Protocol C0311002

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

Statistical Analysis Plan
(SAP)

Version: 3

Date: 01 Sep 2020

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28 Feb 2019	Amendment 3 13 Nov 2018	N/A	N/A
2 15 Jul 2020	Amendment 5 26 Aug 2019	Clarification or completion of prior version	Sections 2.2, 3.4, & 5.2.2. Region and type of injection device are no longer used as stratification variables. Sections 3.3 & 6.3. Subject compliance was added as other endpoint. Sections 3.5.1, 6.6, & 6.6.1. 3-tier approach for summarizing AE data was removed. Section 4. ITT population was removed, Evaluable population was renamed to FAS, PPS was defined. Section 5. ANCOVA model was removed. CCI [redacted] Sections 5.2.1, 5.2.3, & 8. Use of and reference to Gart (1969) was removed. CIs for proportions will use the Wilson score method. Section 5.2.2. Analysis of continuous secondary endpoints will be performed using a linear mixed effects model. Sections 5.3 & 6.1.1.2. Primary endpoint will now be performed on the FAS (completers restriction was removed) and sensitivity analysis on the PPS (completers); BOCF approach was removed.

			Section 6.4. Burdened vs. not burdened was defined. Duplicated subset analysis was removed. Section 6.5.2. Disposition events summary will now be presented by disposition phase. Appendix 1.1. Visit windows for reporting were redefined. Section 6.6.2. Some laboratory data summaries were removed. Section 6.6.3. Vital signs summaries were removed. Other typographical or administrative edits to improve readability and consistency.
3 01 Sep 2020	Amendment 5 26 Aug 2019	Better alignment with regulatory feedback and emerging guidance	CCI [redacted] Section 6.1.1.2. Two new sensitivity analyses were added.

2. INTRODUCTION

Note: In this document any text taken directly from the protocol is *italicised*, with exceptions noted where they appear.

The majority of currently available hGH products require daily or every other day subcutaneous (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.

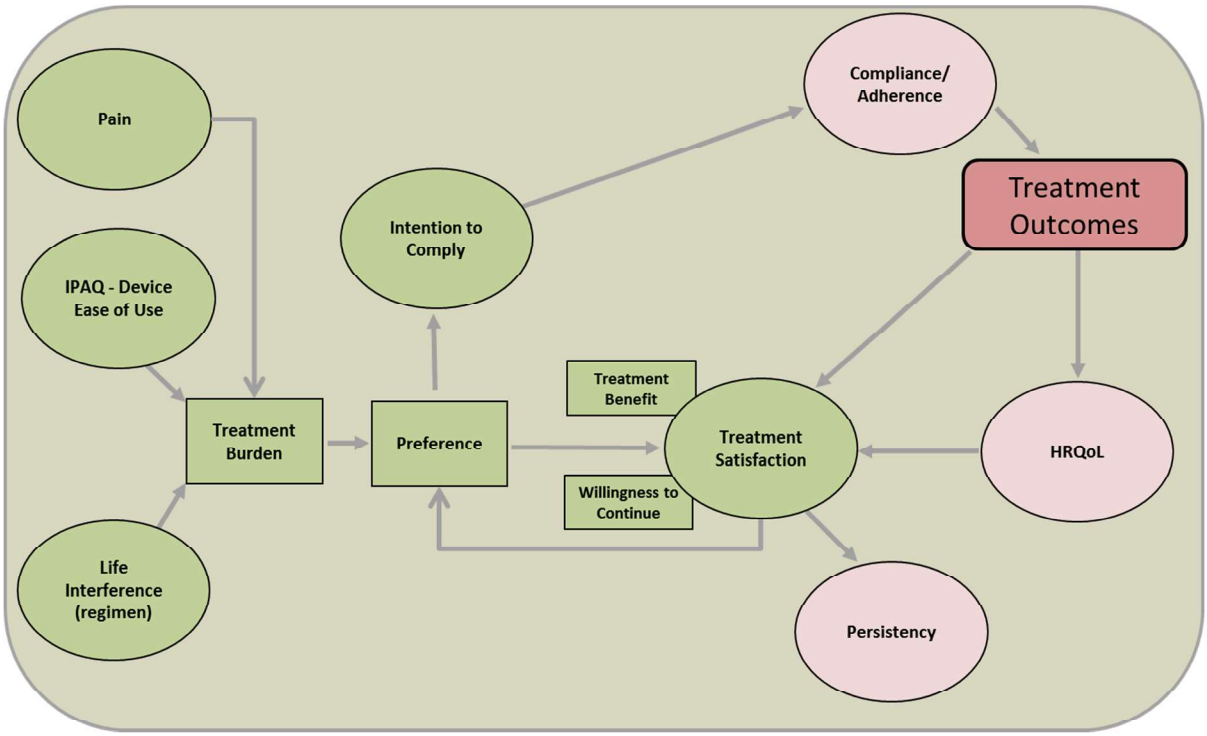
Somatrogon is a long-acting r-hGH for SC administration. It consists of hGH fused to three copies of the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin hCG; one copy at the N-terminus and two copies (in tandem) at the C-terminus.

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 r-hGH 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 r-hGH throughout the study. 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.

Figure 1. Hypothesized Conceptual Model of the Variables Associated with Adherence and Outcomes in GHD



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

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).[2,3] 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.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C0311002. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Primary:

To evaluate the treatment burden of a weekly somatrogon injection schedule and a daily Genotropin® injection schedule.

Secondary:

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, 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.

CCI [redacted]

Safety:

To describe the safety and tolerability of somatrogon.

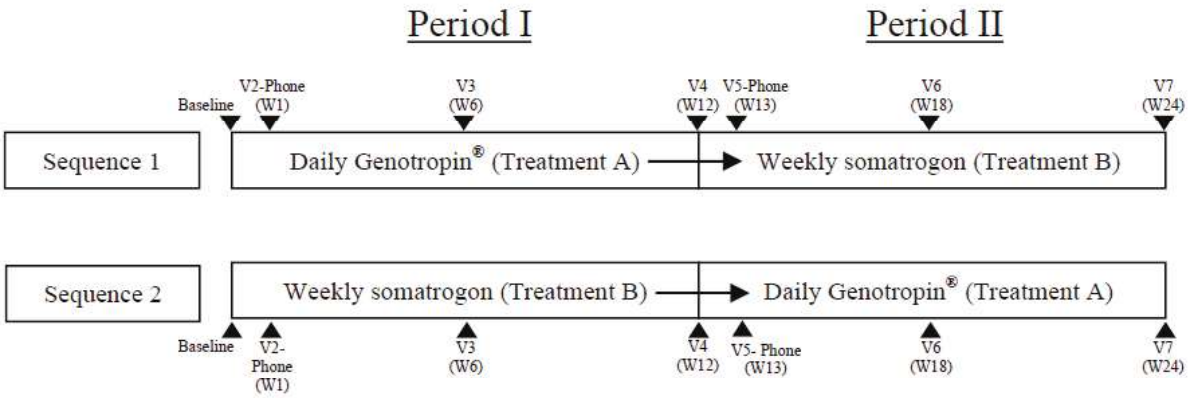
2.2. Study Design

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 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 within the protocol 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



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

In general, all the DCOA and PGIS-IDA assessments employed can be classified into one of six item types with one of the following types of response scales:

1. 11-point numeric rating scale with values 0 – 10: this scale is used for assessing pain, stinging, bruising, and bleeding;

2. 5-point Likert-type scale with values 1 – 5: this scale is used for assessing ease of use, ease of following injection schedule, life interference, and treatment satisfaction;

3. 7-point Likert-type scale with values 1 – 7: this scale is used for assessing convenience of following injection schedule and impact on daily activities;

4. Continuous scale with values 0 – 31 (open field): this scale is used for assessing the number of missed injections;

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[redacted]

[redacted]

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[redacted]

[redacted]

3.1. Primary Endpoint

There are eight variables to assess treatment burden and they are:

1. A measure of the severity of signs and symptoms of pain, stinging, bruising, and bleeding;
2. A multiple dimension assessment of handling characteristics of injection devices;
3. A measure of overall ease of use of the injection pen;
4. A measure of overall ease of use of the injection schedule;
5. A measure of overall convenience of the injection schedule;
6. A measure of life interference (daily activities/social activities/leisure/night away from home/travel);
7. A measure of how often changes are made to life routine; and
8. A measure of how often the growth hormone injections cause bother, respectively.

CCI

[redacted]

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.

3.2. Secondary Endpoints

3.2.1. Treatment Experience Assessed using DCOA 1 Questionnaire

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* (5 questions, 5-point scale each);
- *Ease of the injection schedule* (1 question, 5-point scale);
- *Convenience of the injection schedule* (1 question, 7-point scale);
- *Satisfaction with overall treatment experience* (1 question, 5-point scale);
- *Willingness to continue injection schedule* (1 question, 5-point scale);
- *Injection signs and symptoms (from the patient aged 8 years and over)* (4 questions, 0-10 scale each);
- *Assessment of signs (from the caregiver for children aged <8 years)* (2 questions, 0-10 scale each);
- *Caregiver life interference, including family life interference* (13 questions, 5-point scale each);
- *Missed injections* (1 question, # 0-31 for daily administration, # 0-5 for weekly administration).

3.2.2. Treatment Experience Assessed using DCOA 2 Questionnaire

Proportion of Subjects/Caregiver Dyads that select the weekly injection schedule compared to the daily injection schedule in each of the domains below as assessed by the DCOA 2 Questionnaires completed at Week 24:

- *Choice of injection pen* (1 question);
- *Preferred injection schedule* (1 question);
- *Convenience of injection schedule* (1 question);
- *Easier to follow* (1 question);

- *Pen ease of use* (4 questions);
- *Patient life interference* (6 questions);
- *Caregiver life interference, including family life interference* (11 questions);
- *Benefit relating to the injection schedule* (1 question);
- *Intention to comply* (4 questions).

3.2.3. Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA)

The PGIS-IDA at baseline and at the end of each period (Week 12 and Week 24) – 1 question, 7-point scale.

3.3. Other Endpoint(s)

Subject compliance is defined as ≥80% adherence to injections.

3.4. Baseline Variables

No variables require specific definitions for baseline.

As this is a cross-over study with no washout period after the end of treatment period I and before the start of treatment period II, baseline is calculated as the last pre-dose assessment prior to administering the study drug at Baseline/Visit 1 (Study Day 1 Week 0).

3.5. Safety Endpoints

The following safety endpoints will be analyzed in the study:

- *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).*

For the analysis of safety endpoints, the programming standards defined in Pfizer CDISC Safety Rulebook will be followed. Missing dates for study medication, and adverse events (AE's) will be imputed as implemented within the CaPS algorithms with the exception of vital signs which are shown below.

For Vital Signs:

The following out of expected ranges will be used to identify potential values of clinical concern for the vital signs parameters in reporting the summaries and shift tables where appropriate.

Test	Low Range	High Range
Respiratory rate (breaths/min)	10	40
Heart Rate (beats/min)	50	135
Systolic BP (mm Hg)	80	130
Diastolic BP (mm Hg)	40	90
Body temperature (oC)	35	38

3.5.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment if:

- The event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- The event was seen prior to the start of treatment but increased in severity during treatment.

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time of 7 days, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period.

3.5.2. Laboratory Data

As this is a cross-over study with no washout period after the end of treatment period I and before the start of treatment period II, baseline is calculated as the last pre-dose assessment prior to administering the study drug at Baseline/Visit 1 (Study Day 1 Week 0).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the informed consent document.
Full analysis set (FAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

Population	Description
Per protocol set (PPS)	All participants randomly assigned to study intervention and who completed both treatment periods and their corresponding assessments. Participants will be analyzed according to the intervention they actually received.
Safety	All participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. A randomized but not treated participant will be excluded from the safety analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

The reporting conventions for the study will follow Pfizer's standard operating procedures unless otherwise specified.

For data displays, all tables, listings, and figures will have headers and footers as per the Pfizer's standard operating procedures. At a minimum, the header will contain compound name, protocol number, and page number (X of Y), while the footer will indicate source data, date of reporting dataset creation, and date of the output generated with time.

For summary tables and data listings:

- Data will be summarized by treatment sequence or treatment period and overall where appropriate.
- Descriptive statistics for categorical variables will be count and percentage and will be presented in the format 'n (%)'. Unless otherwise specified, the percentage in summary tables will be calculated using the number of subjects in the population (header N) for each treatment as denominator.
- Descriptive statistics for continuous variables will be number of observations, mean, standard deviation, median, minimum, and maximum.
- Minimum and maximum will be reported to the same level of precision as the original data. Mean and median will be reported to 1 more decimal than the original data. Standard deviation will be reported to 2 more decimals than the original data.
- Model based estimates and confidence intervals will be reported to 1 more decimal than the original data. Standard errors will be reported to 2 more decimal places than the original data. P-values will be reported to 4 decimal places.
- No preliminary rounding will be performed; rounding will only occur after analysis.

- All data collected will be presented in the data listings. Unscheduled assessments or early discontinuation measurements will be presented in the data listings.
- Data from subjects excluded from an analysis population will be presented in the data listings but will not be included in the calculation of summary statistics, where applicable.
- Data listings will be sorted in the order of treatment sequence, subject, and time of assessment, as applicable.

All analyses will be performed using SAS® version 9.4 or higher.

5.1. Hypotheses and Decision Rules

For the primary endpoint analysis conducted after all subjects complete their 24 weeks of treatment (Visit 7), the hypothesis will be tested that overall mean Life Interference score (based on the 7 questions) is lower for weekly somatrogon compared to daily Genotropin.

CCI [redacted] Therefore, results of the primary endpoint hypothesis test, including the two-sided p-value, will be reported, but the p-value does not need to meet a specific threshold.

The sample size for the study was based on internal expert opinion with the following assumptions using a two-sided type-I error of 0.05:

CCI [redacted]

[redacted]

Under the above 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. CCI [redacted]

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Descriptive statistics of binary data will include the number of non-missing observations and frequencies of the observed endpoint as well as the observed proportions. When appropriate, a two-sided 95% CI for the corresponding proportion will be provided using the Wilson score method.

5.2.2. Analyses for Continuous Endpoints

A linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects will be used for analyzing the primary endpoint and continuous secondary endpoints. This model will be used to obtain the estimate, CI, and p-value for the treatment effect and other effects of interest.

5.2.3. Analyses for Categorical Endpoints

Descriptive statistics will include the number of non-missing observations, frequencies and proportions for each category of interest. When appropriate, a two-sided binomial 95% CI for the proportion of a specific category will be provided using the Wilson score method.

5.2.4. Analyses for Time-to-Event Endpoints

Not applicable.

5.3. Methods to Manage Missing Data

Scheduled assessments are the preferred source for visit-level data. If no scheduled assessments are performed for a given visit, and if there are unscheduled assessments performed within the visit window, the last available data within the visit window for a given treatment period will be used for the analysis.

The primary endpoint analysis will be performed on the FAS. In addition, a sensitivity analysis of this endpoint will be performed using the PPS (ie, completers with Week 12 and Week 24 assessments). In general, missing values on outcomes endpoints will not be imputed and will not contribute to the analysis.

For missing safety data, for example, missing dates when required for a calculation in adverse events (AEs), missing severity of an AE, or for start and stop dates of medications used, Pfizer's safety rulebook and the algorithms as implemented within CaPS will be employed.

For somatrogon assay results, values below the limit of quantification (BLQ) at the baseline visit will be treated as 0 in the statistical analysis of the results when required. Internal process for handling missing PK data will be used for concentrations below the limit of quantification, deviations, missing concentrations and anomalous values, and missing pharmacokinetic parameters.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Assessment of Treatment Burden using Life Interference Total Score

6.1.1.1. Main Analysis

Treatment burden will be 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. The analysis uses the available data from the assessments performed at the end of each treatment period (Week 12 and Week 24) and utilizes the FAS population for the primary analysis.

The primary endpoint is treated as a continuous variable and will be analyzed using the appropriate model from Section 5.2.2. This model will be used to test the null hypothesis that the difference in Life Interference Total Score between weekly and daily regimens is zero versus the alternative that the difference is less than zero (weekly minus daily).

Descriptive summary of Overall Life Interference total score will be presented by each treatment period at baseline and at each post-baseline time point. Overall individual item scores will be descriptively summarized as well.

6.1.1.2. Sensitivity Analyses

To support the interpretation, the primary endpoint will be analyzed using the linear mixed effects model described in 6.1.1.1 but repeated using the PPS population as described in Section 4.

To assess the impact of using an alternative method of capturing the responses to the DCOA 1, as opposed to the method described in Section 11.1.1 of the Protocol (questionnaires completed in person using an electronic device), the primary analysis will be repeated as a sensitivity analysis on the FAS excluding those questionnaires. Additionally, the same analysis will be repeated excluding only the questionnaires that were completed using an alternative method due to COVID-19, to assess the impact of the COVID-19 pandemic on the primary endpoint analysis.

6.2. Secondary Endpoint(s)

All secondary endpoints will be analyzed as described in Sections 5.2.1, 5.2.2, and 5.2.3 using the FAS population described in Section 4. Descriptive summaries for each of the secondary endpoints in Sections 6.2.1, 6.2.2, and 6.2.3 and the respective individual domains will be provided.

6.2.1. Treatment Experience Assessed using DCOA 1 Questionnaire

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 questionnaire completed at baseline and after subjects have experienced each treatment schedule:

- 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 aged 8 years and above),
- Assessment of signs (from the caregiver for children <8 years old),
- Caregiver life interference, including family life interference,
- Missed injections.

These variables will be analysed and summarized in the same way as the primary endpoint (Section 6.1.1.1).

6.2.2. Treatment Experience Assessed using DCOA 2 Questionnaire

Proportion of Subjects/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, using methods described in Section 5.2.1 and 5.2.3:

- Choice of injection pen,
- Preferred injection schedule,
- Convenience of injection schedule,
- Easier to follow,
- Pen ease of use,
- Patient life interference,
- Caregiver life interference, including family life interference,
- Benefit relating to the injection schedule,

- Intention to comply.

6.2.3. Patient Global Impression – Impact on Daily Activities (PGIS-IDA)

The PGIS-IDA at baseline and at the end of each period (Week 12 and Week 24) will be summarized descriptively and the overall comparison by treatment will be analyzed using methods described in Section 5.2.2.

6.2.4. Safety Endpoints

The following safety endpoints will be summarized descriptively in each treated group using the Safety population as described in Section 4.

- 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).

6.3. Other Endpoints

Number of subjects satisfying or not satisfying the compliance threshold of ≥80% adherence to injections will be presented by each treatment period (Week 12 and Week 24) and overall by treatment. Additionally, adherence will be summarized descriptively as a continuous variable, where adherence is defined as

$$\left(1 - \frac{\text{number of missed doses}}{\text{total number of doses subjects were supposed to take}}\right) \times 100.$$

6.4. Subset Analyses

Additional analyses for the primary endpoint using the FAS population may be undertaken if adequate number of subjects are available for each analyses. The following sub-analyses on Life Interference may be considered exploratory for this purpose and support the evidence for the potential advantage of weekly somatrogon in comparison to daily administration of Genotropin® as it is expected to result in increased adherence and better acceptance of weekly dosing:

- Aged <8 years vs ≥8 years;
- Aged 3 – 11 vs 12 - <18 years;

- Caregiver injection vs self-injection;
- Burdened vs not burdened, defined by the response at baseline to the question "During the past 4 weeks, how often were you bothered by growth hormone injections?" (question 3 from Patient Life Interference Section I questionnaire), as follows:
  - Not burdened: subjects experiencing little to no burden (never, rarely);
  - Burdened: subjects experiencing at least moderate burden (sometimes, often, always).

6.5. Baseline and Other Summaries and Analyses

The following summaries will utilize the Safety population as described in Section 4 and therefore will not be noted in respective sections.

6.5.1. Baseline Summaries

Descriptive statistics will be used to summarize the following variables:

- Age,
- Age groups (<8 vs ≥8 - <18),
- Sex,
- Ethnicity,
- Race,
- Region,
- Body weight,
- Body height,
- Body mass index.

6.5.2. Study Conduct and Participant Disposition

The number of subjects screened and randomized will be summarized.

The number and percentage of subjects in each analysis set, completing the study and each disposition phase (period I, period II, follow-up) prematurely discontinuing the study by disposition phase, and the reason for subject discontinuation, will be summarized.

6.5.3. Study Treatment Exposure

Extent of exposure will be summarized. Descriptive statistics will be reported for the duration of treatment within each treatment period which is defined as:

- Genotropin: last dose date – first dose date + 1.
- Somatrogon: last dose date – first dose date + 7.

The number and percentage of subjects experiencing a dose reduction due to IGF-1 SDS >2 will be summarized.

6.5.4. Concomitant Medications and Nondrug Treatments

Concomitant medications will be defined as medications that are utilized on or after first dose of study drug date. Medications with missing end dates are considered concomitant. Medications with missing start dates and non-missing end dates will be considered concomitant if the end date is on or after the first dose. Descriptive summaries will be reported.

6.6. Safety Summaries and Analyses

The safety data (eg, AEs, SAEs, physical examinations, laboratory tests) will be summarized in accordance with CDISC and Pfizer Standards (CaPS) using the Safety population as described in Section 4. Descriptive summaries for continuous data will be provided. Safety data that will be specifically summarized include:

- Safety laboratory tests according to CaPS. Shift tables summarizing the changes in laboratory test results from baseline will be presented.
- Clinically significant changes in physical examination.
- AEs of Special Interest as identified in the Safety Narrative Plan.

6.6.1. Adverse Events

Adverse events will be summarized according to CaPS.

The number (%) of subjects who experienced TEAEs will be reviewed and summarized by relatedness to the study drug and severity grade. Descriptive statistics (number and frequency) will be provided for all adverse event summaries. No hypothesis testing will be carried out.

6.6.2. Laboratory Data

Descriptive statistics will be reported for observed and change from baseline laboratory measurements at each visit. Lab tests will be presented alphabetically within each of the following categories:

- Liver function tests;
- IGF-I, IGF-I SDS;
- Hemoglobin A1c.

For each of the following laboratory tests, a shift from baseline will be presented by visit:

- Safety labs (hematology with differential, blood chemistry, liver function tests);
- IGF-I, IGF-I SDS;
- Hemoglobin A1c;
- Urinalysis.

Categories will be 'Low', 'Normal', and 'High'.

For IGF-I, IGF-I SDS, box plots will be created by visit and treatment group.

The number and percentage of subjects with increases in any of the following will be summarized at each visit and anytime post-baseline:

- ALT >2xULN, >3xULN, <5xULN;
- AST >2xULN, >3xULN, <5xULN;
- Bilirubin >3xULN and ALT >2xULN;
- Bilirubin >3xULN and AST >2xULN.

Two eDISH (evaluation of Drug Induced Serious Hepatotoxicity) scatter plots will be produced: maximum bilirubin vs. maximum ALT and maximum bilirubin vs. maximum AST.

6.6.3. Vital Signs

There will be no vital signs summaries.

6.6.4. Electrocardiograms

Not applicable.

6.6.5. Physical Examination

Complete physical examination will be collected at screening. If there is a significant departure in the physical examination, it will be collected as an adverse event after the first dose of the study drug. Therefore, there will be no physical examination summaries.

6.6.6. Somatrogon Concentrations

Somatrogon concentrations will be measured in serum samples collected before treatment and then at either Visit 4 (Week 12) or Visit 7 (Week 24) at the end of the treatment period that subjects received somatrogon. Descriptive statistics (number, mean, median, sd) will be used to summarize concentrations for those who tested positive for anti-hGH or anti-somatrogon antidrug antibodies (ADA) and for those who did not test positive for either.

6.6.7. Immunogenicity

For the immunogenicity data, the percentage of patients with blood samples positive for ADA and neutralizing antibodies (Nab) will be summarized for each treatment period. It is anticipated that patients should not test positive for ADA and NAb to somatrogon at baseline nor during the first period if they are randomized to treatment with rhGH. For patients who are positive for ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. In addition, efforts will be made, as appropriate, to examine possible effect of the ADA on somatrogon concentrations and safety.

The number and percentage of subjects with the presence of each of the following antibodies will be summarized at each visit in which the test was performed:

- Detection of anti-recombinant human GH (r-hGH) antibodies:
  - Neutralizing,
  - Non-neutralizing.
- Detection of anti-somatrogon antibodies:
  - Neutralizing,
  - Non-neutralizing.

Descriptive statistics will be reported for anti-r-hGH and anti-somatrogon antibody titers at each visit.

7. INTERIM ANALYSES

No formal interim analysis is planned 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 PK/PD modeling, and/or to support clinical development.

8. REFERENCES

1. Cohen, J. (1988) Statistical Power analysis for the Behavioral Science. 2nd edn. Lawrence Erlbaum, Hillsdale, New Jersey.

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

3. Oncology Working Party. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. In: EMA/CHMP/292464/2014. London, England: European Medicines Agency; 2014: 9 pages.

9. APPENDICES

Appendix 1. Data Derivation Details

Appendix 1.1. Definition and Use of Visit Windows in Reporting

The visit windows are defined for analysis and reporting purposes only.

Laboratory endpoints will be defined within visit windows determined by the actual day of observation relative to first dose of study drug (Day 1), ie, the actual day = date of assessment – date of first dose of study drug + 1.

The contiguous windows will be used to avoid discarding data. Week will be the time unit with a few exceptions noted in the visit window definitions below.

Visit Label	TARGET VISIT DAY	VISIT WINDOW IN DAYS	
		LOWER	UPPER
Screening	≤0	-99	-31
Baseline / V1 (W0)	1	-30	1
V2 (Week 1)*	8	2	25
V3 (Week 6)	42	26	64
V4 (Week 12)	84	65	90
V5 (Week 13)*	92	91	109
V6 (Week 18)	126	110	148
V7 (Week 24)	168	149	195

Notes:

*Phone call visits only.

Week 24 is the analysis time point.

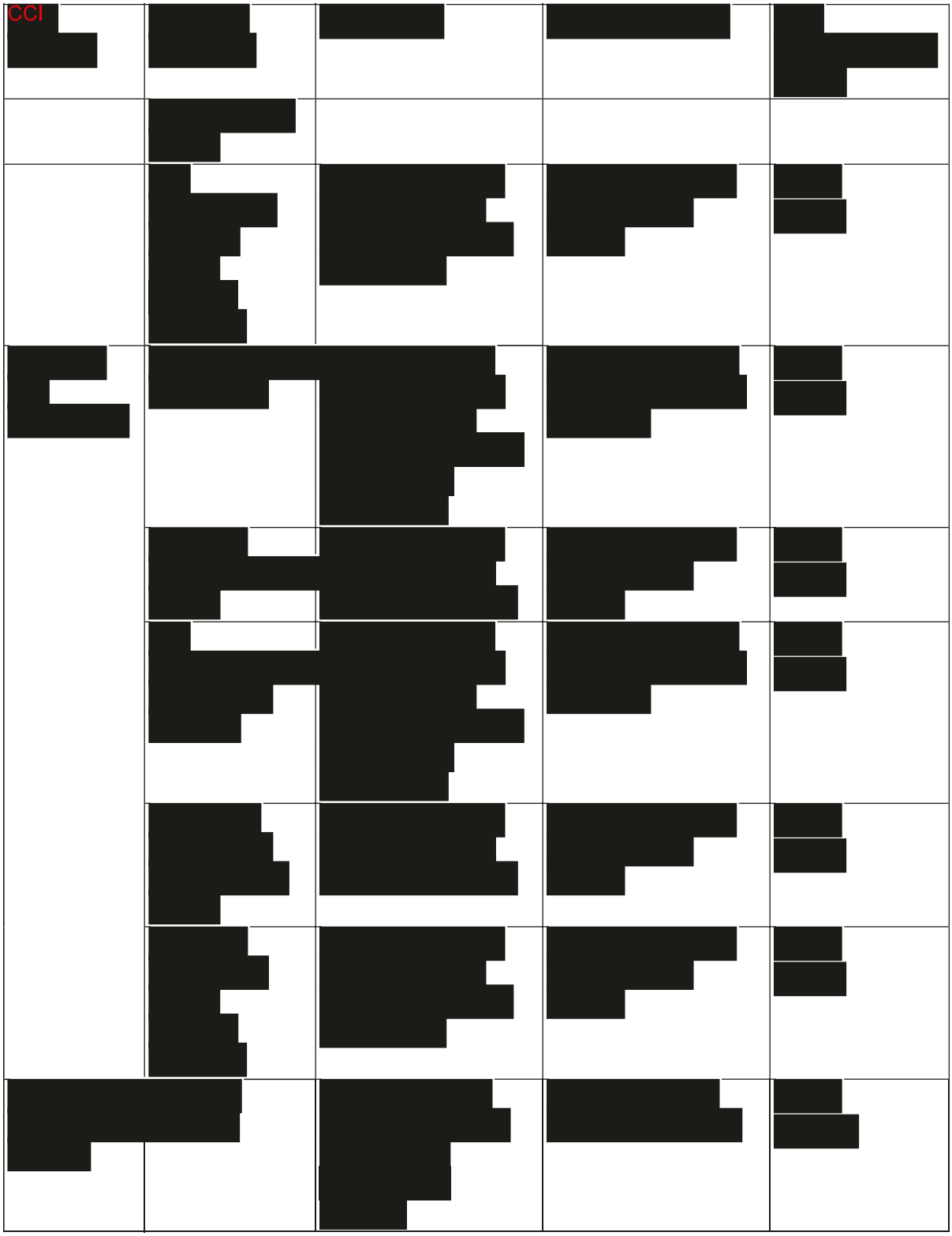
In general, window size is ½ the duration of the time between the previous study visit and the next study visit.

Target Visit Day = Current Visit in weeks × 7 + 1.

[Visit Window in Days Lower] = Current Target Visit Day – ⌊(Current Target Visit Day – Previous Target Visit Day – 1) ÷ 2⌋.

[Visit Window in Days Upper] = Current Target Visit Day + ⌈(Next Target Visit Day – Current Target Visit Day – 1) ÷ 2⌉.

CCI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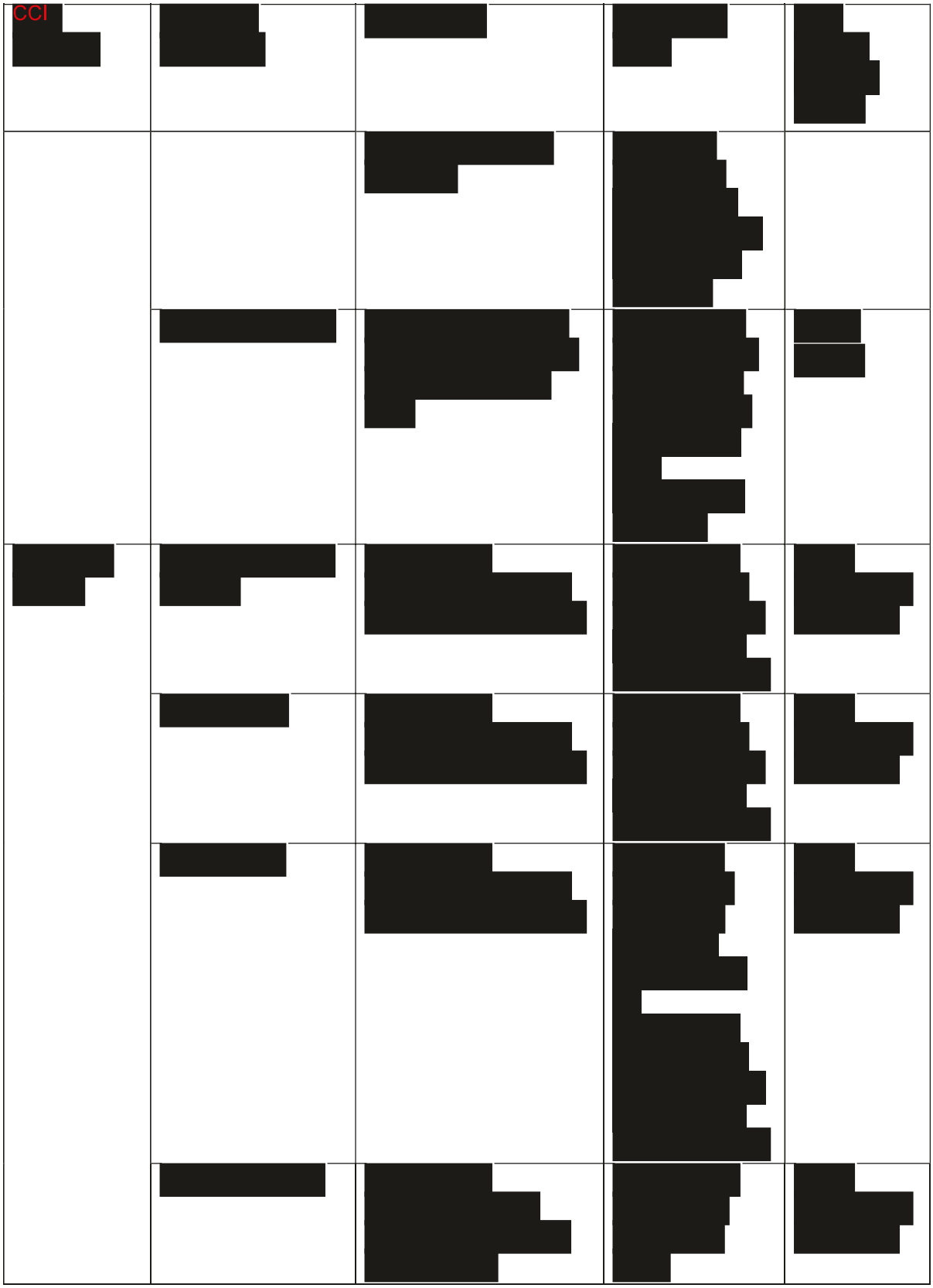

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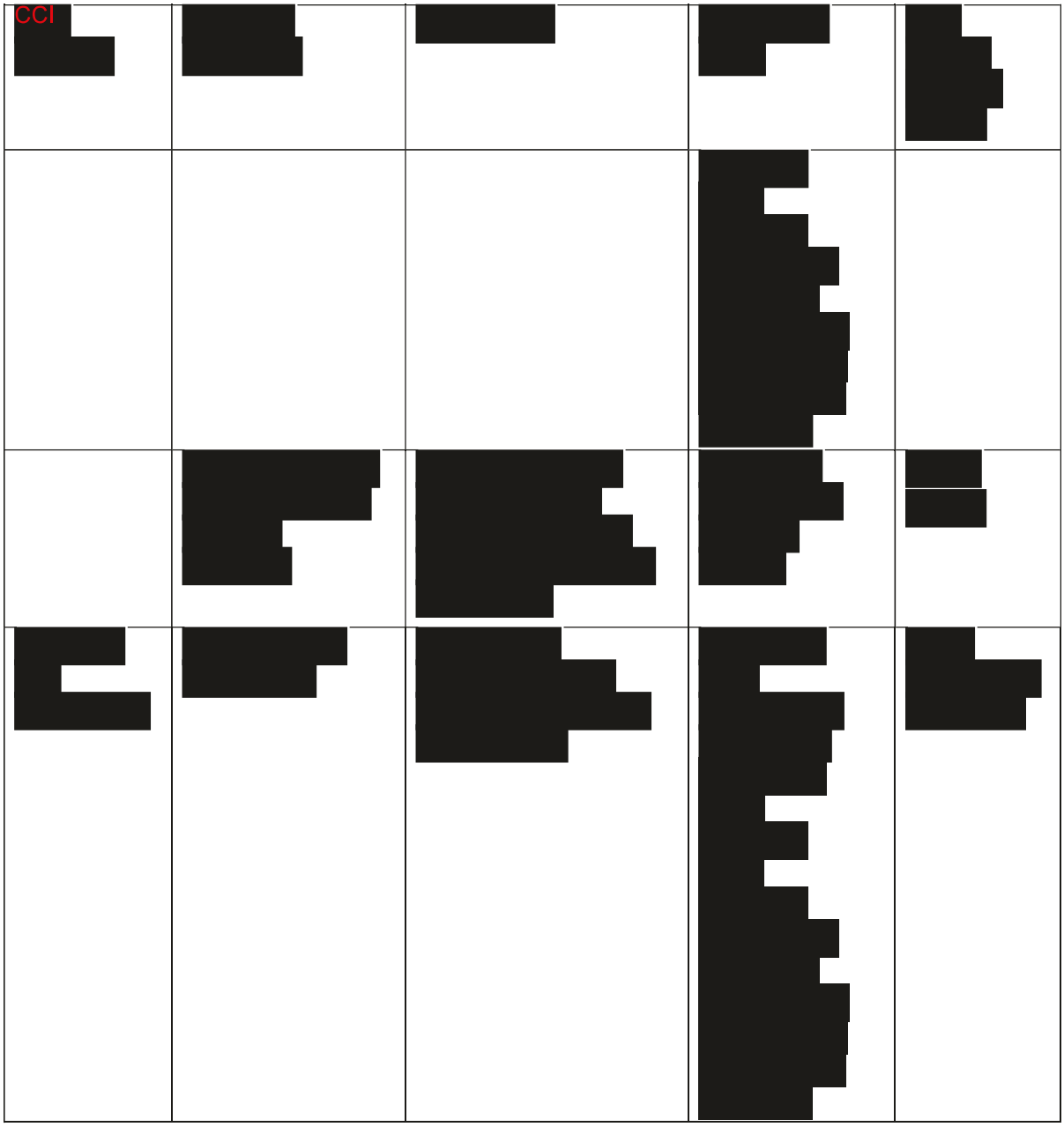

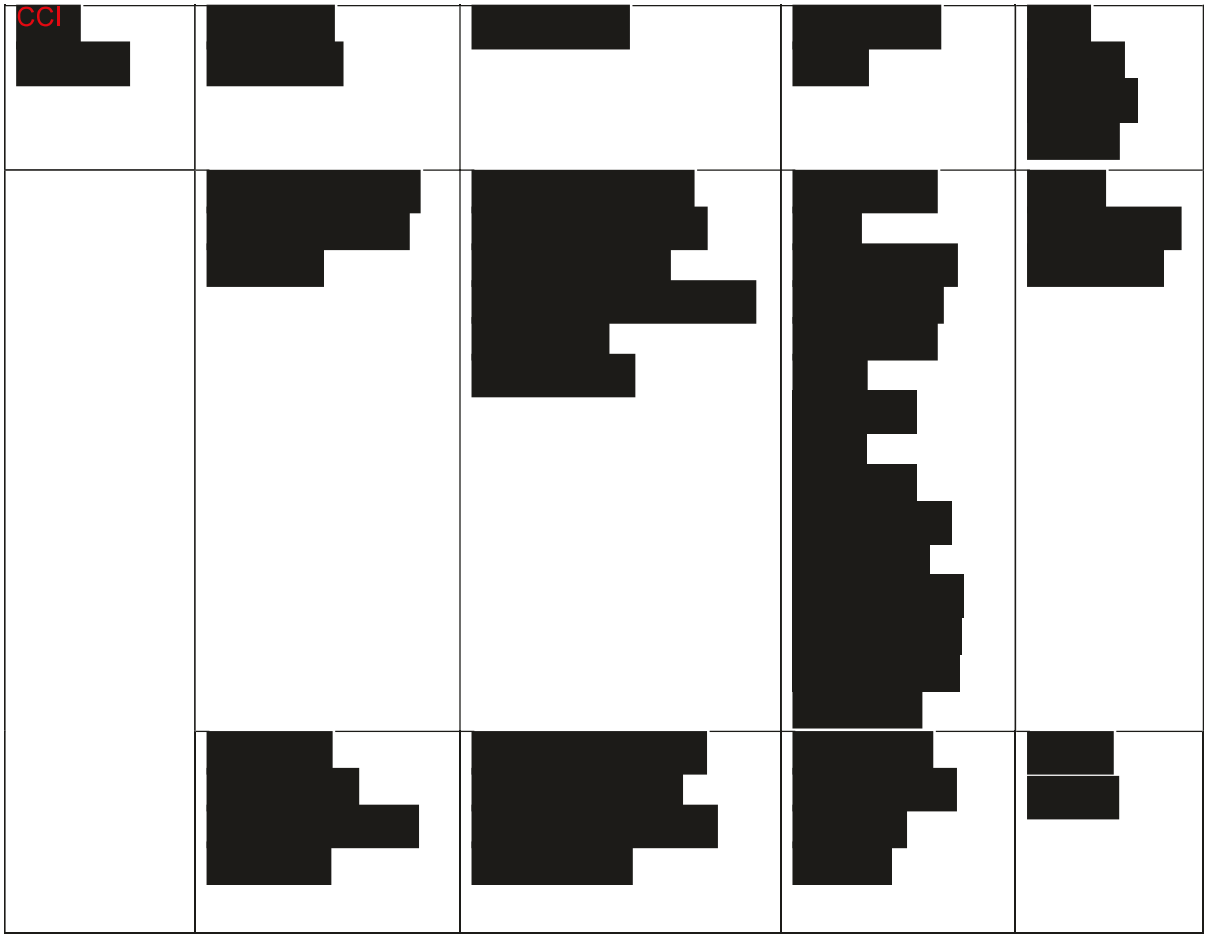
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Appendix 2. Questionnaires Used in the Study

The questionnaires DCOA 1, DCOA 2, PGIS-IDA, and their schedule on daily activities administration to each sub-group within this study are not included again within this SAP. Please refer to the Protocol for the actual instruments or their schedule as shown below:

Instrument	**Source within Protocol**
Dyad Clinical Outcome Assessment Questionnaires	Appendix 3
Patient Global Impression Severity-Impact on Daily Activities	Appendix 4
Schedule of Dyad Clinical Outcomes Assessments and Patient Global Impression Severity-Impact on Daily Activities Administration to Each Sub-group	Appendix 5

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	CDISC and Pfizer Standards
CDISC	Clinical Data Interchange Standards Consortium
CTP	C-terminal peptide
DCOA	Dyad Clinical Outcome Assessment
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GHD	growth hormone deficiency
hCG	human chorionic gonadotropin
hGH	human growth hormone
HRQoL	health-related quality of life
IGF-I	insulin-like growth-factor-I
IGF-1 SDS	insulin-like growth-factor-I standard deviation score
IM	intramuscular
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NAb	neutralizing antibodies
PGIS-IDA	Patient Global Impression Severity-Impact on Daily Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	per protocol set
PRO	patient-reported outcome
rhGH	recombinant human growth hormone
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
ULN	upper limit of normal