2. 'Subjects' changed to 'Subject/Caregiver Dyads' to reflect who will be completing the questionnaires. Section 4.1. Inclusion criterion #2 modified to allow for GHD patients on a wider range of doses to enroll in the study. Section 4.2. Exclusion criterion #5 modified to remove celiac disease as exclusionary. As this is not an efficacy study assessing linear growth, children with celiac disease (which can impact growth) need not be excluded. Section 5. Correction made to investigational (comparator) product commercial label wording. Section 5. Clarification added regarding which body weight measurement is to be used for dosing of somatrogon at Visits 1 and 4. Section 5.3.2. Correction made to investigational (comparator) product commercial label wording. Sections 6.2.1, 6.2.4, & 6.2.7. 'Subject' changed to 'Subject/Caregiver Dyads' to reflect who will be completing the questionnaires. Sections 6.2.1, 6.2.4, & 6.2.7. 'Clinical Site Staff User completes DYAD Questionnaire' added allowing site to indicate the Caregiver that has completed the questionnaires.

Document	Version Date	Summary of Changes and Rationale
		Sections 6.2.3 and 6.2.6. Genotropin drug dispensation added. Section 7.4. Clearer definition of the Subject/Caregiver Dyad is provided. Appendix 2. Clarification added to who answers questions for pain, stinging, bruising, bleeding based on age. Appendix 3. Missed Injections (Weekly Administration) typo fixed '(0-31)' changed to '(0-5)'. Appendix 3. Patient Injection Signs & Symptoms Tables- spacing/alignment adjusted. Appendix 5. 'Child' changed to 'Subject' for consistency and 'Child/Caregiver Dyad' changed to 'Subject/Caregiver Dyad' for consistency. Other typographical or administrative edits to improve readability and consistency.
Original protocol	02 Apr 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale

Human Growth Hormone (hGH) is a 191-amino acid pituitary protein that stimulates hepatic production and release of insulin-like growth factor-I (IGF-I) into the systemic circulation. Growth hormone (GH), via IGF-I, is an important mediator in the promotion of linear growth in children and plays a role in the regulation of metabolism and body composition in adults.[1,2]

Growth Hormone Deficiency (GHD) results in inadequate circulating GH and IGF-I levels and is manifested as abnormal linear growth in children.[3,4] Childhood GHD can be congenital, acquired, or idiopathic. Underlying causes for congenital malformation include pituitary dysfunction due to abnormal neurodevelopment in utero of certain brain regions and genetic abnormalities. Etiology for acquired GHD includes brain tumors in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation and surgical intervention. The idiopathic origin of GHD is poorly understood but it appears to be multifactorial.[5]

Data on incidence and prevalence rates of GHD are scarce. A nationwide study in Denmark reported average incidence rate of 2.58 males, and 1.7 females per 100,000 population for childhood onset of GHD.[6] The prevalence and demographics of childhood GHD in Belgium during the period 1986-2001 was estimated to be 1/5600. The origin of GHD was idiopathic in 41% of the patients, congenital in 20% and acquired in 7%; there was male predominance in all three categories.[7] The number of new cases has remained fairly constant over the last two decades. The Belgian data are comparable to other countries; the prevalence of GHD in the United States in the 1990's was at least 1:3480, with male predominance.[8]

Most morbidity in children with GHD relates to short stature. The inability to achieve normal height can lead to early onset of severe psychosocial problems directly related to short stature. This is confounded by delayed puberty and deficits in facial, dental and (in males) genital development. Approximately 5% of children with GHD have episodes of hypoglycemia, particularly in infancy.[3] Persistency of GHD into adulthood is associated with increased risk of cardiovascular morbidity and mortality.

Recombinant hGH (rhGH) replacement therapy has been used for over 30 years in tens of thousands of patients (primarily children) and has proved to be safe and effective.[9,10] The main therapeutic goal of growth hormone treatment in children with GHD is to enable short children to achieve normal height, with early improvement of the psychosocial problems related to short stature. Treatment is by daily subcutaneous (SC) injection of recombinant hGH. The Growth Hormone Research Society (GRS) consensus guideline recommends a dose range of 0.025-0.05 mg/kg/day, although in Europe generally a dose of 0.025-0.035 mg/kg body weight per day or 0.7-1.0 mg/m² body surface area per day is recommended (according to the summary of product characteristics [SmPC] of somatropin products). Treatment response is assessed by measurement of height and growth velocity and is usually continued until final height, epiphyseal closure, or both have been recorded.

The majority of currently available hGH products require daily or every other day SC or intramuscular (IM) injections to maintain hGH blood levels within the effective therapeutic window. The burden of daily administration and its concomitant side effects (eg, injection site discomfort, transient edema and arthralgia) can cause a reduction in compliance and can limit the therapeutic utility of existing formulations.[11]

Somatrogon is a long-acting rhGH for SC administration. It consists of hGH fused to three copies of the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin hCG; one copy at the N-terminus and two copies (in tandem) at the C-terminus.

Somatrogon is currently being developed for use as a long-term treatment in children with GHD. Five studies have been completed with somatrogon; two Phase 1 studies in healthy adult volunteers, two Phase 2 studies, in children and adults with GHD, and a Phase 3 study in adults with GHD. Results of the Phase 2 Study in children demonstrated pharmacokinetic (PK) and pharmacodynamic (PD) profiles compatible with once weekly administration. The estimated half-life (t½) of somatrogon was 22.4 hours in the 13 children receiving 0.66 mg/kg/week, compared with the t½ of rhGH of 3.5 hours in the 11 children studied. IGF-1 serum levels for children receiving 0.46 mg/kg/week and 0.66 mg/kg/week remained above those of the children treated with rhGH throughout the study.[12] Clinical safety and efficacy was comparable to Genotropin® given once daily with no serious safety events.

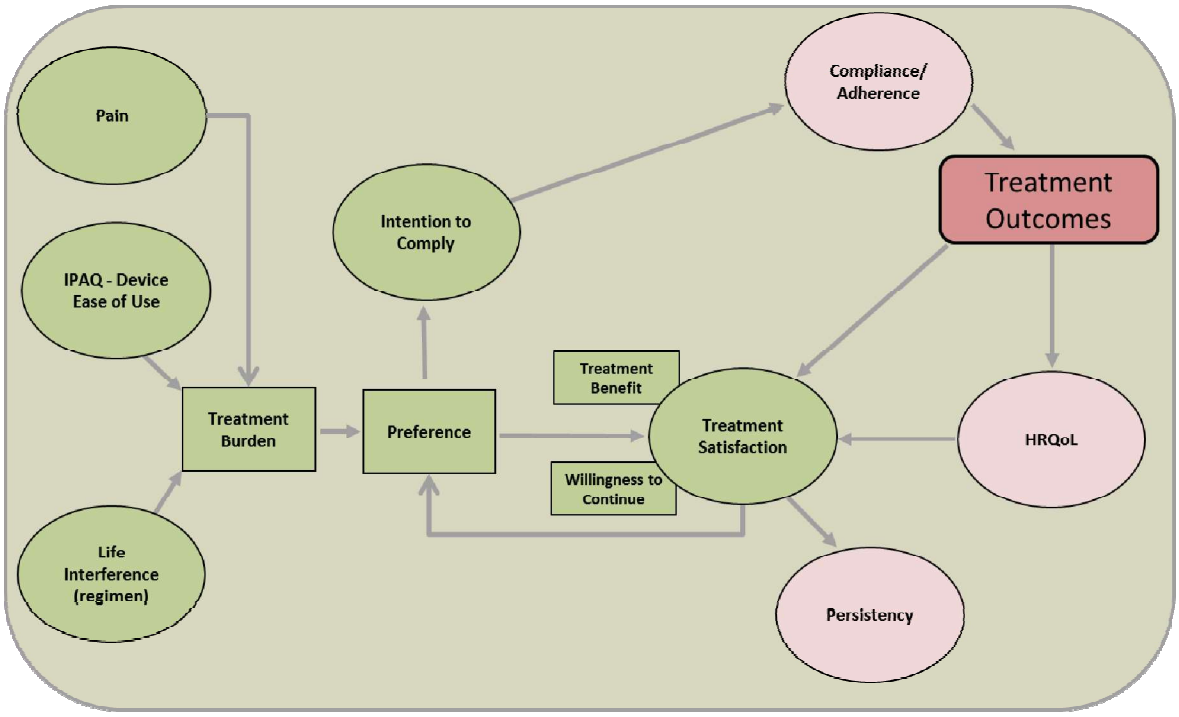
The purpose of this study is to evaluate whether there is a benefit, defined as superior adherence and acceptance, of a once weekly injection schedule to support the benefit/risk profile of somatrogon. Figure 1 presents a conceptual model of the variables (precursors/predictors) hypothesized to be associated with adherence and treatment outcomes in GHD. While it is not possible at this time to evaluate adherence in a clinical trial, it is possible to instead evaluate some of these precursor variables.

One component in this hypothesized model is treatment burden. Treatment burden relates to distress caused by treatment-associated demands (eg, visits to the doctor, medical tests, medication management, changes in lifestyle) which can have wide-ranging impact on patients' lives, and their caregivers. The burden associated with a treatment schedule may be one important consideration for adherence. The focus of the current study is to assess concepts (eg, device ease of use, side effects of treatment [eg, injection signs and symptoms], and life interference) that comprise key aspects of treatment burden in GHD. Specifically, this study tests the hypothesis that, for children with GHD, a once weekly treatment schedule (once weekly somatrogon) has a treatment burden that is less than a daily treatment schedule (Genotropin®).

A Dyad Clinical Outcomes Assessment (DCOA) questionnaire will be used to measure the variables as the growth hormone injection is often a shared experience between patient and caregiver. The DCOA questionnaire has recently been developed, and the development process complies with patient reported outcome (PRO) tool development as recommended by the FDA and EMA.[13,14] The cognitive debriefing process via patient interviews resulted in the final content-valid version of the tools (ie, the relevant aspects of treatment burden etc were evaluated by the patient, and their understanding of the questions was also confirmed).

The second key step was to conduct the Field Study in which the final tools were employed in patients who use daily growth hormone injections to determine the psychometric properties. The results demonstrated that the DCOA questionnaire performs well in this patient group; it is valid and reliable and is fit for purpose.[15]

Hypothesized Conceptual Model of the Variables associated with Adherence and Outcomes in GHD[16,17,18]



IPAQ: Injection Pen Assessment Questionnaire; HRQoL: health related quality of life.

Preference is another sub-concept represented in Figure 1. This study will include a measure of preference that compares daily and weekly treatment. Reducing the treatment burden with a once weekly schedule should translate to a higher preference over the daily schedule. Additionally, a separate discrete choice exercise (conjoint analysis) evaluating patient preferences for treatment has recently completed. A higher expressed preference for a once weekly schedule will influence an individual's behavior around their intention to comply with that particular schedule, and the DCOA questionnaire is also designed to evaluate this change in behavioral intention.

A higher expressed preference should also be reflected by the evaluation of treatment satisfaction with the injection schedule. The DCOA questionnaire is designed to assess this, in terms of willingness to continue with the treatment schedule, perceived benefit of the schedule, and overall satisfaction with the schedule. It is hypothesized that evidence generated from this study demonstrating a preference for the once weekly injection schedule along with a reduced treatment burden will be reflected in the "real world" use, when this

weekly injection receives approval. This should translate to improved adherence which will ultimately lead to improved treatment outcomes and quality of life.

Objectives and Endpoints

Primary Objective:	**Primary Endpoint:**
• To evaluate the treatment burden of a weekly somatrogon injection schedule and a daily Genotropin® injection schedule.	• Treatment burden assessed as the difference in mean Overall Life Interference total scores between the weekly injection schedule and daily injection schedule as assessed by the Patient Life Interference Questionnaire (as part of DCOA 1) completed by the Subject/Caregiver Dyad at baseline and after each treatment schedule experience.
Secondary Objectives:	**Secondary Endpoints:**

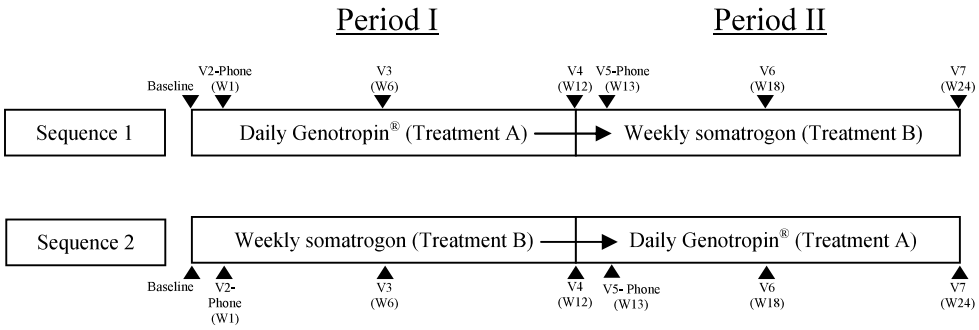
• To evaluate the following aspects of the treatment experience as determined by subject and caregiver self-assessments (dyadic approach) of weekly somatrogon therapy and daily Genotropin® therapy:
  • Life interference.
  • Caregiver life interference.
  • Family life interference.
  • Benefit, satisfaction, willingness to continue.
  • Intention to comply.
  • Injection pen ease of use.
  • Convenience of injection schedule.
  • Ease of the injection schedule.
  • Preferred injection schedule.
  • Choice of injection pen.
  • Injection signs and symptoms (pain, bruising, stinging).
  • Caregiver report of signs (bleeding,
	• Treatment experience assessed as the difference in mean scores between the weekly injection schedule experience and daily injection schedule experience in each of the following variables within DCOA 1 questionnaires completed at baseline and after subjects have experienced both treatment schedules:
	  • Pen ease of use.
	  • Ease of the injection schedule.
	  • Convenience of the injection schedule.
	  • Satisfaction with overall treatment experience.
	  • Willingness to continue injection schedule.
	  • Injection signs and symptoms (from the patient).
	  • Assessment of Signs (from the Caregiver).
	  • Caregiver Life Interference, including Family Life Interference.

bruising).
• Missed injections.
• To use a Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA) at baseline and at the end of each period (Week 12 and Week 24) to support the interpretation of scores from the Dyad Clinical Outcome Assessment (DCOA) 1 and DCOA 2 Questionnaires.
C
C
I
[redacted]
	• Missed injections.
	• Proportion of Subject/Caregiver Dyads that select the weekly injection schedule compared to the daily injection schedule in each of the outcome domains below as assessed by the DCOA 2 Questionnaires completed at Week 24.
	  • Choice of injection pen.
	  • Preferred injection schedule.
	  • Convenience of injection schedule.
	  • Easier to follow.
	  • Ease of the injection schedule.
	  • Patient life interference.
	  • Caregiver Life Interference, including Family Life Interference.
	  • Benefit relating to the injection schedule.
	  • Intention to comply.
	• The Patient Global Impression at baseline and at the end of each period (Week 12 and Week 24).

Safety Objective:	**Safety Endpoints:**
• To describe the safety and tolerability of somatrogon.	• Frequency, severity, and relationship of adverse events to somatrogon. • Serious adverse events. • Discontinuations due to adverse events. • Frequency and severity of abnormal lab values. • Detection of anti-rhGH antibodies (and neutralizing antibodies). • Detection of anti-somatrogon antibodies (and neutralizing antibodies).

Study Design

The study is a randomized, open-label, multi-center, 2-period crossover in children 3 to <18 years of age with GHD. The planned study duration is 24 weeks with a screening period of up to 30 days and a follow-up phone call four weeks after the last clinic visit. Approximately 90 children with GHD who have been stable on treatment with daily Genotropin® for a minimum of 3 months will be enrolled. Subjects will be randomized to one of two sequences, either 12 weeks of continued treatment with daily Genotropin® followed by 12 weeks of treatment with weekly somatrogon, or 12 weeks of treatment with weekly somatrogon followed by 12 weeks of treatment with daily Genotropin® (see Figure 2 below). There will be no treatment wash-out period since these subjects must take growth hormone continually. Subjects will have study visits at Baseline, Weeks 6, 12, 18, and 24. Subjects will also be followed up by phone 8-12 days after each treatment period begins (Week 1 and Week 13). Subjects and caregivers (as a Dyad) will complete the DCOA questionnaires at baseline and at the end of each 12 week treatment period (DCOA 1 at baseline and after Period I and Period II; DCOA 2 after Period II). Subjects and caregivers will also complete the PGIS-IDA at baseline and after Period I and Period II. Appendix 5 describes which sub-group (subject and/or caregiver) completes which part of the questionnaire and at which time point. All subjects/caregivers will receive a follow up phone call at Week 28.



Study Treatments

Subjects will be randomized to one of the following two treatment sequences on Baseline/Visit 1:

- Sequence 1: Treatment with daily Genotropin® for 12 weeks and then switched to weekly somatrogon for 12 weeks;

- Sequence 2: Treatment with weekly somatrogon for 12 weeks and then switched to daily Genotropin® for 12 weeks.

Somatrogon Dose: all subjects will receive 0.66 mg/kg/week administered subcutaneously weekly regardless of which Sequence to which they are randomized. Somatrogon dose (regardless of Sequence) will be based on their weight (rounded to the nearest tenth) taken at baseline/Visit 1. The final dose to administer will be rounded up to the nearest 0.5 mg increment. Refer to IP manual for dose calculations and rounding rules. Subjects on somatrogon should administer their dose at approximately the same time on a regularly scheduled day of the week.

Genotropin® Dose: all subjects receiving Genotropin® prior to the study will receive the same Genotropin® dose that they were receiving at the time of enrollment regardless of which Sequence to which they are randomized. Subjects on Genotropin® during the study should administer their dose once daily at approximately the same time every day as they were injecting their daily growth hormone at the time of screening.

Subjects using the HumatroPen® (USA only) prior to the study will receive Genotropin® given at the same dose (±0.2 mg) as the Humatrope® (USA only) that they were receiving at the time of enrollment regardless of which Sequence to which they are randomized.

Subjects using the Omnitrope® Pen (USA only) prior to the study will receive Genotropin® given at the same dose (±0.2 mg) as the Omnitrope® (USA only) that they were receiving at the time of enrollment regardless of which Sequence to which they are randomized.

Subjects will self-inject at the clinical site during Visits 1 and 4. All other doses of Genotropin® and somatrogon will be self-administered at home.

Statistical Methods

Sample Size Determination[19,20]

In order to estimate the sample size, based on solicited internal expert opinion, the following assumptions were considered using a two-sided type-I error of 0.05:

- The expected difference between the two treatment schedules in the Life Interference Total Score is assumed to be from a distribution with mean = 0.45. This is considered to be a moderate effect size.
- The standard deviation of the individual Total Score is assumed to be 1.
- The within-subject correlation of scores measured on a same subject at two different times is assumed to be at least 0.3.

Under these assumptions, a total of 75 subjects are needed at 90% power from a two-sided paired t-test for mean difference for the proposed study using Life Interference as the primary endpoint. As the Life Interference instrument has not been tested in prior clinical trials, the sample size will be increased by approximately 20% to account for the uncertainty in variability of the life interference endpoint and to account for the potential dropouts, increasing the sample size for the study to approximately 90 subjects.

Analysis of the Primary Endpoint

The primary endpoint will be analyzed using a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects. This model will be used to test the hypothesis that the difference in Life Interference Total Score between weekly and daily regimens is statistically significant.

The primary analysis set will be conducted on the intent to treat (ITT) population. Additional sensitivity analyses will be carried out to understand the impact of missing data and details will be described in the Statistical Analysis Plan.

Analysis of the Secondary Endpoint

The continuous secondary endpoints will be analyzed using a linear mixed effects model including sequence, period, and treatment as fixed effects, and subject within sequence and within-subject error as random effects.

Additional details of the secondary endpoints will be described in the statistical analysis plan.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

		Screening	Baseline	Treatment Period I			Treatment Period II			Follow-Up
Visit Number (Week)			**V1 (W0)**	**V2[1] (W1)**	**V3 (W6)**	**V4 (W12)**	**V5[1] (W13)**	**V6 (W18)**	**V7 (W24)**	**W28[1]**
Study Day		**-30 to 0**	**1**	**8**	**42**	**84**	**92**	**126**	**168**	**196**
Visit Window (Days)				**+4**	**±4**	**+4**	**+4**	**±4**	**±4**	**+7**
Inclusion/Exclusion Criteria		X	X							
Obtain Informed Consent		X								
Register subject in interactive response technology (IRT)		X								
Demographics		X								
Medical History		X								
Complete Physical Examination		X								
Vital Signs (HR, RR, BP, Temp)		X	X		X	X		X	X	
Body Weight		X	X							
Body Height		X								
Concomitant Medications		X	X	X	X	X	X	X	X	
Clinical Laboratory Tests	Safety Labs[2]	X				X			X	
	IGF-I, IGF-I SDS	X				X			X	
	Hemoglobin A1c	X				X			X	
	Urinalysis	X				X			X	
	Urine Pregnancy (WOCBP)	X	X			X			X	
	Somatrogon Level	X				X[3]			X[3]	
	Anti-somatrogon Ab (and neutralizing Ab)	X				X[3]			X[3]	
	Anti-rhGH Ab (and neutralizing Ab)	X				X			X	
Serious and Non-serious Adverse Event Assessment		X	X	X	X	X	X	X	X	X

	Screening	Baseline	Treatment Period I			Treatment Period II			Follow-Up
Visit Number (Week)		**V1 (W0)**	**V2[1] (W1)**	**V3 (W6)**	**V4 (W12)**	**V5[1] (W13)**	**V6 (W18)**	**V7 (W24)**	**W28[1]**
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Visit Window (Days)			**+4**	**±4**	**+4**	**+4**	**±4**	**±4**	**+7**
Contraception Check	X	X		X	X		X	X	X
Brief/Limited Physical Examination		X		X	X		X	X	
Randomization in IRT		X							
Dispense Study Medication		X		X[4]	X		X[4]		
Injection Device Instructions for Use (IFU) Training		X			X				
Inject Study Medication		X			X				
Injection Site Assessment		X	X	X	X	X	X	X	
Instruct/Provide Subject Diary		X		X	X		X		
Query for Injection Device Complaint		X	X	X	X	X	X	X	
Drug Accountability				X	X		X	X	
Review/Collect Subject Diary				X	X		X	X	
DYAD Questionnaire[5]		X			X			X	
DCOA 1		X[6]			X[6]			X[6]	
PGIS-IDA		X[7]			X[7]			X[7]	
DCOA 2								X[6]	

1. Phone call.
2. Fasting lipid profile, hematology with differential, blood chemistry, liver function tests, and free thyroxine (FT4).
3. Only for subjects who have been on somatrogon for the previous 12 weeks of treatment.
4. Only for subjects on Genotropin.
5. Completed by Clinical Site Staff.
6. Refer to Summary of DCOAs (Appendix 2) and DCOA Patient Questionnaires (Appendix 3).
7. Refer to PGIS-IDA (Appendix 4).

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Somatrogon is human growth hormone (hGH) that has been modified using C-terminal peptide (CTP) technology to extend its half-life such that it can be administered (by subcutaneous injection) on a weekly basis for use as a treatment in children and adults with growth hormone deficiency (GHD).

The CTP technology extends the hormone's half-life without the use of polymers, encapsulation techniques, or nanoparticles and is based on the CTP of the beta-chain of human chorionic gonadotropin (hCG), which provides hCG with the required longevity to maintain pregnancy. The beta chain of luteinizing hormone (LH), a gonadotropin that triggers ovulation, is almost identical to hCG but does not include the CTP. As a result, LH has a significantly shorter half-life in blood. Somatrogon is an hGH molecule fused to 3 copies of CTP, one at the N terminus and two at the C-terminus.

1.2. Background and Rationale

hGH is a 191-amino acid pituitary protein that stimulates hepatic production and release of insulin-like growth factor-I (IGF-I) into the systemic circulation. Growth hormone (GH), via IGF-I, is an important mediator in the promotion of linear growth in children and plays a role in the regulation of metabolism and body composition in adults.[1,2]

GHD results in inadequate circulating GH and IGF-I levels and is manifested as abnormal linear growth in children.[3,4] Childhood GHD can be congenital, acquired, or idiopathic. Underlying causes for congenital malformation include pituitary dysfunction due to abnormal neurodevelopment in utero of certain brain regions and genetic abnormalities. Etiology for acquired GHD includes brain tumors in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation and surgical intervention. The idiopathic origin of GHD is poorly understood but it appears to be multifactorial.[5]

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Most morbidity in children with GHD relates to short stature. The inability to achieve normal height can lead to early onset of severe psychosocial problems directly related to short stature. This is confounded by delayed puberty and deficits in facial, dental and (in males) genital development. Approximately 5% of children with GHD have episodes of hypoglycemia, particularly in infancy.[3] Persistency of GHD into adulthood is associated with increased risk of cardiovascular morbidity and mortality.

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The majority of currently available hGH products require daily or every other day SC or intramuscular (IM) injections to maintain hGH blood levels within the effective therapeutic window. The burden of daily administration and its concomitant side effects (eg, injection site discomfort, transient edema and arthralgia) can cause a reduction in compliance and can limit the therapeutic utility of existing formulations.[11]

Somatrogon is a long-acting rhGH for SC administration. It consists of hGH fused to three copies of the CTP of the beta chain of human chorionic gonadotropin hCG; one copy at the N-terminus and two copies (in tandem) at the C-terminus.

Somatrogon is currently being developed for use as a long-term treatment in children with GHD. Five studies have been completed with somatrogon; two Phase 1 studies in healthy adult volunteers, two Phase 2 studies, in children and adults with GHD, and a Phase 3 study in adults with GHD. Results of the Phase 2 Study in children demonstrated pharmacokinetic (PK) and pharmacodynamic (PD) profiles compatible with once weekly administration. The estimated half-life (t½) of somatrogon was 22.4 hours in the 13 children receiving 0.66 mg/kg/week, compared with the t½ of rhGH of 3.5 hours in the 11 children studied. IGF-1 serum levels for children receiving 0.46 mg/kg/week and 0.66 mg/kg/week remained above those of the children treated with rhGH throughout the study.[12] Clinical safety and efficacy was comparable to Genotropin® given once daily with no serious safety events.

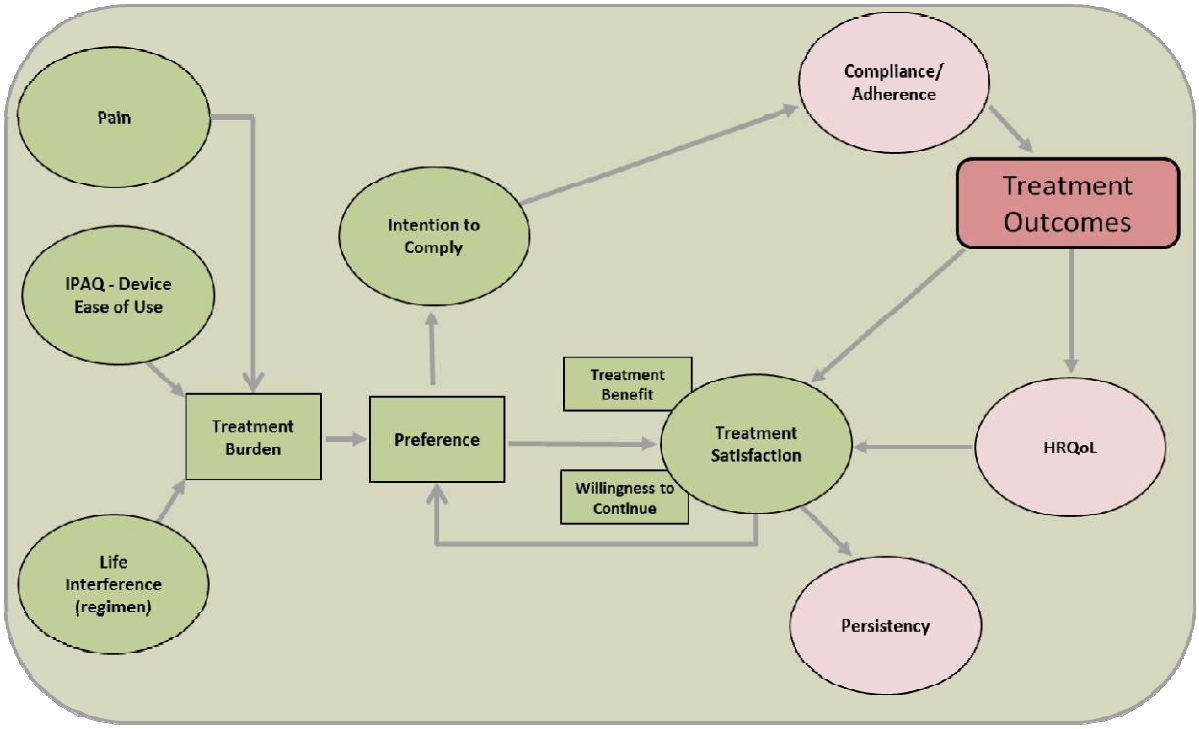
The purpose of this study is to evaluate whether there is a benefit, defined as superior adherence and acceptance, of a once weekly injection schedule to support the benefit/risk profile of somatrogon. Figure 1 presents a conceptual model of the variables (precursors/predictors) hypothesized to be associated with adherence and treatment outcomes in GHD. While it is not possible at this time to evaluate adherence in a clinical trial, it is possible to instead evaluate some of these precursor variables.

One component in this hypothesized model is treatment burden. Treatment burden relates to distress caused by treatment-associated demands (eg, visits to the doctor, medical tests, medication management, changes in lifestyle) which can have wide-ranging impact on patients' lives, and their caregivers. The burden associated with a treatment schedule may be one important consideration for adherence. The focus of the current study is to assess concepts (eg, device ease of use, side effects of treatment [eg, injection signs and symptoms],

and life interference) that comprise key aspects of treatment burden in GHD. Specifically, this study tests the hypothesis that, for children with GHD, a once weekly treatment schedule (once weekly somatrogon) has a treatment burden that is less than a daily treatment schedule (Genotropin®).

A Dyad Clinical Outcomes Assessment (DCOA) questionnaire will be used to measure the variables as the growth hormone injection is often a shared experience between patient and caregiver. The DCOA questionnaire has recently been developed, and the development process complies with patient reported outcome (PRO) tool development as recommended by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).[13,14] The cognitive debriefing process via patient interviews resulted in the final content-valid version of the tools (ie, the relevant aspects of treatment burden etc were evaluated by the patient, and their understanding of the questions was also confirmed). The second key step was to conduct the Field Study in which the final tools were employed in patients who use daily growth hormone injections to determine the psychometric properties. The results demonstrated that the DCOA questionnaire performs well in this patient group; it is valid and reliable and is fit for purpose.[15]

Figure 1. Hypothesized Conceptual Model of the Variables Associated with Adherence and Outcomes in GHD[16,17,18]



IPAQ: Injection Pen Assessment Questionnaire; HRQoL: health related quality of life.

Preference is another sub-concept represented in Figure 1. This study will include a measure of preference that compares daily and weekly treatment. Reducing the treatment burden with a once weekly schedule should translate to a higher preference over the daily schedule. Additionally, a separate discrete choice exercise (conjoint analysis) evaluating patient preferences for treatment has recently completed. A higher expressed preference for a once weekly schedule will influence an individual's behavior around their intention to comply with that particular schedule, and the DCOA questionnaire is also designed to evaluate this change in behavioral intention.

A higher expressed preference should also be reflected by the evaluation of treatment satisfaction with the injection schedule. The DCOA questionnaire is designed to assess this, in terms of willingness to continue with the treatment schedule, perceived benefit of the schedule, and overall satisfaction with the schedule. It is hypothesized that evidence generated from this study demonstrating a preference for the once weekly injection schedule along with a reduced treatment burden will be reflected in the "real world" use, when this weekly injection receives approval. This should translate to improved adherence which will ultimately lead to improved treatment outcomes and quality of life.

1.3. Summary of Safety from Completed Studies with Somatrogon

In total, 289 subjects have received at least one dose of somatrogon in completed studies (54 healthy adult volunteers, 187 adults with GHD, and 48 pediatric patients with GHD).

During the completed Phase 2 study in children with GHD, safety analyses demonstrated that somatrogon was well tolerated with no unexpected adverse events (AE) or serious adverse events (SAE). Expected events were primarily of moderate severity and tended to resolve quickly. None of the patients discontinued or were removed prematurely from the study due to an AE. Relatively few AEs were attributed to somatrogon overall and those that were reported were similar to those expected with rhGH therapy. No accumulation of IGF-1 was observed over the study period, and IGF-1 exceeded +2 standard deviation score (SDS) in only one patient.

Additional details in adults and pediatrics can be found in the Sponsor provided Investigator's Brochure (IB).

1.4. Rationale for Dose Selection

For this study each subject will continue on the Genotropin® dose that they are using at the time of screening. The somatrogon dose that will be used is 0.66 mg/kg/week. This dose is based on the Phase 2 pediatric study and is the same dose that is being used in the somatrogon Phase 3 pediatric efficacy trial.

1.5. Benefits and Risks of Participation

The benefit of participation for all subjects in this study is close monitoring of the safety of the treatment and of their medical condition. The experience to date is that somatrogon has an efficacy and safety profile similar to that of Genotropin®. There is, however, limited experience in switching patients from treatment with Genotropin® to somatrogon. A potential risk of participation for all subjects is the occurrence of injection site reactions.

Additional information for this compound may be found in the single reference safety document (SRSD), which, for this study, is the Sponsor provided IB. The SRSD for the comparator agent is the local product documents (LPD).

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoint:**
• To evaluate the treatment burden of a weekly somatrogon injection schedule and a daily Genotropin® injection schedule.	• Treatment burden assessed as the difference in mean Overall Life Interference total scores between the weekly injection schedule and daily injection schedule as assessed by the Patient Life Interference Questionnaire (as part of DCOA 1) completed by the Subject/Caregiver Dyad at baseline and after each treatment schedule experience.
Secondary Objectives:	**Secondary Endpoints:**

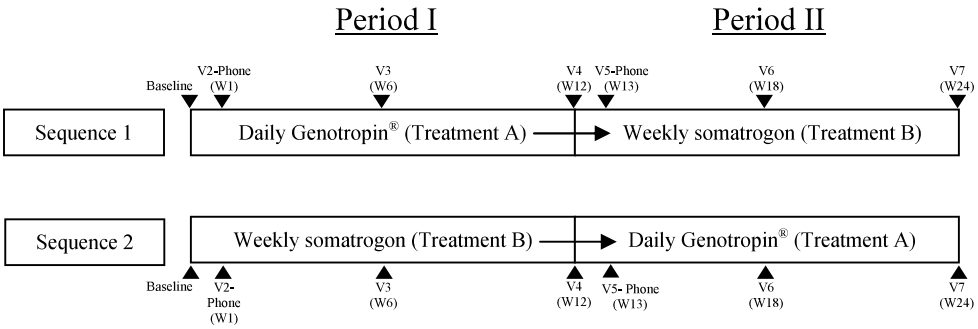
• To evaluate the following aspects of the treatment experience as determined by subject and caregiver self-assessments (dyadic approach) of weekly somatrogon therapy and daily Genotropin® therapy:
  • Life interference.
  • Caregiver life interference.
  • Family life interference.
  • Benefit, satisfaction, willingness to continue.
  • Intention to comply.
  • Injection pen ease of use.
  • Convenience of injection schedule.
  • Ease of the injection schedule.
  • Preferred injection schedule.
	• Treatment experience assessed as the difference in mean scores between the weekly injection schedule experience and daily injection schedule experience in each of the following variables within DCOA 1 questionnaires completed at baseline and after subjects have experienced both treatment schedules:
	  • Pen ease of use.
	  • Ease of the injection schedule.
	  • Convenience of the injection schedule.
	  • Satisfaction with overall treatment experience.
	  • Willingness to continue injection schedule.
	  • Injection signs and symptoms (from the patient).

• Choice of injection pen. • Injection signs and symptoms (pain, bruising, stinging). • Caregiver report of signs (bleeding, bruising). • Missed injections. • To use a Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA) at baseline and at the end of each period (Week 12 and Week 24) to support the interpretation of scores from the Dyad Clinical Outcome Assessment (DCOA) 1 and DCOA 2 Questionnaires. [redacted]	• Assessment of Signs (from the Caregiver). • Caregiver Life Interference, including Family Life Interference. • Missed injections. • Proportion of Subject/Caregiver Dyads that select the weekly injection schedule compared to the daily injection schedule in each of the outcome domains below as assessed by the DCOA 2 Questionnaires completed at Week 24. • Choice of injection pen. • Preferred injection schedule. • Convenience of injection schedule. • Easier to follow. • Ease of the injection schedule. • Patient life interference. • Caregiver Life Interference, including Family Life Interference. • Benefit relating to the injection schedule. • Intention to comply. • The Patient Global Impression at baseline and at the end of each period (Week 12 and Week 24).
Safety Objective:	**Safety Endpoints:**
• To describe the safety and tolerability of somatrogon.	• Frequency, severity, and relationship of adverse events to somatrogon. • Serious adverse events. • Discontinuations due to adverse events. • Frequency and severity of abnormal lab values. • Detection of anti-rhGH antibodies (and neutralizing antibodies). • Detection of anti-somatrogon antibodies (and neutralizing antibodies).

3. STUDY DESIGN

The study is a randomized, open-label, multi-center, 2-period crossover in children 3 to <18 years of age with GHD. The planned study duration is 24 weeks with a screening period of up to 30 days and a follow-up phone call four weeks after the last clinic visit. Approximately 90 children with GHD who have been stable on treatment with daily Genotropin® for a minimum of 3 months will be enrolled. Subjects will be randomized to one of two sequences, either 12 weeks of continued treatment with daily Genotropin® followed by 12 weeks of treatment with weekly somatrogon, or 12 weeks of treatment with weekly somatrogon followed by 12 weeks of treatment with daily Genotropin® (see Figure 2 below). There will be no treatment wash-out period since these subjects must take growth hormone continually. Subjects will have study visits at Baseline, Weeks 6, 12, 18, and 24. Subjects will also be followed up by phone 8-12 days after each treatment period begins (Week 1 and Week 13). Subjects and caregivers (as a Dyad) will complete the DCOA questionnaires at baseline and at the end of each 12 week treatment period (DCOA 1 at baseline and after Period I and Period II; DCOA 2 after Period II). Subjects and caregivers will also complete the PGIS-IDA at baseline and after Period I and Period II. Appendix 5 describes which sub-group (subject and/or caregiver) completes which part of the questionnaire and at which time point. All subjects/caregivers will receive a follow up phone call at Week 28.

Figure 2. Study Design



4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol. A minimum of 20% of subjects recruited will be ages 3 to <12 years old at the time of screening.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Children aged ≥3 years old and <18 years (17 years and 364 days) on the date of ICF signature with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiencies.

2. Currently on treatment with either Genotropin Pen®, Genotropin GoQuick Pen®, HumatroPen® (United States of America [USA] only), or Omnitrope® Pen (USA only) ≥3 months and have been compliant on a stable dose (±10%) for at least 3 months prior to screening.

3. IGF-I SDS <2.

4. Subjects on hormonal replacement therapy for other hypothalamic-pituitary-axis (HPA) hormonal deficiencies and/or diabetes insipidus must be on an optimized and stable treatment regimen, as determined by the Investigator, for at least 3 months prior to screening.

5. Women of childbearing potential and fertile men must agree to use a highly effective method of contraception as outlined in this protocol (see Section 4.4.1) during the study until at least 28 days after the last dose of investigational product. Fertile men must agree to a barrier contraceptive (condom). Vasectomy older than 6 months is also acceptable.

    a. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

        i. Premenarchal;

        ii. Have undergone a documented hysterectomy and/or bilateral oophorectomy;[1]

        iii. Have medically confirmed ovarian failure.

    b. Male subjects Tanner stage 3 and above are to be considered fertile.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

[1]. Can also be confirmed by ultrasound.

6. Evidence of a personally signed and dated informed consent document (and written assent where applicable based on age and country regulation) indicating that the subject or a legally acceptable representative/parent(s)/legal guardian has been informed of all pertinent aspects of the study.

7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Subjects and/or caregiver must express the ability to understand, read, and write in the language native to the country in which the study is being conducted. In the U.S., subjects and/or caregiver must express the ability to understand, read, and write English.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study.

1. History of leukemia, lymphoma, sarcoma or any other cancer.

2. History of radiation therapy or chemotherapy.

3. Children with psychosocial dwarfism.

4. Children born small for gestational age (SGA) – birth weight and/or birth length <-2 SDS for gestational age.

5. Other causes of short stature such as uncontrolled primary hypothyroidism and rickets.

6. Chromosomal abnormalities including Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Russell-Silver syndrome, short stature homeobox (SHOX) mutations/deletions or skeletal dysplasias.

7. Treatment with regularly scheduled daily or weekly injectable medications other than Genotropin® Pen, Genotropin GoQuick®, HumatroPen® (USA only), or Omnitrope® Pen (USA only).

8. Diabetes Mellitus.

9. Current treatment with Genotropin MiniQuick®.

10. History of any exposure to a long-acting hGH preparation.

11. Known or suspected human immunodeficiency virus (HIV)-positive patient, or patient with advanced diseases such as acquired immunodeficiency syndrome (AIDS) or tuberculosis.

12. Drug, substance, or alcohol abuse.

13. Known hypersensitivity to the components of the medication.

14. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

15. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

16. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

17. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

18. Patient and/or the parent/legal guardian are likely to be non-compliant with respect to study conduct.

19. Subject and/or the parent/legal guardian are unable to understand written and/or verbal instructions on the proper use of growth hormone injection devices.

20. Children with closed epiphyses (this determination can be based on available existing clinical data).

4.3. Randomization Criteria

Subjects will be randomized into the trial provided they have satisfied all subject selection criteria. A computer generated randomization schedule will be used to assign subjects to one of the two study sequences in a 1:1 ratio. Region (USA or European Union [EU]) and the type of Genotropin® injection device used (Genotropin Pen® or Genotropin GoQuick®) will be used as strata.

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential, as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s), must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee,

in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, implanted, transdermal), provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational or product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is:

- Somatrogon 60 mg/1.2 mL solution for injection.

Somatrogon will be provided in a multi-dose disposable prefilled pen and administered subcutaneously once weekly.

For this study, the following additional investigational (comparator) products will be utilized. Refer to the IP manual for the availability of sourced Genotropin® products with the EU countries.

In the USA region, the following IP will be supplied:

- Genotropin Pen® 5 or 12 Growth Hormone Delivery Device. This delivery device will be used with the corresponding Genotropin® lyophilized powder (somatropin [rDNA origin] for injection) two-chamber cartridge.

- Genotropin® 5 mg or 12 mg lyophilized powder (somatropin [rDNA origin] for injection). This product is provided as a two-chamber cartridge for subcutaneous use with the corresponding Genotropin Pen® Growth Hormone Delivery Device.

In the EU region, the following IP will be supplied:

- Genotropin (somatropin) Pen® 5.3 or 12 Multi-Dose Device. This delivery device will be used with the corresponding Genotropin® powder and solvent for solution for injection (somatropin) two-chamber cartridge.

- Genotropin® 5.3 mg or 12 mg powder and solvent for solution for injection (somatropin). This product is provided as a two-chamber cartridge for subcutaneous use with the corresponding Genotropin Pen® Multi-Dose Device.

- Genotropin GoQuick® 5.3 mg or 12 mg powder and solvent for solution for injection (somatropin) prefilled pen. This product is a disposable multidose prefilled pen for subcutaneous use.

Refer to the Investigational Product (IP) Manual and the Instructions for Use on how to dispense and prepare investigational products for administration.

Subjects will be randomized to one of the following two treatment sequences on Baseline/Visit 1:

- Sequence 1: Treatment with daily Genotropin® for 12 weeks and then switched to weekly somatrogon for 12 weeks.

- Sequence 2: Treatment with weekly somatrogon for 12 weeks and then switched to daily Genotropin® for 12 weeks.

Somatrogon Dose: all subjects will receive 0.66 mg/kg/week administered subcutaneously weekly regardless of which Sequence to which they are randomized. Somatrogon dose (regardless of sequence) will be based on their weight (rounded to the nearest tenth) taken at baseline/Visit 1. The final dose to administer will be rounded up to the nearest 0.5 mg increment. Refer to IP manual for dose calculations and rounding rules. Subjects on somatrogon should administer their dose at approximately the same time on a regularly scheduled day of the week.

Genotropin® Dose: all subjects receiving Genotropin® prior to the study will receive the same Genotropin® dose that they were receiving at the time of enrollment regardless of which Sequence to which they are randomized.

Subjects using the HumatroPen® (USA only) prior to the study will receive Genotropin® given at the same dose (±0.2 mg) as the Humatrope® (USA only) that they were receiving at the time of enrollment regardless of which Sequence to which they are randomized.

Subjects using the Omnitrope® Pen (USA only) prior to the study will receive Genotropin® given at the same dose (±0.2 mg) as the Omnitrope® (USA only) that they were receiving at the time of enrollment regardless of which Sequence to which they are randomized.

Subjects on Genotropin® during the study should administer their dose once daily at approximately the same time every day as they were injecting their daily growth hormone at the time of screening.

Subjects will self-inject at the clinical site during Visits 1 and 4. All other doses of Genotropin® and somatrogon will be self-administered at home.

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) (interactive Web-based response system [IWRS]). The IRT system will provide a confirmation report containing the subject number, randomization number, and dispensable units (DU) or container numbers assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Subject Compliance

Subjects will be directed to bring any completely used pens and/or cartridges to each clinic visit. Subjects will be directed to bring all used and unused pens and/or cartridges to Visits 4 and 7. Lost containers, damaged unused pen devices, etc, should not be counted as completed dose administrations. Subjects who fail to dose between visits should be counseled about the importance of maintaining the dosing schedule. In the event of an adverse event or reaction, subjects may be counseled to interrupt dosing temporarily or permanently. Subjects will be provided a diary and instructed on how to complete it. The diary will be used to assess compliance and injection site reactions. Compliance is defined as ≥80% adherence to injections. Compliance will be determined by review of the subject diary. Subjects who are non-compliant at 2 consecutive visits may be withdrawn.

5.3. Investigational Product Supplies

5.3.1. Dosage Forms and Packaging

Somatrogon 60 mg/1.2 mL solution for injection is a multi-dose disposable prefilled pen for single patient use intended for subcutaneous self-injection. The pen is assembled and ready to use and will be packaged in single unit packaging.

In the USA region, Genotropin Pen® 5 and 12 Growth Hormone Delivery Devices are for use with the corresponding Genotropin® 5 mg or 12 mg lyophilized powder (somatropin [rDNA origin] for injection) two-chamber cartridge. Genotropin® two-chamber cartridge contains a lyophilized powder in the front chamber and a diluent in the rear chamber. Genotropin® is intended for subcutaneous injection. Both Genotropin Pen® growth hormone delivery devices and Genotropin® two-chamber cartridges will be supplied in their primary commercial packaging.

In the EU region, the following products will be supplied:

- Genotropin Pen® 5.3 and 12 Multi-Dose Device for use with the corresponding Genotropin® 5.3 mg or 12 mg powder and solvent for solution for injection (somatropin) two-chamber cartridge. Genotropin® two-chamber cartridge contains a white lyophilized powder in the front compartment for reconstitution with a clear solution in the rear compartment. Genotropin® is intended for subcutaneous injection. Both Genotropin Pen® Multi-dose Devices and Genotropin® two-chamber cartridges will be supplied in their primary commercial packaging.

- Genotropin GoQuick® 5.3 mg and 12 mg powder and solvent for solution for injection (somatropin) prefilled pens contain a two-chamber cartridge which includes a white powder in the front compartment for reconstitution with a clear solution in the rear compartment. Genotropin GoQuick® prefilled pen is intended for subcutaneous use and supplied in its primary commercial packaging.

Refer to the IP manual for the availability of sourced Genotropin® products with the EU countries.

Note: In some regions/countries, Genotropin® may be classified as a controlled substance. In such cases, the product should be handled according to local/regional laws and procedures.

5.3.2. Preparation and Dispensing

Refer to the Instructions for Use (IFU) on how to prepare and administer somatrogon 60 mg/1.2 mL solution for injection in prefilled pen. The investigational product must not be used after 28 days of opening.

The following investigational (comparator) products are utilized:

In the USA region:

- Genotropin Pen® 5 or 12 Growth Hormone Delivery Device;

- Genotropin® 5 mg or 12 mg lyophilized powder (somatropin [rDNA origin] for injection) two-chamber cartridge.

In the EU region:

- Genotropin Pen® 5.3 or 12 Multi-Dose Device;
- Genotropin 5.3 mg or 12 mg powder and solvent for solution for injection (somatropin) two-chamber cartridge;
- Genotropin GoQuick® 5.3 mg or 12 mg powder and solvent for solution for injection (somatropin) prefilled pen.

Products will be dispensed using an IRT drug management system by a qualified staff member. The products will be assigned according to the unique container numbers printed on the container labels, and dispensed in appropriate quantities so that subjects will receive enough supplies to cover the number of doses required for that period (Visit 1 & 4). The subject should be instructed to maintain the product in the containers provided, and the containers should not be opened until the investigational product is to be administered.

5.4. Administration

Site personnel will be trained on how to instruct subjects on the proper administration of the investigational product. Subjects will be provided the instructions on how to properly administer the investigational product using the appropriate injection device based upon treatment assignment. At Visit 1 and Visit 4 subjects will be observed for proper injection technique by site personnel while self-injecting using the appropriate injection pen device (Genotropin Pen® device with corresponding cartridge, Genotropin GoQuick®, or somatrogon prefilled pen) that they will be using during Period I and Period II. Study staff and subjects should refer to the appropriate IFU for specific instructions on the handling and administration of the study drugs.

Subjects shall administer the appropriate study drug in the clinic on Visit Day 1 after all required procedures and assessments are complete and the subject is randomized to one of the following two treatment sequences:

- Sequence 1: Treatment with once daily Genotropin® for 12 weeks and then switched to once weekly somatrogon for 12 weeks;
- Sequence 2: Treatment with once weekly somatrogon for 12 weeks and then switched to once daily Genotropin® for 12 weeks.

Prior to randomization, subjects should be assessed for their ability and willingness to receive self-administered injections. If, however, following randomization, the subject is unable to physically use the product, the subject will be discontinued from the study and their attempts will be recorded as part of the study data.

The initial dose of Genotropin® or somatrogon for Period II will be administered in the clinic at Visit 4 by the subject after all required procedures and assessments are complete. Genotropin® and somatrogon will be administered according to the IFU and the Subject Study Medication Dosing and Instruction Booklet, which will be provided to all subjects. Training of subjects on Genotropin® administration will be in line with the training provided to patients for the licensed product. Clinical site personnel will review the IFU with the subject as well as provide guidance and assistance to ensure the subject is able to perform a self-injection. This first injection by the subject will be considered part of the training.

Genotropin® shall be administered subcutaneously into the thigh, buttocks, abdomen, or arm. Somatrogon should be injected into the thigh, buttocks, abdomen, or arm. Subjects will be instructed to rotate sites of administration.

5.4.1. Dose Modifications

There are no planned dose modifications for somatrogon or Genotropin® in this study. Throughout the study, reported adverse events (AEs) that are drug related may lead to a dose adjustment at the discretion of the investigator and medical monitor. If the severity will be reported as “moderate”, the dose may be reduced by 25% and if the severity will be reported as “severe“, the next dose may be held and the following dose may be reduced by 50%. The Investigator and Study Medical Monitor will communicate to track and assess dose modifications.

5.4.2. Missed Doses

Subjects on somatrogon should administer their dose once weekly at approximately the same time on a regularly scheduled day of the week. If a subject on somatrogon misses a dose, they should administer that dose as soon as they remember, provided it is no more than 72 hours after their regularly scheduled dose. If the dose is more than 72 hours from their regularly scheduled day of the week, then the patient shall skip the dose for that week and resume dosing on their next regularly scheduled day of the following week. Note: Doses that are administered within 72 hours of their regularly scheduled day of the week will not be considered a missed dose.

Subjects on Genotropin® should administer their dose once daily at approximately the same time every day as they were at the time of screening. If a subject on Genotropin® misses a dose, they should administer that dose as soon as they remember, provided it is within 10 hours of their regularly scheduled dose. If more than 10 hours have passed the subject should resume administration of the study medication at the next scheduled time. Subjects should not double any doses to make up for a missed dose.

Subjects will be trained that if an injection is started (ie, the injection device is placed on the skin with the needle inserted into the skin and the button is depressed) no further attempts at injection should be made for that scheduled dose even if there is uncertainty that the full dose was received.

Subjects will record dose administration in the subject diary; this is how compliance will be determined.

A question involving missed doses and reason for missing is part of DCOA1 but is not being used to determine compliance.

5.5. Switching between Genotropin® and Somatrogon

- Subjects that will be switching from Genotropin® to somatrogon in Sequence 1 should administer their final injection of Genotropin® 36 hours (±24 hours) prior to their first injection with somatrogon; their somatrogon dose will be based on their weight (rounded to the nearest tenth) taken at baseline/Visit 1.

- Subjects that will be switching from somatrogon to Genotropin® in Sequence 2 should administer their final injection of somatrogon 7 days (±72 hours) prior to their first injection with Genotropin®.

- Subjects in Sequence 1 that have completed the study should restart their regularly prescribed supply of Genotropin®, Humatrope®, (USA only) or Omnitrope® (USA only) 7 days after their final somatrogon injection. Their Genotropin®, Humatrope® (USA only), or Omnitrope® (USA only) dose should be the same dose that they were receiving at the end of Period I unless directed otherwise by their provider.

- Subjects in Sequence 2 that have completed the study should restart their regularly prescribed supply of Genotropin®, Humatrope®, (USA only) or Omnitrope® (USA only) 24 hours after their last study dose of Genotropin® was received. Their Genotropin®, Humatrope®, (USA only) or Omnitrope® (USA only) dose should be the same dose that they were receiving at the end of the study unless directed otherwise by their provider.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable label and regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual for storage conditions of the product.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. Completely used study drug must be returned to the investigator site at each visit. All used and unused study drug must be returned to the investigator site at the end of each period (Weeks 12 and 24).

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatments

In general, subjects should remain on stable dosages of permitted concomitant medications throughout the study. Any medications (including prescription, over-the-counter, herbal and food supplements and health store products) required to treat concurrent medical conditions are permitted during the course of the study (other than those in Section 4.2), consistent with local regulatory labeling, at the discretion of the Investigator. All subjects will be questioned about concomitant medication at each visit. Medications started after the first dose of study medication will be documented as concomitant medications. Concomitant medications will be recorded in the appropriate section of the case report form (CRF). All concomitant medications started after the first dose of study drug must be recorded with dose and date of administration.

5.8.1. Prohibited Concomitant Medications

The only concomitant medications not allowed during the study are any regularly scheduled daily or weekly injectable medications other than study treatment medications Genotropin® Pen, Genotropin GoQuick® or somatrogon.

6. STUDY PROCEDURES

For Screening, Visits 4 and 7 only, subjects will be required to fast (water only) for at least 10 hours prior to the study visit. Subjects should take prescribed permitted oral concomitant medication, as needed, prior to study visit if it can be administered with water only; prescribed permitted concomitant medications that must be taken with food or after meals should NOT be taken until after the visit procedures have been completed. Subjects who do not fast will be required to return for fasting laboratory tests, at the earliest possible time, before the next scheduled study visit.

6.1. Screening

6.1.1. Visit Days -30 to 0

The Screening Visit will occur 0 to 30 days prior to the Baseline/Randomization Visit. The following procedures and assessments will be performed during this visit:

- Obtain written informed consent – the investigator will obtain a written informed consent from each subject before any trial related activity is initiated. If the subject consents to the investigator contacting their primary care provider, the investigator should ascertain that the subject's primary care provider has been informed of the subject's participation in the trial and that safety will be monitored;

- Verify trial eligibility by checking and documenting inclusion and exclusion criteria (Sections 4.1 and 4.2);

- Register subjects with IRT. The IRT must be contacted before screening assessments begin in order to obtain a subject screening identification number (SSID);

- Obtain and record demographics and general medical history;

- Measure and record vital signs: heart rate, temperature, respiratory rate and blood pressure (Section 7.2.2);
- Measure and record body weight and body height;
- Conduct complete physical examination (Section 7.2.4);
- Obtain and record prior medications and instruct subjects on the use of concomitant medications (Section 5.8).
- Collect fasting (10 hours) specimens for laboratory exams:
    - Blood for fasting lipid profile, hematology with differential, blood chemistry, liver function tests, free thyroxine (FT4), IGF-I, IGF-I SDS, hemoglobin A1c, somatrogon level, anti-somatrogon Ab (and neutralizing Ab), and anti-rhGH Ab (and neutralizing Ab);
    - Urine for urinalysis;
    - Urine for pregnancy test (women of child bearing potential (WOCBP)).
- Provide contraception recommendations (Section 4.4.1);
- Inquire for and record adverse events;
- Inform subject/caregiver of date of next visit;
- Instruct all subjects to administer their final injection of Genotropin®, Humatrope® (USA only), or Omnitrope® (USA only) 36 hours (±24 hours) prior to their next visit (Visit 1).

Re-screening is allowed in the event of lost or damaged laboratory samples, in which case only the lost or damaged laboratory tests need to be repeated. Additionally, subjects who cannot complete the baseline visit within 30 days of start of screening due to unforeseen circumstances, such as but not limited to, delays in study drug shipment to the clinical site or acts of nature (snowstorms, hurricanes, earthquakes, etc.) may be re-screened. In this case all eligibility criteria need to be reviewed, and pregnancy test (if applicable), medical history and concomitant medications need to be redone/updated.

6.2. Study Period (for both Treatment Period I and Treatment Period II)

6.2.1. Baseline/Visit 1 (Study Day 1, Week 0)

This visit can occur as soon as the laboratory results from the screening visit are available provided all other eligibility requirements have been met. The following procedures and assessments should be made before randomization and subject injection:

- Verify trial eligibility by checking and documenting inclusion and exclusion criteria (Sections 4.1 and 4.2);
- Measure and record vital signs: heart rate, temperature, respiratory rate and blood pressure (Section 7.2.2);
- Measure and record body weight;
- Obtain and record ongoing medications and instruct the subject on the use of concomitant medications (Section 5.8);
- Conduct brief/limited physical exam (Section 7.2.4);
- Inquire for and record adverse events;
- Conduct contraception check (Section 4.4.1).
- Collect specimens for laboratory exams:
    - Urine for pregnancy test (WOCBP).
- Randomization:
    - Access IRT to obtain randomization number for the subject.
- Questionnaire Administration:
    - Provide DCOA1 questionnaire and train Subject/Caregiver Dyad on completion;
    - Subject/Caregiver Dyad completes DCOA1 questionnaire;
    - Subject/Caregiver Dyad completes PGIS-IDA question;
    - Clinical Site Staff completes DYAD Questionnaire.
- Drug dispensation and dosing:
    - Dispense investigational product based on IRT randomization code and container number on the container;

- Instruct subject on injection;
- Subject will inject study treatment;
- Instruct and provide subjects with the subject diary corresponding to the treatment they are assigned.

- Assessment during and after subject injection:
  - Injection site assessment;
  - Inquire for and record adverse events;
  - Inquire for and record injection device complaints;
  - Inform subject/caregiver of date of next visit and required dates of administration of study drug.

6.2.2. Visit 2 (Study Day 8 + 4 days, Week 1)

Visit 2 is a follow-up phone call that will occur 8-12 days following Visit 1. The following assessments should be made:

- Obtain and record ongoing medications and instruct the subject on the use of concomitant medications (Section 5.8);
- Injection site assessment;
- Inquire for and record adverse events;
- Inquire for and record injection device complaints;
- Inform subject/caregiver of date of next visit and that subject should bring all used study medication containers, used cartridges and/or injection devices, and subject diary to that visit.

6.2.3. Visit 3 (Study Day 42 ±4 days, Week 6)

Visit 3 is at the clinical site and the following procedures and assessments should be made:

- Obtain and record ongoing medications and instruct the subject on the use of concomitant medications (Section 5.8);
- Measure and record vital signs: heart rate, temperature, respiratory rate and blood pressure (Section 7.2.2);
- Conduct brief/limited physical exam (Section 7.2.4);

- Conduct contraception check (Section 4.4.1);
- Collect all used study medication containers (drug accountability);
- Collect all used cartridges and/or injection devices (drug accountability);
- Review and collect subject diary and instruct/provide subject with new subject diary for the remainder of treatment period;
- Injection site assessment;
- Inquire for and record adverse events;
- Inquire for and record injection device complaints;
- Drug Dispensation:
  - Dispense Genotropin to subjects in Sequence 1.
- Inform subject/caregiver of date of next visit and that subject should bring all used and unused study medication containers, used and unused cartridges and/or injection devices, and subject diary to that visit;
- Inform subjects that regarding the next visit (Visit 4):
  - Subjects that will be switching from Genotropin® to somatrogon should administer their final injection of Genotropin® 36 hours (±24 hours) prior to Visit 4;
  - Subjects that will be switching from somatrogon to Genotropin® should administer their final injection of somatrogon 7 days (±72 hours) prior to Visit 4.

6.2.4. Visit 4 (Study Day 84 + 4 days, Week 12) – Crossover/Treatment Change

Visit 4 is at the clinical site and is where subjects will be switched based on their assigned sequence from Genotropin® to somatrogon or from somatrogon to Genotropin®.

Subjects who discontinue study treatment prior to beginning Period II of the study will be asked to complete the assessments and procedures outlined in Visit 4 (except for drug dispensation, and dosing and assessments during and after subject injection).

The following procedures and assessments should be made before subject self-injection:

- Obtain and record ongoing medications and instruct the subject on the use of concomitant medications (Section 5.8);

- Measure and record vital signs: heart rate, temperature, respiratory rate and blood pressure (Section 7.2.2);
- Conduct brief/limited physical exam (Section 7.2.4);
- Conduct contraception check (Section 4.4.1);
- Collect all used and unused study medication containers (drug accountability);
- Collect all used and unused cartridges and/or injection devices (drug accountability);
- Review and collect subject diary;
- Injection site assessment;
- Inquire for and record adverse events;
- Inquire for and record injection device complaints;
- Collect fasting (10 hours) specimens for laboratory exams:
    - Blood for fasting lipid profile, hematology with differential, blood chemistry, liver function tests, FT4, IGF-I, IGF-I SDS, hemoglobin A1c, somatrogon level and anti-somatrogon Ab (and neutralizing Ab) (only for subjects who have been on somatrogon for the previous 12 weeks of treatment), and anti-rhGH Ab (and neutralizing Ab);
    - Urine for urinalysis;
    - Urine for pregnancy test (WOCBP).
- Questionnaire Administration:
    - Provide DCOA1 questionnaire and train Subject/Caregiver Dyad on completion;
    - Subject/Caregiver Dyad completes DCOA1 questionnaire;
    - Subject/Caregiver Dyad completes PGIS-IDA question;
    - Clinical Site Staff completes DYAD Questionnaire.
- Drug dispensation and dosing:
    - Confirm for subjects switching from Genotropin® to somatrogon that it has been 36 hours (±24 hours) since their most recent injection of Genotropin® relative to this visit;

- Confirm for subjects switching from somatrogon to Genotropin® that it has been 7 days (±72 hours) since their most recent injection of somatrogon relative to this visit;
- Dispense new study treatment based on randomization;
- Instruct subject on injection;
- Subject will inject study treatment;
- Instruct/provide subjects with a new subject diary corresponding to the treatment they are switching to.

- Assessments during and after subject injection:
  - Injection site assessment;
  - Inquire for and record adverse events;
  - Inquire for and record injection device complaints;
  - Inform subject/caregiver of date of next visit and required dates of administration of study drug.

6.2.5. Visit 5 (Study Day 92 + 4 days, Week 13)

Visit 5 is a follow-up phone call that will occur 7-11 days following Visit 4. The following assessments should be made:

- Obtain and record ongoing medications and instruct the subject on the use of concomitant medications (Section 5.8);
- Injection site assessment;
- Inquire for and record adverse events;
- Inquire for and record injection device complaints;
- Inform subject/caregiver of date of next visit and that subject should bring all used study medication containers, used cartridges and/or injection devices, and subject diary to that visit.

6.2.6. Visit 6 (Study Day 126 ±4 days, Week 18)

Visit 6 is at the clinical site and the following procedures and assessments should be made:

- Obtain and record ongoing medications and instruct the subject on the use of concomitant medications (Section 5.8);

- Measure and record vital signs: heart rate, temperature, respiratory rate and blood pressure (Section 7.2.2);
- Conduct brief/limited physical exam (Section 7.2.4);
- Conduct contraception check (Section 4.4.1);
- Collect all used study medication containers (drug accountability);
- Collect all used cartridges and/or injection devices (drug accountability);
- Review and collect subject diary and instruct/provide subject with new subject diary for the remainder of treatment period;
- Injection site assessment;
- Inquire for and record adverse events;
- Inquire for and record injection device complaints;
- Drug Dispensation:
  - Dispense Genotropin to subjects in Sequence 2.
- Inform subject/caregiver of date of next visit and that subject should bring all used and unused study medication containers, used and unused cartridges and/or injection devices, and subject diary to that visit.

6.2.7. Visit 7 (Study Day 168 ±4 days, Week 24) – End of Study Visit

Visit 7 is at the clinical site and is the last visit of the study prior to follow up phone contact.

Subjects who discontinue treatment during Period II but before the end of study visit will be asked to complete the assessments and procedures outlined in Visit 7. The following procedures and assessments should be made:

- Obtain and record ongoing medications;
- Measure and record vital signs: heart rate, temperature, respiratory rate and blood pressure (Section 7.2.2);
- Conduct brief/limited physical exam (Section 7.2.4);
- Conduct contraception check (Section 4.4.1);
- Collect all used and unused study medication containers (drug accountability);

- Collect all used and unused cartridges and/or injection devices (drug accountability);
- Review and collect subject diary;
- Inquire for and record injection site reactions;
- Inquire for and record adverse events;
- Collect fasting (10 hours) specimens for laboratory exams:
    - Blood for fasting lipid profile, hematology with differential, blood chemistry, liver function tests, FT4, IGF-I, IGF-I SDS, hemoglobin A1c, somatrogon level and anti-somatrogon antibody (and neutralizing Ab) (only for subjects who have been on somatrogon for the previous 12 weeks of treatment), and anti-rhGH antibody (and neutralizing Ab);
    - Urine for urinalysis;
    - Urine for pregnancy test (WOCBP).
- Inquire for and record injection device complaints;
- Injection site assessment;
- Questionnaire Administration:
    - Provide DCOA1 and DCOA2 questionnaires and train Subject/Caregiver Dyad on completion;
    - Subject/Caregiver Dyad completes DCOA1 and DCOA2 questionnaires;
    - Subject/Caregiver Dyad completes PGIS-IDA question;
    - Clinical Site Staff completes DYAD Questionnaire.

6.2.8. Follow-up Contact

Follow-up contact via a phone call will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section).

6.3. Subject Withdrawal/Early Termination

6.3.1. Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should

notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.

6.3.2. Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

6.3.3. Withdrawal for Other Reason:

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal/Early Termination section)) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational products, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

6.3.3.1. Discontinuation of Study Treatment with Continued Study Participation

All subjects who discontinue study treatment early will be encouraged to complete the study and follow an abbreviated study visit schedule.

6.3.3.1.1. Discontinuation During Period I Prior to Visit 4

Subjects who discontinue study treatment during Period I prior to Visit 4 will be asked to come to the clinic within seven days of discontinuing study treatment to complete the assessments and procedures outlined in Visit 4 except for: Drug dispensing and dosing, and Assessment during and after subject injection. Subjects should follow-up again 12 weeks (+4 days) later to complete the assessments and procedures that are outlined in Visit 7 except for: Questionnaire administration. Follow up contact will be attempted as described in Section 6.2.8.

6.3.3.1.2. Discontinuation During Period II Prior to Visit 7

Subjects who discontinue study treatment during Period II prior to Visit 7 will be asked to come to the clinic within seven days of discontinuing study treatment to complete the assessments and procedures outlined in Visit 7. Follow up contact will be attempted as described in Section 6.2.8.

6.3.3.1.3. Treatment of GHD after Discontinuation of Study Treatment

Upon discontinuation of study treatment, subjects should resume standard of care treatment under the direction of the investigator.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, before investigational product administration at the baseline visit, at Visit 4 & 7 (end of the study visit) to confirm the subject has not become pregnant during the study, and at the early-withdrawal visit (if applicable).

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

7.2. Safety

7.2.1. Laboratory

Laboratory tests for safety will be performed at times defined in the Schedule of Activities of this protocol. Subject eligibility based on these tests will be determined at screening.

7.2.1.1. Local Laboratory Tests

Urine pregnancy test will be performed locally using the kits provided by the central lab. If local urine pregnancy testing is positive, serum pregnancy tests should be submitted to the central laboratory.

7.2.1.2. Central Laboratory Tests

A central laboratory will be used to analyze hematology, blood chemistry, liver function, thyroid function, and urinalysis tests (as listed in Table 1 below), as well as hormones and to ensure accuracy and consistency in test results. The central laboratory will transmit all results for protocol tests, scheduled and unscheduled, to the sponsor for inclusion in the clinical data base. Urinalysis will be performed on mid-stream, clean catch specimens.

The following safety laboratory tests will be performed at times defined in the Schedule of Activities and STUDY PROCEDURES sections of this protocol.

Table 1. Laboratory Tests

Hematology	Chemistry	Liver Function	Lipid Profile	Urinalysis	Additional
Hemoglobin Hematocrit Red blood cell (RBC) count Mean cell volume (MCV) Mean cell Hemoglobin (MCH) Mean cellular hemoglobin concentration (MCHC) Platelet count White blood cell (WBC) count Total neutrophils (Absolute [Abs]) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine BUN/Creatinine Ration Glucose Ca++ Na+, K+, Cl Total CO2 (Bicarbonate) Uric acid Albumin Total protein LDH Magnesium Phosphorus CK GFR	AST ALT GGT Total bilirubin Direct bilirubin Indirect bilirubin Alkaline phosphatase	Total Cholesterol HDL Cholesterol LDL Cholesterol VLDL Cholesterol Triglycerides	pH Specific gravity Bilirubin Nitrite Leukocyte Esterase Glucose (qual) Protein (qual) Blood (qual) Ketones Microscopic (if necessary)	IGF-I IGF-I SDS Hemoglobin A1c Free thyroxine (FT4) Urine pregnancy (WOCBP) Serum pregnancy (if needed for WOCBP) Somatrogon Level Anti-somatrogon Ab (and neutralizing Ab) Anti-rhGH Ab (and neutralizing Ab)

7.2.2. Vital Signs

Temperature, heart rate (HR), Respiratory Rate (RR) and blood pressure (BP) will be measured at times specified in the Schedule of Activities of this protocol. Additional collection times, or changes to collection times of HR, RR, and BP will be permitted, as necessary, to ensure appropriate collection of safety data.

Sitting BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. The same size BP cuff, which has been properly sized and calibrated, will be used to measure BP each time. The use of automated devices for measuring BP and PR is preferred, although when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

7.2.3. Weight and Height

Height will be measured without shoes according to the Schedule of Activities.

Body weight will be measured according to the Schedule of Activities in indoor clothing without shoes.

7.2.4. Physical Exam

Physical exam will be performed according to the Schedule of Activities.

Complete Physical Examination

The following parameters and body systems will be examined and any abnormalities described: General appearance, weight and height, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

Brief/Limited Examination

An abbreviated physical examination will be performed assessing the following: examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes. Any clinically significant changes from the baseline examination should be recorded as AEs.

7.2.5. Immunogenicity

7.2.5.1. Anti-somatrogon Antibodies, Anti-rhGH Antibodies, and Neutralizing Antibodies (NAb)

Blood samples (approximately 4 mL of whole blood) will be collected for determination of ADA and NAb into appropriately labeled tubes at visits specified in the Schedule of Activities.

Details regarding the collection, processing, storage and shipping of the serum immunogenicity samples will be provided in the Laboratory Manual. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure that resulted in compromised sample integrity will be considered a protocol deviation.

Samples will be analyzed using validated analytical methods in accordance with Pfizer standard operating procedures. Samples determined to be positive for ADA may be further characterized for NAb.

As part of understanding the immunogenicity of the study drug, study-samples may be used for additional characterization of the immune response and/or evaluation of the bioanalytical methods. These data will be used for exploratory purposes and may be included in the clinical report.

7.3. Pharmacokinetics

7.3.1. Serum for Analysis of Somatrogon

During all study periods, blood samples (approximately 4 mL) to provide a minimum of 2 mL serum for pharmacokinetic (PK) analysis will be collected into appropriately labeled tubes containing no anticoagulant at times specified in the Schedule of Activities section of the protocol.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the same time as the sample to assess immunogenicity.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the CSR.

7.4. Dyad Clinical Outcomes Assessment (DCOA) and Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA)

DCOA 1 and 2 and the PGIS-IDA question will be administered according to the Schedule of Activities and Appendix 5. DCOA 1 and 2 and PGIS-IDA are completed by the Subject/Caregiver Dyad which includes the subject (child who is being treated) and their adult caregiver. The adult caregiver should be the primary adult overseeing the growth hormone treatment of the subject. In the event that the role of oversight of treatment is shared by more than one person, the selection of the adult caregiver in the Dyad is left to the discretion of the investigator. However, the adult member of the dyad must be familiar with and participate in the preparation and administration of the medication at least some of the time. It is important that the same Subject/Caregiver Dyad complete all questionnaires together and every effort should be made to ensure that the same adult caregiver completes DCOA 1 and 2, and PGIS-IDA with the subject throughout the study. Questions from the DYAD questionnaire will be included on the electronic patient reported outcome (ePRO) device for the Clinical Staff Site user to complete in order to capture information about the primary adult overseeing treatment and the adult caregiver completing the questionnaires at Visits 1, 4 and 7. Refer to Appendices Appendix 2, Appendix 3, Appendix 4, Appendix 5.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a

subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal/Early Termination section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.2.1. Injection Site Reactions

Injection site reactions can be reported/recorded in four different ways.

- Injection pain, bruising, and stinging will each be scored by subjects by way of the Injection Sign and Symptom Assessment as part of the DCOA1. This assessment will be completed by subjects once for each treatment (once after completion of Period I and once after completion of Period II). Scores ≥8 for any sign or symptom (pain, bruising, bleeding, or stinging) will be recorded as an AE.

- Subjects will record injection site reactions in the subject diary.

- Subjects will be assessed for injection site reactions by the investigator at Visits 1, 2, 3, 4, 5, 6, and 7.

- Subjects will be instructed to call with any concerns regarding an injection site reaction.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST **OR** ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- The administration of an incorrect dosage; or missed dose (Section 5.4.1);
- The administration of investigational product outside the dosing schedule;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, should be reported to Pfizer within 24 hours of the investigator's awareness of the event.

Somatrogon device complaints will be reported using the Somatrogon Prefilled Pen Feedback and Complaint Form. Genotropin device complaints will be reported using the Investigational Drug Product and Medical Device Complaint Submission Form.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination[19,20]

In order to estimate the sample size, based on solicited internal expert opinion, the following assumptions were considered using a two-sided type-I error of 0.05:

- The expected difference between the two treatment schedules in the Life Interference Total Score is assumed to be from a distribution with mean = 0.45. This is considered to be a moderate effect size.
- The standard deviation of the individual Total Score is assumed to be 1.
- The within-subject correlation of scores measured on a same subject at two different times is assumed to be at least 0.3.

Under these assumptions, a total of 75 subjects are needed at 90% power from a two-sided paired t-test for mean difference for the proposed study using Life Interference as the primary endpoint. As the Life Interference instrument has not been tested in prior clinical trials, the sample size will be increased by approximately 20% to account for the uncertainty in variability of the life interference endpoint and to account for the potential dropouts, increasing the sample size for the study to approximately 90 subjects.

9.2. Analysis of the Primary Endpoint

The primary endpoint will be analyzed using a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects. This model will be used to test the hypothesis that the difference in Life Interference Total Score between weekly and daily regimens is statistically significant.

The primary analysis set will be conducted on the intent to treat (ITT) population. Additional sensitivity analyses will be carried out to understand the impact of missing data and will be described in the Statistical Analysis Plan.

9.3. Analysis of Secondary Endpoints

The continuous secondary endpoints will be analyzed using a linear mixed effects model including sequence, period, and treatment as fixed effects, and subject within sequence and within-subject error as random effects.

Additional details of the secondary endpoints will be described in the statistical analysis plan.

9.4. Safety Analysis

- Adverse events (Screening, Visits 1, 2, 3, 4, 5, 6, 7, and follow-up);
- Injection site reactions (Visits 1, 2, 3, 4, 5, 6, 7);
- Injection device complaints (Visits 1, 2, 3, 4, 5, 6, 7);
- Vital signs (Screening, Visits 1, 3, 4, 6, 7);
- Body weight (Screening, Visits 1 and 7);
- Physical exam (Screening, Visits 1, 3, 4, 6, 7);
- Urine pregnancy (if applicable) (Screening, Visits 1, 4, and 7);
- Routine clinical safety lab testing, IGF-I, IGF-I SDS, hemoglobin A1c, FT4 (Screening, Visits 4 and 7), somatrogon level (Screening, Visit 4[2] and Visit 7[2]), anti-somatrogon Ab (and neutralizing Ab) (Screening, Visit 4[2] and Visit 7[2]), and anti-rhGH Ab (and neutralizing Ab) (Screening, Visits 4 and 7).

Safety data will be tabulated and listed according to Pfizer's standard reporting algorithms.

[2] Only for subjects who have been on somatrogon for the previous 12 weeks of treatment.

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.1.1. Electronic Patient Reported Outcome (ePRO)

Electronic devices (eg, tablets) will be utilized in this study by subjects to capture the responses to the DCOA 1 and 2 and PGIS-IDA (ePRO data). All users will receive training on ePRO completion using this electronic data entry system. It is anticipated that completion of all ePRO questionnaires, for both the primary endpoint (Life Interference) and all secondary endpoints, by each enrolled subject will take approximately 30 to 40 minutes at each of the specified time points. Screen shots are included in the ePRO reference document. Access to the mechanism for entry of the subject data on the ePRO device must be restricted to the subject, by use of the subject number and a PIN known only to the subject. The ePRO vendor is responsible for controlling access to ePRO source data and reports on the vendor's database on behalf of the sites. Access controls that conform to relevant regulatory regulations and guidance will be documented by the ePRO vendor and approved by the sponsor study team. Access to source data or reports via the ePRO vendor's web portal and to other study data on the ePRO vendor's server must be strictly controlled by use of security features that include individual logons, assignment of logons to appropriate security groups, and private passwords known only to the individual user.

The ePRO data entered into the devices is stored there temporarily. Once sent to the ePRO vendor's database, the source data is on the database, not the device. The ePRO vendor is responsible for safeguarding the source data on behalf of the sites. The investigator Initiation Package will provide details of site data handling responsibilities. The Study Monitoring Plan will provide details of the Site Monitor's responsibilities for monitoring subject compliance, checking on the site's efforts to monitor subject compliance, and comparing source data kept at the site with comparable data in the ePRO vendor's database.

The ePRO vendor will transfer ePRO data to Pfizer (or its designated representative) at regular intervals. The Clinical Data Management team at Pfizer (or its representative) will review the data to identify inconsistencies and request clarifications from the ePRO vendor or the study site. All requests for changes and deletions of clinical data must be approved by the investigator (or designee). Before any approved change or deletion may be carried out by the vendor, it must also be reviewed by the sponsor study team to verify that it conforms to Good Clinical Practice.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the

person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial

End of trial in all participating countries is defined as last subject last visit (LSLV). For participating subjects, the trial ends on study Day 168 ±4 (randomization to last dose).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of somatrogon at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 15 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Ab	antibody
ADA	anti-drug antibodies
AE	adverse event(s)
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CI	confidence interval
CK	creatine kinase
CRF	case report form
CSA	clinical study agreement
CT	computerized tomography
CT	clinical trial
CTP	C-terminal peptide
DCOA	dyad clinical outcomes assessment
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
ePRO	electronic patient reported outcome
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	good clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GH	growth hormone
GHD	growth hormone deficiency
GRS	The Growth Hormone Research Society
hCG	human chorionic gonadotropin
HEENT	Head, Eyes, Ears, Nose, and Throat
hGH	human growth hormone
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary axis
HR	heart rate
HRQoL	health-related quality of life

Abbreviation	Term
IB	investigator's brochure
ICH	International Conference on Harmonisation
IFU	instructions for use
IGF-I	insulin-like growth-factor-I
IGF-I SDS	insulin-like growth-factor-I standard deviation score
IM	intramuscular
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPAQ	injection pen assessment questionnaire
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IWRS	interactive web-based response system
LFT	liver function test
LH	luteinizing hormone
LPD	local product documents
LSLV	last subject last visit
Mg	milligram
mIU	milli-International Units
mL	milliliter
MRI	magnetic resonance imaging
N/A	not applicable
NYHA	New York Heart Association
PCD	primary completion date
PD	pharmacodynamics(s)
PGI	patient global impression
PGIS-IDA	Patient Global Impression Severity-Impact on Daily Activities
PI	principal investigator
PIN	personal identification number
PK	pharmacokinetic(s)
PRO	patient reported outcomes
PT	prothrombin time
rhGH	recombinant human growth hormone
RR	respiratory rate
SAE	serious adverse event(s)
SAP	statistical analysis plan
SC	subcutaneous
SDS	standard deviation score
SGA	small for gestational age
SHOX	short stature homeobox

Abbreviation	Term
SmPC	summary of product characteristics
SRSD	single reference safety document
SSID	subject screening identification number
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USA	United States of America
WOCBP	woman of child bearing potential

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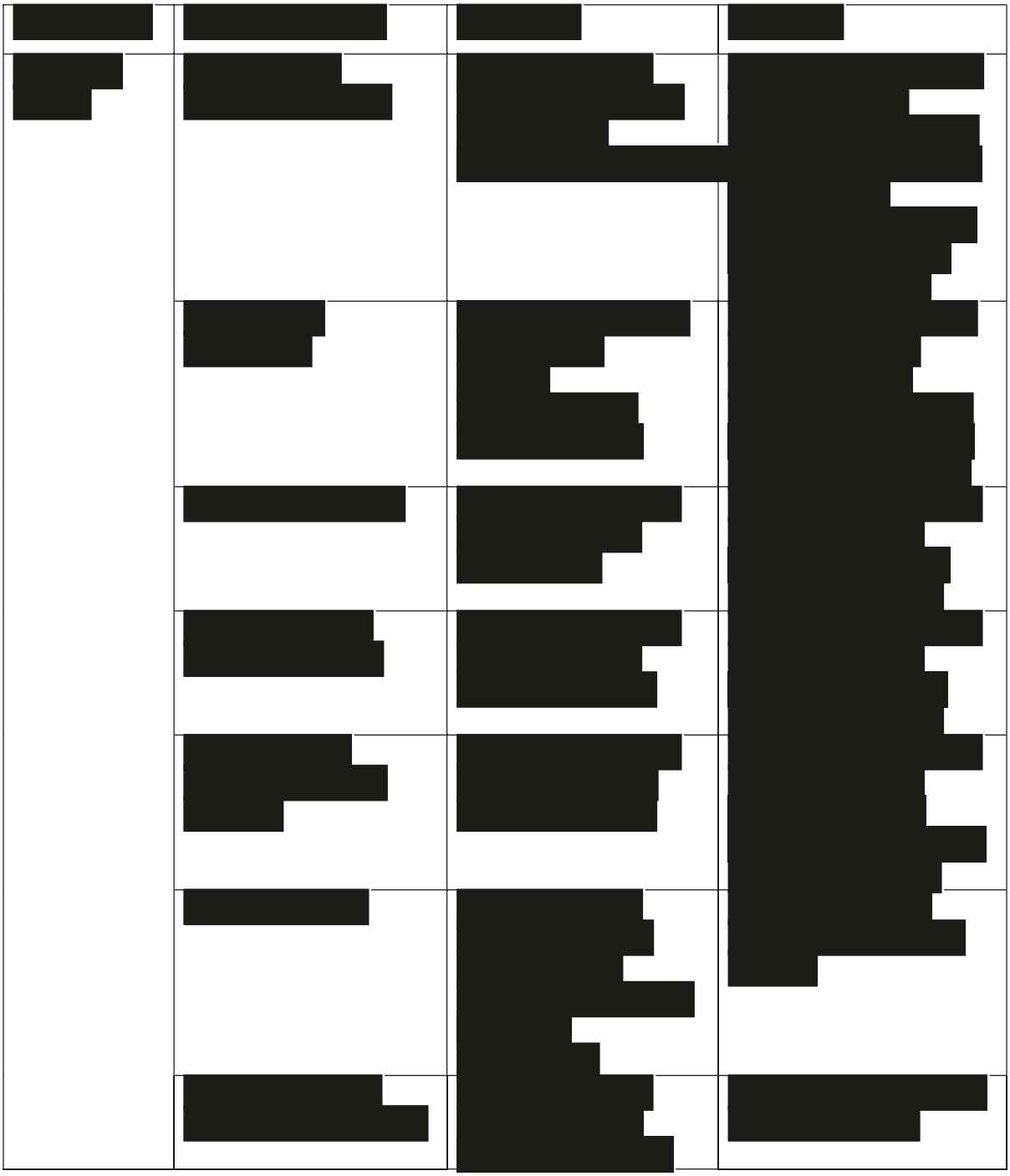

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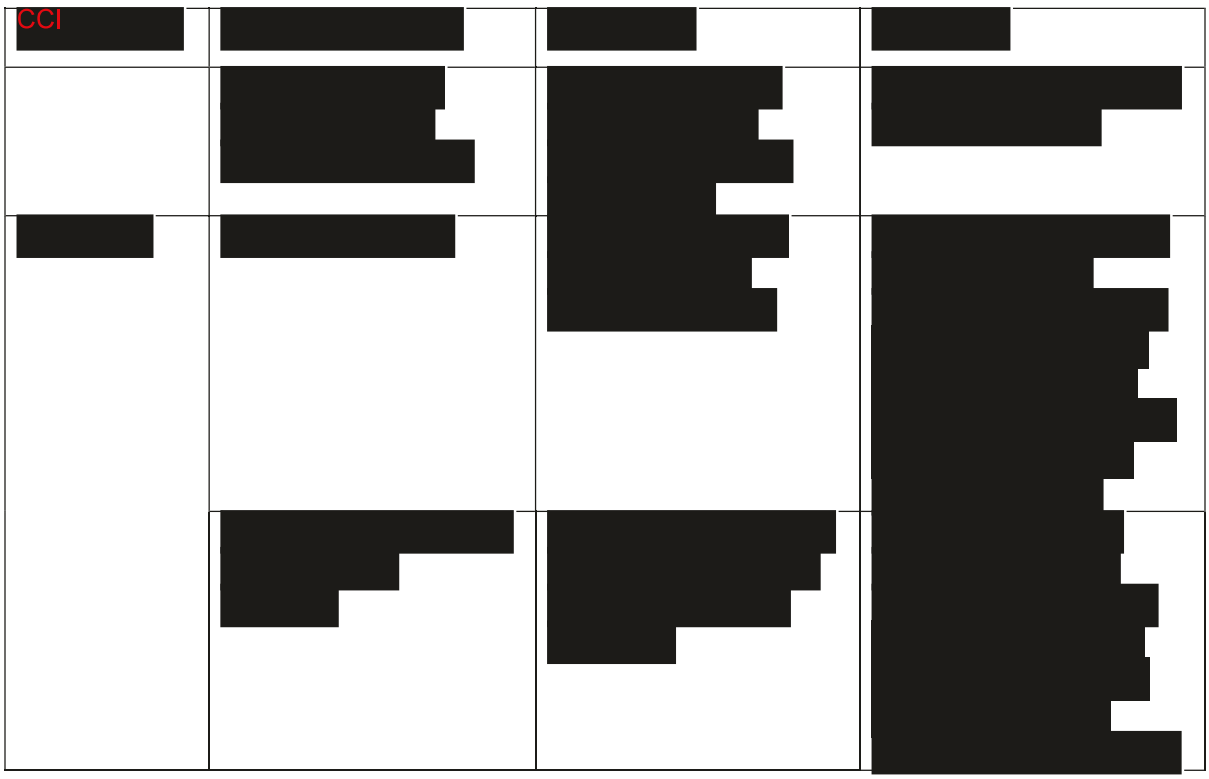

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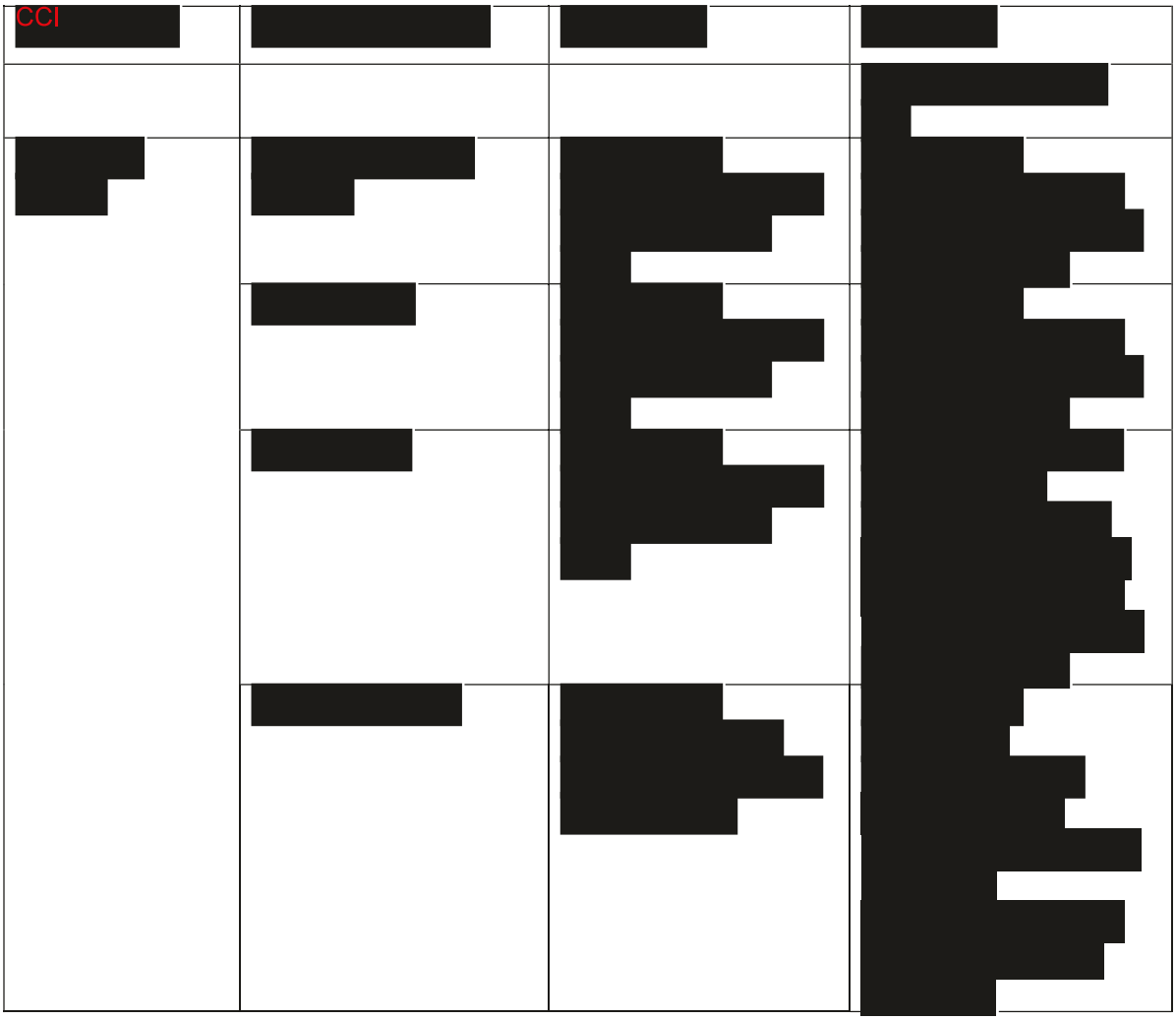
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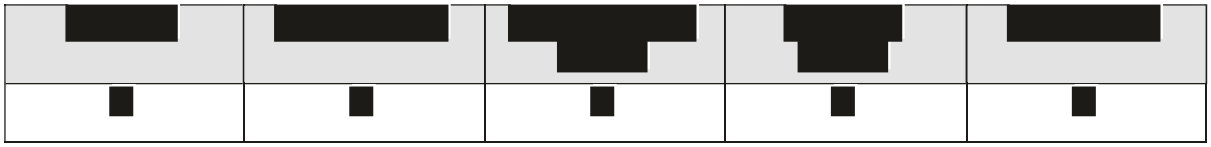

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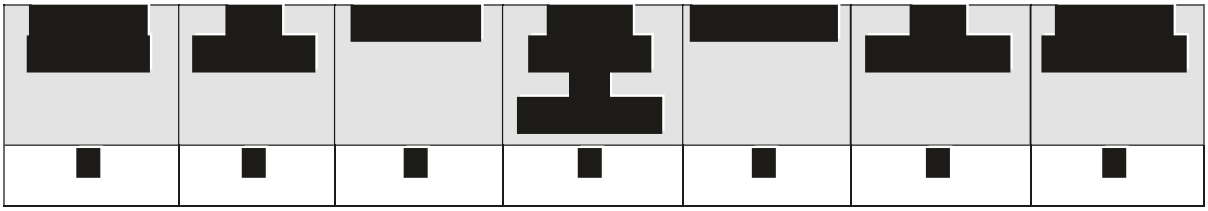

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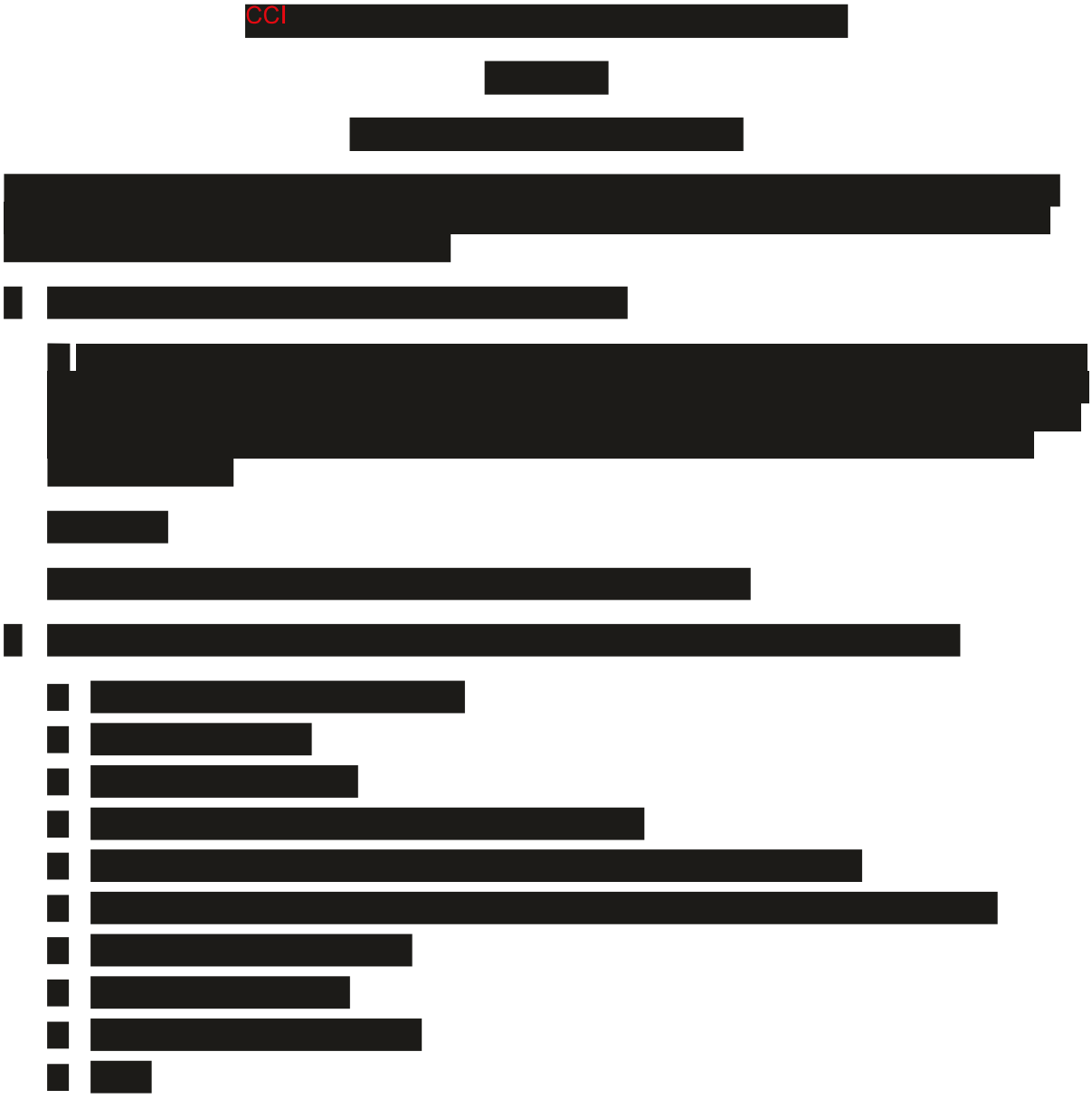
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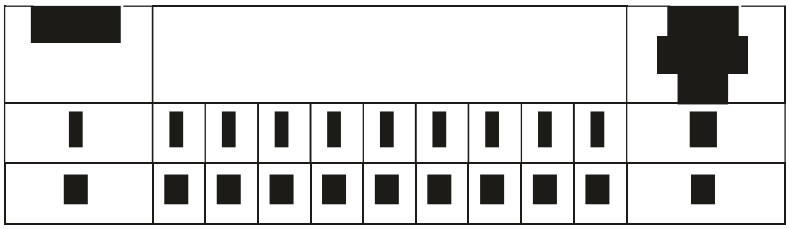

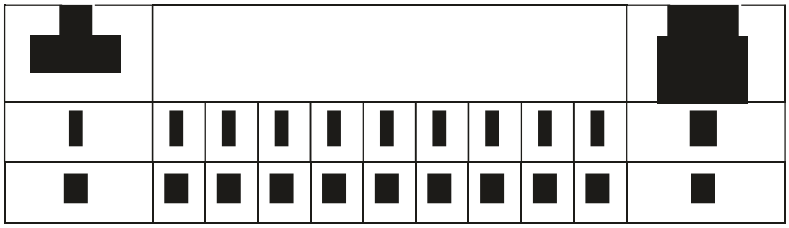

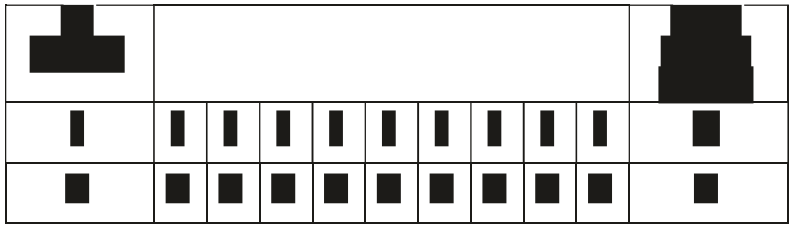

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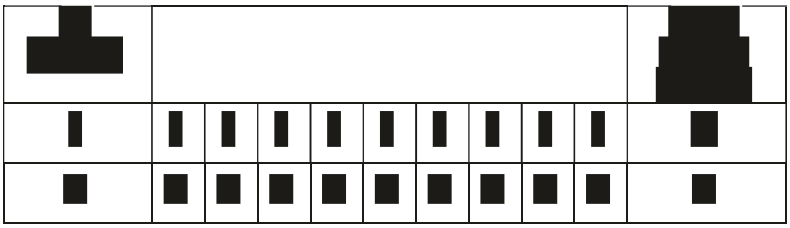

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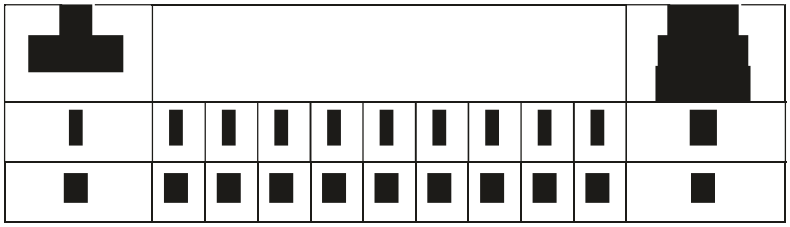

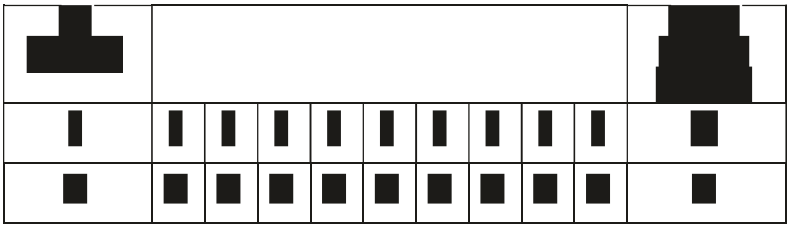

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Appendix 4. Patient Global Impression Severity-Impact on Daily Activities

Please rate the severity of the impact on daily activities due to the treatment administration during the past 4 weeks?

1. -“not present”.
2. -“very mild”.
3. -“mild”.
4. -“moderate”.
5. -“moderately severe”.
6. -“severe”.
7. -“extremely severe”.

Appendix 5. Schedule of Dyad Clinical Outcomes Assessments and Patient Global Impression Severity-Impact on Daily Activities Administration to Each Sub-group

Timepoint	Questionnaire	Subject only, aged 8-17 years	Subject/Caregiver Dyad	Caregiver only
Baseline	The Injection Pen Assessment Questionnaire (v2.0) Pen Ease of Use SECTION I The Injection Pen Assessment Questionnaire (v2.0) Ease of Injection Schedule SECTION I Patient Life Interference SECTION I Satisfaction & Willingness to Continue SECTION I Missed Injections (DAILY ADMINISTRATION) SECTION Patient Injection Signs & Symptoms (Ages 8 – 17 years) SECTION I	X	X X X X X	
Baseline	PGIS-IDA		X	
Baseline	Caregiver Assessment of Signs (Caregiver report for children aged below 8 years SECTION I) Caregiver Life Interference SECTION I			X X
Week 12 and week 24	The Injection Pen Assessment Questionnaire (v2.0) Pen Ease of Use SECTION I The Injection Pen Assessment Questionnaire (v2.0) Ease of Injection Schedule SECTION I Patient Life Interference SECTION I Satisfaction & Willingness to Continue SECTION I Missed Injections (DAILY ADMINISTRATION) SECTION I Missed Injections (WEEKLY ADMINISTRATION) SECTION I Patient Injection Signs & Symptoms (Ages 8 – 17 years) SECTION I	X	X X X X X X	

Timepoint	Questionnaire	Subject only, aged 8-17 years	Subject/Caregiver Dyad	Caregiver only
Week 12 and week 24	PGIS-IDA		X	
Week 12 and week 24	Caregiver Assessment of Signs (Caregiver report for children aged below 8 years SECTION I) Caregiver Life Interference SECTION I			X X
Week 24 only	The Injection Pen Assessment Questionnaire (v2.0) SECTION II Patient Life Interference SECTION II Satisfaction & Willingness to Continue SECTION II Patient Intention to Comply with Treatment SECTION II		X X X X	
Week 24 only	Caregiver Life Interference SECTION II			X