Sponsor: Pfizer, Inc.

Investigational Product: Somatrogon (PF-06836922)

Clinical Study Report Synopsis: Protocol C0311002

Protocol Title: 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

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None.

Study Initiation Date: First Subject First Visit: 07 February 2019

Study Completion Date: Last Subject Last Visit: 28 August 2020

Report Date: 17 December 2020

Previous Report Date(s): Not applicable

Phase of Development: Phase 3
Primary and Secondary Study Objectives and Endpoints:

Table S1. 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 Dyad Clinical Outcome Assessment [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: | 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: |
| Life interference. | Pen ease of use. |
| Caregiver life interference. | Ease of the injection schedule. |
| Family life interference. | Convenience of the injection schedule. |
| Benefit, satisfaction, willingness to continue. | Satisfaction with overall treatment experience. |
| Intention to comply. | Willingness to continue injection schedule. |
| Injection pen ease of use. | Injection signs and symptoms (from the patient). |
| Convenience of injection schedule. | Assessment of Signs (from the Caregiver). |
| Ease of the injection schedule. | Caregiver Life Interference, including Family Life Interference. |
| Preferred injection schedule. | Missed injections. |
| Choice of injection pen. | 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 |
| Injection signs and symptoms (pain, bruising, stinging). | |
| Caregiver report of signs (bleeding, bruising). | |
| Missed injections. | |
### Table S1. Study Objectives and Endpoints

| Study Objectives                                                                 | Questionnaires completed at Week 24.                                                                 |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| To use a PGIS-IDA at baseline and at the end of each period (Week 12 and Week 24) to support the interpretation of scores from the DCOA 1 and DCOA 2 Questionnaires. | • Choice of injection pen.                                                                      |
| To confirm the psychometric properties and sensitivity of the DCOA Questionnaires in patients who have experienced both a weekly injection schedule and a daily injection schedule. | • 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.                                             |
|                                                                                   | • SAEs.                                                                                                                 |
|                                                                                   | • Discontinuations due to AEs.                                                                                         |
|                                                                                   | • Frequency and severity of abnormal lab values.                                                                      |
|                                                                                   | • Detection of anti-rhGH antibodies (and neutralizing antibodies).                                                    |
|                                                                                   | • Detection of anti-somatrogon antibodies (and neutralizing antibodies).                                              |

AE = adverse event; DCOA = Dyad Clinical Outcome Assessment; PGIS-IDA = Patient Global Impression Severity-Impact on Daily Activities; anti-rhGH = recombinant human growth hormone; SAE = serious adverse event.
METHODS

Study Design: This was a randomized, open-label, multi-center, 2-period crossover study in children 3 to <18 years of age with growth hormone deficiency (GHD). The treatment duration was 24 weeks, with a screening period of up to 30 days and a follow-up phone call 4 weeks after the last clinic visit.

Subjects (also referred to as participants) had been stable on treatment with daily Genotropin for a minimum of 3 months prior to enrollment. They were then randomized in a 1:1 ratio to one of 2 sequences, either 12 weeks of treatment with daily Genotropin followed by 12 weeks of treatment with once weekly somatrogon, or 12 weeks of treatment with once weekly somatrogon followed by 12 weeks of treatment with daily Genotropin.

Diagnosis and Main Criteria for Inclusion:

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

- 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.

- Insulin-like growth factor-1 (IGF-I) standard deviation score (SDS) <2.

Study Treatment: Participants were to administer somatrogon weekly by subcutaneous (SC) injection at approximately the same time on a regularly scheduled day of the week. Participants were to administer Genotropin daily by SC administration at the same time of day as they were injecting their daily growth hormone at the time of screening. Study intervention information is provided in Table S2.
Table S2. Investigational Product Description

| Investigational Product Description | Vendor Lot No. | Pfizer Lot No. | Strength/Potency | Dosage Form |
|-------------------------------------|----------------|----------------|------------------|-------------|
| Genotropin pen 12 multi-dose device | W28996         | 18-000056      | N/A              | COMMERCIAL PRODUCT |
| Genotropin Pen 5.3 Multi-dose Device | T88153         | 18-000058      | N/A              | COMMERCIAL PRODUCT |
| Somatropin 12 mg powder and solvent for injection multi-dose pre-filled pen | W18639         | 18-000059      | 12 mg            | COMMERCIAL PRODUCT |
| Somatropin 5.3 mg powder and solvent for injection multi-dose pre-filled pen | W32058         | 18-000062      | 5.3 mg           | COMMERCIAL PRODUCT |
| Somatropin 12 mg for Injection | W42820         | 18-000063      | 12 mg            | COMMERCIAL PRODUCT |
| Somatropin 5.3 mg Cartridge (2 x chamber, 1 x powder and 1 liquid) Genotropin Pen 12 | T82011         | 18-000064      | 5.3 mg           | COMMERCIAL PRODUCT |
| Genotropin Pen 5 | T76165         | 18-000692      | N/A              | COMMERCIAL PRODUCT |
| Somatropin 5 mg Lyophilized Powder for Injection cartridge | W47500         | 18-000693      | 5 mg             | COMMERCIAL PRODUCT |
| Somatropin 12 mg Lyophilized Powder for Injection cartridge | W22433         | 18-000694      | 12 mg            | COMMERCIAL PRODUCT |
| PF-06836922 (MOD-4023) multidose disposable prefilled Pen-C, 60 mg/1.2 mL | W47488         | 18-001233      | 60 mg            | DEVICE |
| PF-06836922 (Somatrogon) Multidose Disposable Prefilled Pen-C, 60 mg/1.2 mL (GC2K) | W96066         | 18-001735      | 60 mg            | DEVICE |
| Somatropin 5.3 mg powder and solvent for injection multi-dose pre-filled pen | AG8004         | 19-000664      | 5.3 mg           | COMMERCIAL PRODUCT |
| Somatropin 5.3 mg Cartridge (2 x chamber, 1 x powder and 1 liquid) Genotropin Pen 5 | AF5662         | 19-000665      | 5.3 mg           | COMMERCIAL PRODUCT |
| Genotropin Pen 5 | AA7119         | 19-002628      | N/A              | COMMERCIAL PRODUCT |
| Genotropin Pen 12 | AF7621         | 19-002629      | N/A              | COMMERCIAL PRODUCT |
| Genotropin Pen 5.3 Multi-dose Device | AW1721         | 19-004085      | N/A              | COMMERCIAL PRODUCT |
| Genotropin pen 12 multi-dose device | X63092         | 19-004152      | N/A              | COMMERCIAL PRODUCT |

N/A = Not applicable; No. = Number.
Efficacy Evaluations: Not Applicable.

Other Evaluations: The primary and secondary endpoints were as described in Table S1.

Safety Evaluations: Safety assessments were based on adverse events (AEs), vital signs, body weight, physical examination, urine pregnancy, and laboratory assessments (including hematology, blood chemistry, liver function, lipid profile, urinalysis, IGF-1 levels, immunogenicity, and somatrogon level).

Statistical Methods:

Primary Endpoint Analysis: The primary endpoint was 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 was used to obtain the estimate, confidence interval (CI), and p-value for the treatment effect and other effects of interest. The model was 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).

A descriptive summary of Overall Life Interference total score was presented by each treatment period at baseline and at each post-baseline time point. Overall individual item scores were also summarized descriptively.

Secondary endpoints Analysis:

- For binary data (from the DCOA 2 questionnaire), descriptive statistics included 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 was provided using the Wilson score method.

- For categorical endpoints (from the DCOA 2 questionnaire), descriptive statistics included 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 was provided using the Wilson score method.

- Continuous endpoints (from the DCOA 1 and PGIS-IDA questionnaires) were analyzed using the method described above for the primary endpoint.

In general, missing values on outcomes endpoints were not imputed and did not contribute to the analysis. If no scheduled assessments are performed for a given visit, and if there were unscheduled assessments performed within the visit window, the last available data within the visit window for a given treatment period were used for the analysis.

Safety: Descriptive statistics were reported for AEs, serious adverse events (SAEs), clinical laboratory measurements, and immunogenicity.
Psychometric Properties and Sensitivity of the DCOA Questionnaire

The DCOA Life Interference scale score was evaluated through the following analyses: descriptive statistics, item-to-item (inter-item) correlations, corrected item-total correlations, test retest reliability, internal consistency reliability, construct-related validity (tests of convergent and discriminant validity, known groups analysis), ability to detect change, and interpretation of scores (anchor- and distribution-based methods).

RESULTS

This study was not temporarily stopped and was completed in accordance with the protocol.

Subject Disposition and Demography: A total of 107 participants were enrolled, of which 87 were randomized (43 participants to the Genotropin then somatrogon sequence and 44 participants to somatrogon then Genotropin sequence). All 87 randomized participants received at least 1 dose of study intervention. Two participants discontinued the study (1 due to an AE during Treatment Period 1; 1 due to a protocol deviation during Treatment Period 2). The safety analysis set was identical to the full analysis set (FAS), which consisted of the 87 participants who were randomized and received at least 1 dose of study intervention. The per protocol set (PPS) consisted of 81 participants who completed both treatment periods and the corresponding assessments.

Demographic and baseline characteristics were generally balanced across both treatment sequences. The median age of participants was 11 years (range: 3 to 17 years) and 69 [79.3%]) participants were aged ≥ 8 years. Most participants were male (72 [82.8%]) and White (81 [93.1%]).

Efficacy Results: Efficacy evaluations were not done.

Other Results:

Primary Endpoint: Treatment Burden: Difference in Mean Overall Life Interference Total Scores Between the Weekly Injection Schedule and the Daily Injection Schedule (DCOA 1)

This study met the primary endpoint by demonstrating the treatment burden, as evaluated by the Patient Life Interference questionnaire, of the once weekly somatrogon injection schedule was lower than that of the once daily Genotropin injection schedule (Table S3):

- The least squares mean of the Overall Life Interference total score was lower for the once weekly somatrogon injection schedule than for the once daily Genotropin injection schedule.

- The mean difference (somatrogon-Genotropin) was -15.49 (95% CI: -19.71, -11.27).
The difference in mean Overall Life Interference scores for somatrogon once weekly for 12 weeks, compared with administration of Genotropin once daily for 12 weeks, was statistically significant (p<0.0001).

| Overall (drug received during any period) | During Genotropin Treatment (N=86) | During Somatrogan Treatment (N=87) |
|-----------------------------------------|-----------------------------------|-----------------------------------|
| N                                      | 85                                | 82                                |
| Mean (SD)                               | 24.1 (20.0)                       | 8.4 (11.0)                        |
| Median (Min, Max)                       | 21.4 (0.0, 82.1)                  | 3.6 (0.0, 50.0)                   |
| Model-based mean (95% CI)b              | 24.13 (20.61, 27.65)              | 8.63 (5.05, 12.22)                |
| Somatrogan vs Genotropin Difference in overall scores (95% CI)b | -15.49 (-19.71, -11.27)           | p-valueb                         |
|                                         |                                   | <0.0001                           |

Secondary Endpoints:

Treatment Experience: Difference in Mean Scores Between the Weekly Injection Schedule Experience and Daily Injection Schedule Experience – DCOA 1 Questionnaire

The estimated mean score differences for most variables within the DCOA 1 questionnaire showed an improvement (ie, negative estimated mean difference) during the once weekly somatrogan injection schedule compared with the once daily Genotropin injection schedule:

- These estimated mean score differences (95% CI) were statistically significant (p<0.05) for the following variables:
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- Pen ease of use: -5.39 (-8.69, -2.09)
- Ease of the injection schedule: -13.60 (-19.74, -7.45)
- Convenience of the injection schedule: -24.34 (-30.10, -18.57)
- Willingness to continue injection schedule: -17.60 (-25.15, -10.06)
- Caregiver life interference (including Family life interference): -13.47 (-17.59, -9.35)
- Missed injections: -2.76 (-5.16, -0.36).

The point estimate of the mean [model-based mean (95% CI)] satisfaction with the overall treatment experience score was lower (ie, improved) for participants in the once weekly somatrogon injection schedule [21.13 (14.61, 27.65)] than for participants in the once daily Genotropin injection schedule [28.95 (22.55, 35.36)]; however, the estimated mean difference was not statistically significant (p=0.0739).

Overall mean scores were similar between both injection schedules for injection signs and symptoms (for participants 8 years and above: 13.6 for both injection schedules) and the assessment of signs (as reported by the caregiver for the children aged <8 years: 9.4 for the once daily Genotropin injection schedule and 9.7 for the once weekly somatrogon injection schedule).

Proportion of Participant/Caregiver Dyads Responding to the DCOA 2 Questionnaires at Week 24

- **Choice of injection pen**: A larger proportion of participant/caregiver dyads (ie, lower bound of 95% CI >50%) selected the once weekly injection pen (somatrogon: 74 [88.1%] participants, 95% CI: 79.5, 93.4) compared with those who selected the once daily injection pen (Genotropin: 10 [11.9%] participants).

For the DCOA 2 questions that asked participant/caregiver dyads to compare both injection schedules, a larger proportion of those dyads (ie, lower bound of 95% CI > 50%) selected the once weekly somatrogon injection schedule compared with those who selected the once daily Genotropin injection schedule or expressed no difference between the injection schedules for the following DCOA 2 variables, except for Ease of Injection Schedule.

- **Preferred injection schedule**: somatrogon: 77 (91.7%) participants, (95% CI: 83.8, 95.9); Genotropin: 6 (7.1%) participants; no preference: 1 (1.2%) participant.

- **Convenience of injection schedule**: somatrogon: 80 (95.2%) participants (95% CI: 88.4, 98.1); Genotropin: 4 (4.8%) participants; no difference: 0 participants.
Easier to follow: somatrogon: 72 (85.7%) participants (95% CI: 76.7, 91.6); Genotropin: 8 (9.5%) participants; no preference: 4 (4.8%) participants.

Choice of injection pen – easier to use: A larger proportion of participant/caregiver dyads reported the somatrogon pen was easier to use compared with those who selected the Genotropin pen or expressed no difference based on preparing the injection pen: somatrogon: 54 (64.3%) participants (95% CI: 53.6, 73.7); Genotropin: 7 (8.3%) participants; no difference: 23 (27.4%) participants.

However, these proportions were less than 50% for the 3 items of setting the dose, injecting the medicine, and storing the pen. The proportion of these dyads who indicated there was no difference in these items between the 2 pens ranged from 29.8% to 64.3%.

Patient life interference (5 items): somatrogon: 66 (78.6%) participants (95% CI: 68.7, 86.0) to 73 (86.9%) participants (95% CI: 78.1, 92.5); Genotropin: 2 (2.4%) to 3 (3.6%) participants; no difference: 8 (9.5%) to 15 (17.9%) participants.

Caregiver life interference (5 items): somatrogon: 67 (79.8%) participants (95% CI: 70.0, 87.0) to 72 (85.7%) participants (95% CI: 76.7, 91.6); Genotropin: 1 (1.2%) to 2 (2.4%) participants; no difference: 10 (11.9%) to 15 (17.9%) participants.

Family life interference (5 items): somatrogon: 61 (72.6%) participants (95% CI: 62.3, 81.0) to 67 (79.8%) participants (95% CI: 70.0, 87.0); Genotropin: 1 (1.2%) participants; no difference: 16 (19.0%) to 22 (26.2%) participants.

Benefit relating to the injection schedule: Most of the participant/caregiver dyads, regardless of treatment sequence, responded it would be extremely beneficial (48 [57.1%]) or very beneficial (25 [29.8%]) to take injection less often.

Intention to comply (4 items): somatrogon: 57 (67.9%) participants (95% CI: 57.3, 76.9) to 69 (82.1%) participants (95% CI: 72.6, 88.9); Genotropin: 2 (2.4%) to 5 (6.0%) participants; no difference: 13 (15.5%) to 22 (26.2%) participants.

Patient Global Impression at Week 12 and Week 24

The overall mean PGIS-IDA score was significantly lower for participants in the once weekly somatrogon injection schedule than for participants in the once daily Genotropin injection schedule with an estimated mean score difference (95% CI) of -14.58 (-18.72, -10.44), p <0.0001.

Psychometric Properties of DCOA Questionnaires

Life Interference 7-Item and Scale Score Distribution
At baseline, the Life Interference scale scores ranged from 0 to 78.6 and the mean [SD] was 28.4 [18.8]. At Week 12, the Life Interference scale scores ranged from 0 to 60.7 and the mean [SD] was 16.2 [16.0]. At Week 24, the Life Interference scale scores ranged from 0 to 82.1 and the mean [SD] was 15.5 [19.4]

**Inter-item Correlations**

Results from the Life Interference Pearson inter-item correlation analyses showed correlations ($r > 0.70$) between Item 4 (interference with spending the night away from home) and Item 5 (interference with travel) at baseline, Week 12, and Week 24; Item 2 (interference with social activities) and Item 1 (interference with usual daily activities) at Week 24; and Item 2 (interference with social activities) and Item 3 (interference with recreation and leisure activities) at Week 24. Although medium ($r=0.30-0.49$) to strong ($\geq 0.50$) relationships existed among some other items, all were $r < 0.70$ across timepoints and no item correlations suggested redundancy ($r > 0.80$). Similar results were generally observed for Spearman ($\rho$) inter-item correlations.

**Correlated Item-Total Corrections**

All Life Interference items correlated (Pearson [$r$] and Spearman [$\rho$] $\geq 0.40$) with the total Life Interference scale score at all timepoints, except for Item 7 (bothered by growth hormone injections) at Week 12.

**Score Reliability (Internal Consistency and Test-Retest Reliability)**

Internal consistency reliability results showed that the Life Interference scale score exceeded Cronbach’s $\alpha > 0.70$ threshold for group-level comparisons at baseline ($\alpha=0.814$), Week 12 ($\alpha=0.807$), and Week 24 ($\alpha=0.896$).

Test retest reliability results for the Life Interference scale showed ICC $>0.70$ for analyses that used data from the more limited sample of participants (ie, participants in the once daily Genotropin injection schedule at Week 12 and those in the once daily Genotropin injection schedule at Week 24), yet lower for analyses conducted using data from the other defined test-retest analysis populations in this study (TRT 1 through TRT-4).

**Construct-Related Validity**

**Tests of Convergent and Discriminant Validity**

At baseline, the Life Interference scale score demonstrated strong correlations ($r \geq 0.50$) with Ease of the Injection Schedule, Caregiver Life Interference, Family Life Interference, total Caregiver Life Interference/Family Life Interference, and PGIS-IDA; moderate correlations ($r=0.30$ to $r=0.49$) with the Pen Ease of Use, Satisfaction and Willingness to Continue Treatment, and Willingness to Continue; and weak to negligible correlations ($r=0.00$ to $r=0.29$) with Satisfaction with Overall Experience, Signs and Symptoms (ie, injection signs
and symptoms reported by the participant), Caregiver-Reported Symptoms, and Missing Injections. Similar results were generally observed at Weeks 12 and 24. Results were similar for the Spearman (ρ) correlations.

**Tests of Known Groups Validity**

The Life Interference scale scores differed significantly at baseline for participants reporting differing levels of: severity of impact on daily activities due to treatment based on the PGIS IDA (p <0.001); convenience of the injection schedule based on the DCOA Convenience item (p <0.001); and satisfaction based on the DCOA Satisfaction item (p=0.011). A similar pattern of results was observed at Weeks 12 and 24.

**Ability to Detect Change**

Overall, the Life Interference scale score decreased from baseline to Week 12, and from Week 12 to Week 24.

Strong correlations (r >0.50) were observed between the change scores of the Life Interference scale score and the Ease of the Injection Schedule, Caregiver Life Interference, and the total Caregiver Life Interference/Family Life Interference at Week 12.

Moderate to strong (r=0.3 to r=0.49) correlations were observed between the change scores of the Life Interference scale score with the Pen Ease of Use, Satisfaction and Willingness to Continue Treatment, and Family Life Interference scale scores, and PGIS-IDA at Week 12.

Negligible to weak correlations (r <0.3) were observed between the change scores of the Life Interference scale score with the Satisfaction with the Overall Experience, Signs and Symptoms, and Caregiver-Reported Signs.

Similar results were generally observed for correlations of change scores from Week 12 to Week 24.

**Interpretation of Scores**

Overall, results from the anchor-based analyses indicated that participants who experienced a 1-point (out of 7 points) improvement on the PGIS-IDA (defined as minimally improved) had experienced a mean [SD] improvement of the Life Interference scale score of -18.8 [16.4] points from baseline to Week 12.

Linear regression approach showed that a 1-unit change in the PGIS-IDA corresponds to a change score of -18.3 in the Life Interference scale score and a 2-unit change in the PGIS IDA corresponds to a change score of -25.8 in the Life Interference scale score.

The estimate based on the half SD [SEM] of assessment of Life Interference scores at baseline was 9.4 [15.7].
Safety Results: The proportion of participants with all-causality treatment-emergent adverse events (TEAEs) was higher during the once weekly somatrogon injection schedule than during the once daily Genotropin injection schedule (Table S4). A similar trend was observed in the treatment-related TEAEs.

- All TEAEs were mild or moderate; none were severe.
- No participants reported any SAEs and 1 participant discontinued the study due to an AE (injection site pain of moderate severity during the once weekly somatrogon injection schedule that was considered by the investigator to be related to study intervention).
- No deaths were reported during this study.
- Three participants had a temporary discontinuation due to an AE (during the once daily Genotropin injection schedule).
- No participants reported any AEs related to COVID-19.

| Table S4. Treatment-Emergent Adverse Events (All Causalities) - Safety Analysis Set (Protocol C0311002) |
|----------------------------------|----------------------------------|----------------------------------|
|                                   | During Genotropin Treatment<sup>a</sup> (N=86) | During Somatrogon Treatment<sup>b</sup> (N=87) | Overall Total During Both Treatments (N=87) |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| **Number (%) of Subjects**       | n (%)                            | n (%)                            | n (%)                            |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Subjects evaluable for adverse events | 86                               | 87                               | 87                               |
| Number of adverse events         | 93                               | 106                              | 199                              |
| Subjects with adverse events     | 38 (44.2)                        | 47 (54.0)                        | 58 (66.7)                        |
| Subjects with serious adverse events | 0                               | 0                                | 0                                |
| Subjects with severe adverse events | 0                               | 0                                | 0                                |
| Subjects discontinued from study due to adverse events<sup>3</sup> | 0                               | 1 (1.1)                          | 1 (1.1)                          |
| Subjects with dose reduced or temporary discontinuation due to adverse events | 3 (3.5)                          | 0                                | 3 (3.4)                          |
Table S4. Treatment-Emergent Adverse Events (All Causalities) - Safety Analysis Set (Protocol C0311002)

| Number (% of Subjects) | During Genotropin Treatment\(^a\) (N=86) | During Somatrogon Treatment\(^b\) (N=87) | Overall Total During Both Treatments (N=87) |
|------------------------|----------------------------------------|----------------------------------------|------------------------------------------|
| n (%)                  | n (%)                                  | n (%)                                  | n (%)                                    |

Includes data up to 7 days after last dose of study drug.
Except for the number of adverse events, participants are counted only once per treatment in each row.
Participants are counted only once per AE in overall total column.
SAEs according to the investigator’s assessment.
\(^a\) Occurred during treatment with Genotropin regardless of sequence.
\(^b\) Occurred during treatment with somatrogon regardless of sequence.
Participants who have an AE record that indicates the AE caused the participant to be discontinued from the study.
MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 24SEP2020 (04:31) Source Data: Table 16.2.7 Output
File: ./C0311002/C0311002_CSR/adae_s020 Date of Generation: 09OCT2020 (15:32)
Table 14.3.1.2 Somatrogon is for Pfizer internal use.

The most frequently reported all-causality TEAE by System Organ Class (SOC) was Infections and Infestations (18 [20.7%] participants during the once weekly somatrogon injection schedule; 19 [22.1%] during the once daily Genotropin injection schedule).

The number of participants who experienced at least 1 injection site reaction AE (General Disorders and Administration Site Conditions System Organ Class [SOC]) was higher during the once weekly somatrogon injection schedule (19 [21.8%]) than during the once daily Genotropin injection schedule (14 [16.3%]).

- Injection site pain and injection site haematoma were the most frequently reported Preferred Terms (PTs) during both injection schedules.

- All injection site reaction AEs were mild, except for 2 participants who reported moderate events of injection site pain during the once weekly somatrogon injection schedule.

- Except for 1 participant, none of these injection site reactions resulted in study discontinuation.

- All of these injection site reaction events were considered by the investigator to be related to the study intervention.

No clinically meaningful differences between treatment groups were observed for chemistry, hematology, liver function test, IGF-1 and IGF-1 SDS, glucose metabolism, and urinalysis parameters.
No participant in either treatment sequence met the criteria for Hy’s Law or Temple’s Corollary.

Four participants in the somatrogon then Genotropin sequence tested positive for anti-drug antibodies (ADA) during the first 12 weeks of Treatment Period 1, but none of these participants tested positive for neutralizing antibodies (NAb) during the study.

Conclusion(s):

- In this study, the treatment burden, as assessed by the difference in the mean Overall Life Interference total scores, was lower for children with GHD and their caregivers during the once weekly somatrogon injection schedule than during the once daily Genotropin injection schedule.

- Improvements in most variables for treatment experience, as assessed by estimated differences in mean score within the DCOA 1 questionnaire, were also observed during the once weekly somatrogon injection schedule compared with the once daily Genotropin injection schedule.
  - The point estimate of the mean satisfaction with the overall treatment experience improved for participants and their caregivers in the once weekly somatrogon injection schedule compared with those in the once daily Genotropin injection schedule, but the estimated mean difference was not statistically significant.
  - No differences between injection schedules were observed for injection signs and symptoms (participants ≥8 years) and assessment of signs (participants <8 years).

- The majority of participant/caregiver dyads preferred the once weekly somatrogon injection schedule compared with those who preferred the once daily Genotropin injection schedule or no difference/no preference between injection schedules for most variables within the DCOA 2 questionnaire, except for:
  - Pen ease of use: Although the majority of participant/caregiver dyads reported the somatrogon pen was easier to use based on preparing the pen, less than half of them indicated the somatrogon pen was easier to use for setting the dose, injecting the medicine, and storing the pen.

- Most of the participant/caregiver dyads responded it would be extremely or very beneficial to take injection less often.

- The once weekly somatrogon injection schedule had less impact on the daily activities than the once daily Genotropin injection schedule based on the lower overall mean PGIS-IDA score.
In this study, once weekly somatrogon administration was generally well tolerated in children with GHD.

- Common AEs for both injection schedules included injection site pain, injection site haematoma, nasopharyngitis, and headache. The incidence of common AEs was comparable for both injection schedules, except for injection site haematoma, which was higher for participants in the once daily Genotropin injection schedule. No participant reported a severe TEAE.

- No SAEs or deaths were reported during this study.

- The incidence of injection site reactions was higher for participants in the once weekly somatrogon injection schedule than for those in the once daily Genotropin injection schedule. All but 2 events were mild and only 1 participant discontinued from the study due to an AE of injection site pain that occurred while receiving somatrogon.

- No clinically meaningful differences were observed for laboratory parameters. No participants met the criteria for Hy’s Law or Temple’s Corollary.

- Four participants tested positive for somatrogon ADA while receiving once weekly somatrogon therapy; none of these subjects developed NAb.