

Treatment Burden of Weekly Somatrogen vs Daily Somatropin in Children With Growth Hormone Deficiency: A Randomized Study

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Abstract

Context: Somatrogen is a long-acting recombinant human growth hormone treatment developed as a once-weekly treatment for pediatric patients with growth hormone deficiency (GHD).

Objective: Evaluate patient and caregiver perceptions of the treatment burden associated with the once-weekly somatrogen injection regimen vs a once-daily Somatropin injection regimen.

Methods: Pediatric patients (≥ 3 to < 18 years) with GHD receiving once-daily somatropin at enrollment were randomized 1:1 to Sequence 1 (12 weeks of once-daily Somatropin, then 12 weeks of once-weekly somatrogen) or Sequence 2 (12 weeks of once-weekly somatrogen, then 12 weeks of once-daily Somatropin). Treatment burden was assessed using validated questionnaires completed by patients and caregivers. The primary endpoint was the difference in mean overall life interference (LI) total scores after each 12-week treatment period (somatrogen vs Somatropin), as assessed by questionnaires.

Results: Of 87 patients randomized to Sequence 1 ($n = 43$) or 2 ($n = 44$), 85 completed the study. Once-weekly somatrogen had a significantly lower treatment burden than once-daily Somatropin, based on mean overall LI total scores after somatrogen (8.63) vs Somatropin (24.13) treatment (mean difference -15.49 ; 2-sided 95% CI -19.71 , -11.27 ; $P < .0001$). Once-weekly somatrogen was associated with greater convenience, higher satisfaction with treatment experience, and less LI. The incidence of treatment-emergent adverse events (TEAEs) for Somatropin and somatrogen was 44.2% and 54.0%, respectively. No severe or serious AEs were reported.

Conclusion: In pediatric patients with GHD, once-weekly somatrogen had a lower treatment burden and was associated with a more favorable treatment experience than once-daily Somatropin.

Keywords: growth hormone, growth hormone deficiency, long-acting growth hormone, somatrogen, Somatropin, NGENLA

Abbreviations: AE, adverse event; AESI, adverse event of special interest; DCOA, Dyad Clinical Outcome Assessment; GHD, growth hormone deficiency; hGH, human growth hormone; LI, life interference; PGIS-IDA, Patient Global Impression Severity Scale—Impact on Daily Activities; rhGH, recombinant human growth hormone; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Since the first published use of human growth hormone (hGH) to treat a child in 1958 [1], regular administration of hGH has gradually become standard of care for children with GH deficiency (GHD). In the 1980s, recombinant hGH (rhGH) became available thanks to advances in protein production technology. Subsequently, 6 or 7 subcutaneous (SC) injections of rhGH per week, administered by injection

devices before bedtime, became established as the best-known mode of long-term therapy. Treatment with rhGH has been demonstrated to promote linear growth velocity in children with GHD, as well as maintaining healthy body composition, normal blood glucose concentrations, and a favorable lipid profile [2]. Somatropin (somatropin) was one of the first rhGH products to be registered in Europe, the United

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States, Japan, and other countries worldwide [3-5], and has a well-established efficacy and safety profile [2]. Currently, Somatropin is administered once-daily as a SC injection [2].

Despite treatment with rhGH, many children with GHD fail to achieve their target adult height. Poor adherence to treatment has been suggested as one of the main reasons for the reduced efficacy of rhGH observed in some children [6-8]. Based on a recent systematic review, the prevalence of nonadherence to daily rhGH treatment may be as high as 71% [9]. Given the long-term use of rhGH over many years during childhood, daily injections can become a substantial emotional and physical burden to both children and their parents/caregivers [6, 10, 11]. Physical burdens include the discomfort, pain, and bruising associated with injections [10, 11]; emotional burdens consist of fear of injections and worries or embarrassment about treatment [10]. Parents/caregivers also feel the emotional burden of daily treatment because they worry about treatment and causing their children pain [10]. rhGH treatment can also interfere with daily activities and travel, with the administration [10], storage [11], and reconstitution [11] of the injections being reported as burdens. A recent patient preference study conducted as a discrete-choice experiment showed patients with GHD preferred a less-frequent injection schedule [12].

In order to better characterize and understand the treatment experience, including the burden of rhGH injections from the child and caregiver perspective, we developed a new Dyad Clinical Outcome Assessment (DCOA) questionnaire (also known as the Life Interference Questionnaire for Growth Hormone Deficiency) [13]. The development process was in accordance with measurement science best practices, described in the relevant regulatory guidance. The questionnaire content and structure are understood by children and parents. The reliability and validity of the questionnaire was established in a cross-sectional, observational field study of 224 participants that included a cohort of children with GHD and their caregivers [13]. Given that the injection procedure in children involves both patients and their caregivers, the questionnaire was intended to be completed by the patient-caregiver dyad (patient and caregiver answer questions together) [13].

The introduction of a longer-acting rhGH treatment (administered as a once-weekly injection) to reduce treatment burden could potentially improve adherence and, ultimately, clinical outcomes. Somatrogon is a long-acting rhGH comprising the amino acid sequence of hGH fused to 3 copies of the carboxy terminal peptide from human chorionic gonadotropin (hCG) [14]. The carboxy terminal peptides from hCG extend the half-life of the attached rhGH [15], allowing longer intervals between injected doses. Somatrogon is currently approved in Canada, Australia, Japan, the UK, and the EU as a once-weekly SC injection for the treatment of children with growth disturbance due to insufficient secretion of GH, also referred to as pediatric GHD. Results from a global Phase 3 study indicate that once-weekly somatrogon was generally well tolerated and demonstrated noninferiority to once-daily Somatropin in promoting growth in pediatric patients with GHD [16].

The aim of this study was to evaluate and compare patient and caregiver perceptions of the treatment burden associated with once-weekly somatrogon injections compared with once-daily somatropin injections (administered as Somatropin)

for pediatric GHD, primarily through the validated DCOA questionnaire. Although the evidence from this study helps to describe treatment burden, several of the endpoints are also directly linked to adherence.

Materials and Methods

Study Overview

This Phase 3, randomized, open-label, multicenter, 2-period crossover study was carried out at 20 centers in Bulgaria, the Czech Republic, Slovakia, the United Kingdom, and the United States. This study used the DCOA questionnaire to evaluate perceptions of the treatment burden associated with once-weekly somatrogon compared with once-daily Somatropin, in children aged ≥ 3 to < 18 years with GHD who had received stable daily rhGH therapy for ≥ 3 months. A crossover study design was used to enable comparison of patient and caregiver experience with each treatment schedule.

Ethics

The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki and was registered on ClinicalTrials.gov (NCT03831880). This protocol was approved by the institutional review board and/or independent ethics committee of the participating centers. Parents or guardians of each patient provided signed informed consent before any study procedures commenced.

Participants

Eligible patients were aged ≥ 3 to < 18 years at consent, with either isolated GHD or GHD as part of multiple pituitary hormone deficiencies; had insulin-like growth factor 1 SD score (SDS) < 2 (prior to first initiation of rhGH therapy); had been receiving treatment with once-daily SC injections of somatropin (Somatropin Pen, Somatropin GoQuick Pen, HumatroPen [USA only], or Omnitrope Pen [USA only]) and had been compliant on a stable dose ($\pm 10\%$) for ≥ 3 months prior to screening. Patients were excluded if they had a history of cancer, radiation therapy, or chemotherapy, had psychosocial dwarfism, were born small for gestational age with birth weight and/or birth length ≤ 2 SDS for gestational age, had chromosomal abnormalities, including Turner syndrome, other known causes of short stature, or diabetes mellitus. Patients were also excluded if they had regularly scheduled daily injectable medications other than Somatropin Pen, Somatropin GoQuick Pen, HumatroPen, or Omnitrope, or had ever received a long-acting rhGH preparation. Patients were also excluded if they had closed epiphyses, as determined by existing clinical data.

Procedures

The screening period was up to 30 days, with a follow-up phone call 4 weeks after the last clinic visit. Patients were randomized 1:1 to either Sequence 1 (12 weeks of once-daily Somatropin followed by 12 weeks of once-weekly somatrogon) or Sequence 2 (12 weeks of once-weekly somatrogon followed by 12 weeks of once-daily Somatropin). The first dose of each treatment period (baseline and week 12) was self-administered at the clinic site; the remaining doses were self-administered at home. Regardless of the sequence to

which they were randomized, all patients were to receive a somatrogen dose of 0.66 mg/kg/week and a Somatropin dose equivalent to their daily rhGH dose before the study commenced. There was no treatment washout period, as these patients required continual GH treatment.

The primary objective of this study was to evaluate the treatment burden of a once-weekly somatrogen injection regimen compared with a once-daily Somatropin injection regimen. Secondary objectives included an evaluation of different aspects of the treatment experience of each injection regimen, including caregiver burden, injection schedule preference, convenience, and satisfaction with injection schedule. Secondary objectives also included the Patient Global Impression Severity Scale—Impact on Daily Activities (PGIS-IDA) question, which asks about the impact of daily and weekly treatment administration on daily activities, rated on a 7-point scale from “Not present” to “Extremely severe.” The safety objective of the study was to describe the safety and tolerability of once weekly somatrogen.

Study Assessments and Endpoints

Treatment burden and experience, including preferred injection schedule

The recently developed, validated DCOA questionnaire [13], and the PGIS-IDA, were administered electronically using a computer tablet.

The DCOA questionnaire comprises 2 parts (DCOA 1 and 2). DCOA 1 includes a comprehensive list of questions to determine the treatment burden. DCOA 2 asks the dyad to indicate their preference for either daily injections or weekly injections to a suite of questions asking about their treatment experience (Table 1). The questionnaire was to be completed as a dyad, or by the patient or caregiver alone (depending on who was most involved with the injections), with some specific questions intended only for the patient or caregiver separately (Table 1). At baseline and after each 12-week treatment period, patient/caregiver dyads completed DCOA 1 (rating treatment experience) and the PGIS-IDA (Fig. 1 and Table 1). At 24 weeks, after experiencing both treatment schedules, patient/caregiver dyads also completed DCOA 2, indicating their preference for the once-daily or once-weekly injection schedule (Fig. 1 and Table 1).

The primary endpoint of treatment burden was assessed as the difference in mean overall life interference (LI) total scores between once-weekly somatrogen and once-daily Somatropin injections after each 12-week treatment period, based on a subset of DCOA 1 items. The LI total score is based on 7 items: impact on daily activities, social activities, recreation/leisure, spending a night away, travel, changes to life routine, and bother due to injections. The remaining DCOA 1 questions were evaluated as secondary endpoints. All DCOA 2 items were evaluated as secondary endpoints at week 24 and reported as the proportion of patient/caregiver dyads preferring the weekly injection schedule over the daily injection schedule. The PGIS-IDA was evaluated as a secondary endpoint.

Safety

Safety evaluations included all AEs, injection site reactions, vital signs, body weight, physical examination, and laboratory assessments, which consisted of insulin-like growth

factor 1 concentration, free thyroxine concentration, glycated hemoglobin A1c, hematology, blood chemistry, liver and thyroid function, and urinalysis. Immunogenicity was assessed in terms of the presence of antidrug antibodies, specifically anti-hGH antibodies, antisomatrogen antibodies, and neutralizing antibodies. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23. The severity or intensity of an adverse event (AE) was classified as being mild, moderate, or severe. AEs of special interest (AESI) were chosen from a set of class-based potential identified risks relating to somatropin-containing products.

The safety endpoints were frequency, severity, and relationship of AEs, serious AEs (SAEs), discontinuation due to AEs, frequency and severity of abnormal laboratory values, and immunogenicity (detection of antidrug antibodies and neutralizing antibodies).

Statistical Analyses

The primary endpoint and continuous secondary endpoints were 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 test the hypothesis that the difference in LI total score between weekly and daily regimens is statistically significant. The main analyses of the primary and secondary endpoints were conducted in the full analysis set (all randomized patients who received ≥ 1 dose of study drug). A sensitivity analysis was performed on the primary endpoint using the linear mixed effects model described earlier but repeated using the per protocol set (randomized patients who completed both treatment periods and their corresponding assessments).

Results

Patients and Treatment

This study was conducted between February 7, 2019, and August 28, 2020, and enrolled patients at 20 centers in Bulgaria, the Czech Republic, Slovakia, the United Kingdom, and the United States. Of 107 screened patients, 87 were randomized ($n = 43$ to Sequence 1 and $n = 44$ to Sequence 2) and treated with ≥ 1 dose of study drug (Fig. 1). Most patients in the study were male (82.8%) and White (93.1%), with over half of the patients from the United States (59.8%) and the remaining 40.2% from Europe (Table 2). Patients randomized to Sequence 1 had similar baseline demographics to those randomized to Sequence 2 (Table 2).

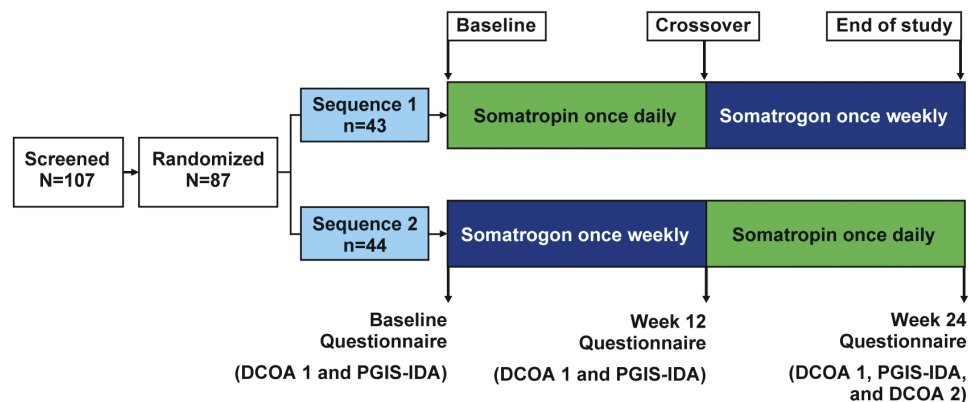
Treatment Burden

Once-weekly somatrogen demonstrated a lower (ie, improved) treatment burden, as shown by a reduced patient LI score, compared with once-daily Somatropin (Fig. 2). The least squares mean (95% CI) of the overall Life Interference total score was 8.63 (5.05, 12.22) for once-weekly somatrogen and 24.13 (20.61, 27.65) for once-daily Somatropin (Fig. 2). The treatment mean difference (somatrogen – Somatropin) was statistically significant based on the linear mixed effects model; it was -15.49 (95% CI $-19.71, -11.27$) ($P < .0001$), confirming that the treatment burden of the once-weekly somatrogen injection schedule is lower than that of the once-daily Somatropin injection schedule.

Table 1. Study questionnaires

	DCOA 1	PGIS-IDA	DCOA 2
Administration schedule	Administered at baseline and at the end of each treatment period (week 12 and week 24)	Administered at baseline and at the end of each treatment period (week 12 and week 24)	Administered at the end of the study, after both treatments have been completed (week 24)
Assessments	Questions focused on the most recently completed injection schedule (either daily or weekly) and assessed treatment burden and treatment experience	Question focused on how severely the most recently completed treatment impacted patients' daily activities	Questions focused on comparing 1 injection schedule with the other, e.g. which schedule was preferred in terms of treatment burden and intention to comply
Completed by patient/caregiver dyad vs individual	Most questions were completed by the patient/caregiver dyad, except for the following: <ul style="list-style-type: none"> • <i>injection signs and symptoms</i>—patient completed (children aged 8–17 years) • <i>caregiver assessment of injection signs</i>—caregiver completed (for children aged <8 years) • <i>caregiver and family life interference</i>—caregiver completed 	Question completed by patient/caregiver dyad	Most questions were completed by the patient/caregiver dyad, except for the following: <ul style="list-style-type: none"> • <i>caregiver and family life interference</i>—caregiver completed

DCOA; Dyad Clinical Outcome Assessment; PGIS-IDA, Patient Global Impression Severity Scale—Impact on Daily Activities.

**Figure 1.** Study design and patient flow.

Treatment Experience

DCOA 1

The estimated mean score differences for most variables within DCOA 1 demonstrated a statistically significant improvement (negative estimated mean difference) with once-weekly somatrogen compared with once-daily Somatropin (Fig. 3). The variables that did not show a statistically significant difference between treatments included overall mean scores for injection signs and symptoms (patients ≥ 8 years old; $P = .61$), the assessment of injection signs (reported by caregivers for patients <8 years old; $P = .84$), and satisfaction with the overall treatment experience ($P = .07$). Although not statistically significant, the point estimate of the mean satisfaction with the overall treatment experience score was lower (increased satisfaction) for patients receiving once-weekly somatrogen compared with once-daily Somatropin.

PGIS-IDA

Patients receiving once-weekly somatrogen reported a lower overall mean PGIS-IDA score compared with once-daily Somatropin (Fig. 3), indicating that once-weekly somatrogen had a less severe impact on daily activities. The mean score

difference (95% CI) of -14.58 ($-18.72, -10.44$) was statistically significant ($P < .0001$).

DCOA 2

The majority of patients/caregivers preferred the once-weekly somatrogen dosing regimen over the once-daily Somatropin regimen on every domain of the DCOA 2, except pen ease of use (Fig. 4). A much larger proportion of patients/caregivers preferred once-weekly somatrogen compared with once-daily Somatropin in terms of the choice of injection pen (88.1% vs 11.9%), preferred injection schedule (91.7% vs 7.1%), convenience of injection schedule (95.2% vs 4.8%), and the ease of following the injection schedule (85.7% vs 9.5%). The proportion of patients/caregivers who had no preference for injection schedule (1.2%) or who reported no difference in the ease of following either injection schedule (4.8%) was small. Most patients/caregivers reported that the once-weekly somatrogen injection schedule interfered less with patient life as well as caregiver and family life (daily activities, social activities, recreation/leisure, night away from home, and travel) than the once-daily Somatropin injection schedule (Fig. 4). Although the majority of patients/caregivers

Table 2. Patient demographics and baseline characteristics

	Sequence 1: Somatropin then somatrogen (n = 43)	Sequence 2: somatrogen then Somatropin (n = 44)	Total (N = 87)
Age, years			
Mean (SD)	10.8 (3.4)	10.7 (3.7)	10.7 (3.5)
Median (min, max)	12.0 (4, 16)	11.0 (3, 17)	11.0 (3, 17)
Sex, n (%)			
Female	9 (20.9)	6 (13.6)	15 (17.2)
Male	34 (79.1)	38 (86.4)	72 (82.8)
Race, n (%)			
Asian	0	1 (2.3)	1 (1.1)
Black or African American	3 (7.0)	1 (2.3)	4 (4.6)
White	39 (90.7)	42 (95.5)	81 (93.1)
Other	0	0	0
Not reported	1 (2.3)	0	1 (1.1)
Ethnicity, n (%)			
Hispanic or Latino	3 (7.0)	2 (4.5)	5 (5.7)
Not Hispanic or Latino	39 (90.7)	42 (95.5)	81 (93.1)
Not reported	1 (2.3)	0	1 (1.1)
Country, n (%)			
Bulgaria	4 (9.3)	6 (13.6)	10 (11.5)
Czech Republic	9 (20.9)	7 (15.9)	16 (18.4)
Slovakia	1 (2.3)	4 (9.1)	5 (5.7)
UK	3 (7.0)	1 (2.3)	4 (4.6)
USA	26 (60.5)	26 (59.1)	52 (59.8)
Height, cm			
Mean (SD)	138.6 (20.4)	138.2 (20.4)	138.4 (20.3)
Median (min, max)	142.1 (92, 181)	139.7 (96, 177)	141.5 (92, 181)
Weight, kg			
Mean (SD)	37.5 (20.0)	34.3 (13.7)	35.8 (17.1)
Median (min, max)	35.7 (13, 131)	31.4 (14, 68)	33.8 (13, 131)
BMI, kg/m ²			
Mean (SD)	18.5 (4.8)	17.2 (2.6)	17.8 (3.8)
Median (min, max)	17.0 (13, 40)	16.4 (14, 25)	16.7 (13, 40)
Type of rhGH injection pen used prior to study start, n (%)			
Somatropin GoQuick Pen	8 (18.6)	13 (29.5)	21 (24.1)
Somatropin Pen	25 (58.1)	25 (56.8)	50 (57.5)
HumatroPen	7 (16.3)	5 (11.4)	12 (13.8)
Omnitrope Pen	3 (7.0)	1 (2.3)	4 (4.6)

Percentages are based on the number of patients in the treatment sequence group.
Abbreviations: BMI, body mass index; rhGH, recombinant human growth hormone.

reported that the somatrogen pen was easier to use with regards to preparing the pen, less than half of the patients/caregivers preferred the somatrogen pen in terms of setting the dose, injecting the medicine, and storing the pen. For these 3 items of the pen ease of use domain in DCOA 2, a substantial proportion of patients had no preference between the somatrogen vs Somatropin pens (38.1%, 29.8%, and 64.3%, respectively). Most patients/caregivers felt it would be extremely or very beneficial to take injections less often (86.9%; n = 84). A higher proportion of patients/caregivers indicated a greater intention to comply with the treatment

schedule for once-weekly somatrogen compared with once-daily Somatropin.

Safety

Of 87 patients randomized, 86 were treated with both study drugs. During the somatrogen period, 1 patient discontinued the study due to a nonserious treatment-emergent adverse event (TEAE) of moderate injection site pain, which was considered related to the study drug. This patient did not cross over to the Somatropin treatment period. During the Somatropin treatment period, 3 patients had a temporary

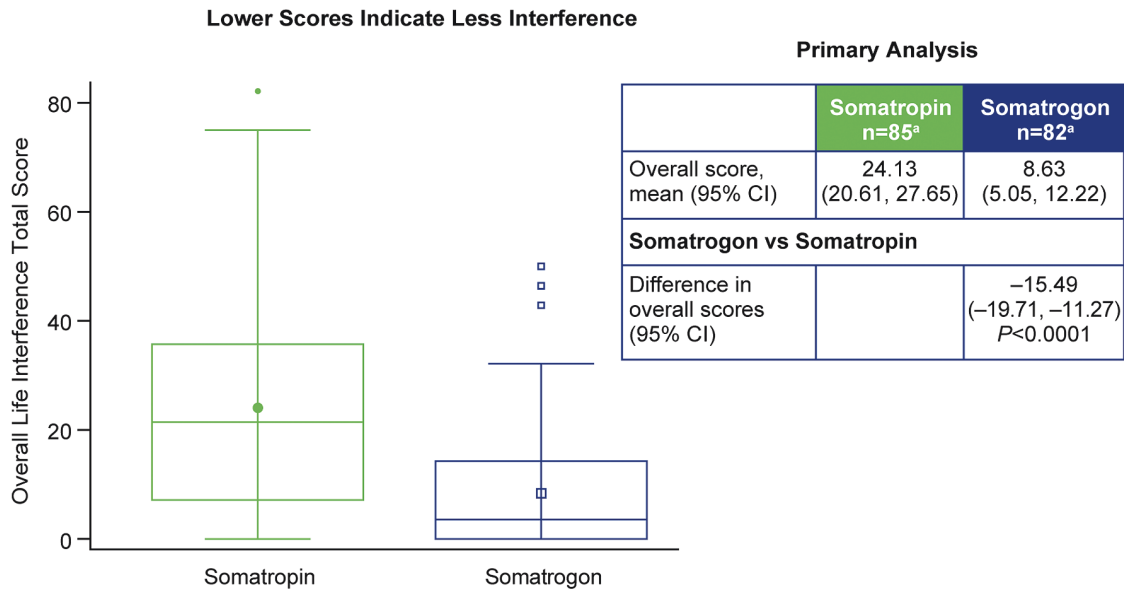


Figure 2. Overall Life Interference total scores (DCOA 1). All scores were transformed from raw scores and converted to a 0 to 100 scale. Box shows interquartile range (IQR); whiskers include observed values within 1.5× IQR from the box edges. ^aNumber of patients with non-missing values. Model results based on a linear mixed-effects model, including sequence, period, and treatment as fixed effects and subject-within-sequence and within-subject error as random effects. Sensitivity analysis in the per protocol set (randomized patients who completed both treatment periods and corresponding assessments; n = 81 for both treatments) showed similar results (mean difference in overall scores: -14.85; 95% CI -19.03, -10.66; *P* < .0001). DCOA, Dyad Clinical Outcome Assessment.

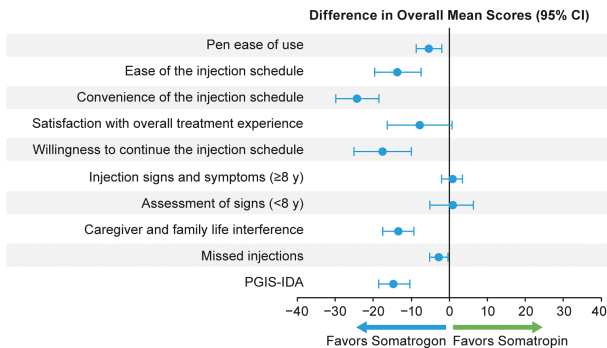


Figure 3. Patient and caregiver assessments of treatment experience (DCOA 1). Results based on a linear mixed-effects model, including sequence, period, and treatment as fixed effects and subject-within-sequence and within-subject error as random effects. Assessment of signs: Caregivers completed the assessment of signs for children <8 years old. All scores were transformed from raw scores and converted to a 0 to 100 scale. Lower scores represent less life interference/less impact on daily activities (better outcome). DCOA, Dyad Clinical Outcome Assessment; PGIS-IDA, Patient Global Impression Severity—Impact on Daily Activities.

discontinuation due to a total of 4 TEAEs (viral upper respiratory tract infection, nasopharyngitis, otitis media, and viral infection); all 4 TEAEs were mild and were considered unrelated to the study drug. There were no TEAEs that led to dose reduction.

Both study drugs had a similar safety profile, with all-causality TEAEs reported in 54.0% of somatrogen-treated patients and 44.2% of Somatropin-treated patients (Table 3). All TEAEs were mild to moderate in severity and no severe TEAEs or SAEs were reported. Injection site pain was the most common TEAE during treatment with somatrogen (14.9%) and Somatropin (12.8%) and most cases were rated

as mild (84.6% and 100%, respectively). Other TEAEs (≥5%) reported during treatment with somatrogen vs Somatropin were nasopharyngitis (6.9% vs 5.8%), headache (6.9% vs 5.8%), and injection site hematoma (4.6% vs 9.3%). The overall incidence of treatment-emergent AESI was higher for the somatrogen treatment period (26.4%) than for the Somatropin treatment period (18.6%) and this was due mainly to the higher incidence of injection site reactions in the somatrogen period (21.8%) than in the Somatropin period (16.3%).

The overall incidence of laboratory test abnormalities was higher for patients receiving once-weekly somatrogen than for patients receiving once-daily Somatropin, though these differences were not clinically meaningful.

Five patients in Sequence 1 tested positive to antidrug antibodies to hGH at the study screening visit. Subsequently, 1 additional subject in this sequence tested positive for hGH antidrug antibodies at week 12. None of these participants developed antidrug antibodies to somatrogen. Four patients in Sequence 2 tested positive for somatrogen antidrug antibodies at week 12, with the antidrug antibodies showing specificity to the hGH component of the molecule. In addition, 3 patients in Sequence 2, for whom antidrug antibodies against hGH results were either missing or negative at week 12 tested positive for anti-hGH at week 24. Almost all of the positive results for antidrug antibodies were low titer. None of the patients in the study developed neutralizing antibodies.

Discussion

This is the first Phase 3 study to evaluate and compare the treatment burden of once-weekly somatrogen injections with once-daily rhGH injections, utilizing a crossover design to compare both treatments. Once-weekly somatrogen demonstrated a statistically significant reduction in overall LI score

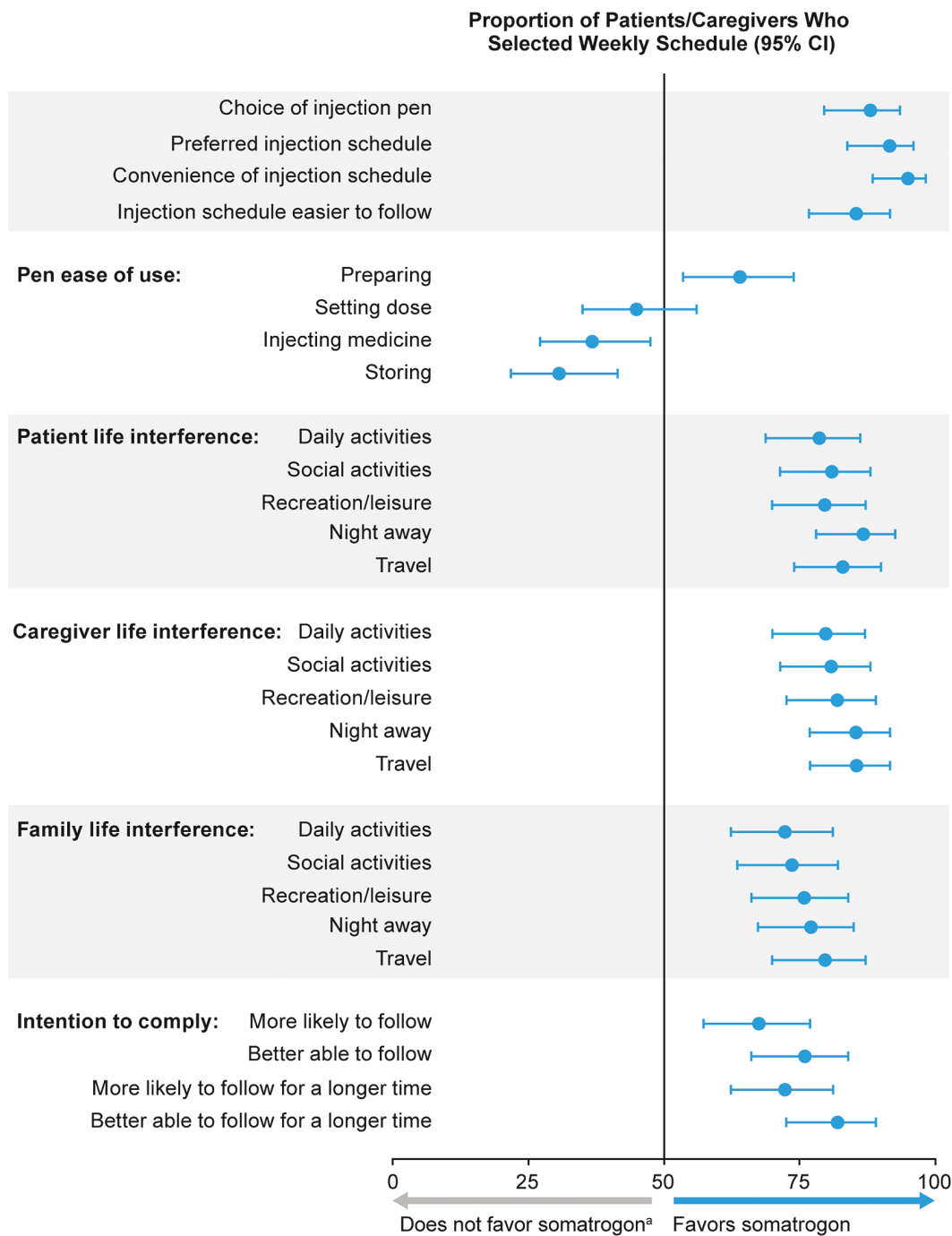


Figure 4. Patient and caregiver preference for weekly or daily injections (DCOA 2). ^a“Does not favor somatrogen” includes Somatropin and No preference/No difference. For the 3 items of the “pen ease of use” domain where <50% of patients preferred somatrogen, a substantial proportion of patients had no preference (38.1%, 29.8%, 64.3%, for setting the dose, injecting the medicine, and storing the pen, respectively) between the injection schedules. Two-sided 95% CI computed using the Wilson score method. DCOA, Dyad Clinical Outcome Assessment

compared with once-daily Somatropin, reflecting a lower treatment burden associated with once-weekly injections. The results, in totality, which showed an overall benefit in treatment experience with the somatrogen once-weekly dosing regimen compared with the Somatropin once-daily dosing regimen, can be interpreted as being clinically meaningful to patients. Given that children with GHD require many years of treatment, the lower treatment burden, strong preference for, and higher intention to comply with once-weekly somatrogen treatment may increase adherence and improve

treatment response relative to once-daily Somatropin in the longer term.

Despite its efficacy, the once-daily rhGH injection regimen constitutes a substantial burden on patients and their caregivers [10], and a number of studies have highlighted the extent to which treatment interferes with the lives of the patients and their families [10, 17]. This study showed that once-weekly somatrogen had a lower treatment burden than once-daily Somatropin, quantified as a statistically significant difference in mean overall LI total score after 12 weeks of

Table 3. All-causality treatment-emergent adverse events

n (%)	During Treatment With ^a	
	Somatogron (n = 87)	Somatropin (n = 86)
Any AE	47 (54.0)	38 (44.2)
Discontinued study due to AE	1 (1.1)	0
Dose reduced or temporary discontinuation due to AEs	0	3 (3.5)
Most common AEs ^b		
Injection site pain	13 (14.9)	11 (12.8)
Injection site hematoma	4 (4.6)	8 (9.3)
Nasopharyngitis	6 (6.9)	5 (5.8)
Headache	6 (6.9)	5 (5.8)

n, number of patients with ≥ 1 event.

Abbreviation: AE, adverse event.

^aAEs are presented during the treatment they were reported (regardless of sequence).

^bBy preferred term, with $\geq 5\%$ incidence in either treatment period.

treatment. This finding was supported by patient evaluations of the other aspects of injection experience in the DCOA 1 that were consistent with this, reflecting an overall improvement in treatment experience with somatogron administered once weekly compared with Somatropin administered once daily (Fig. 3). After completing both treatment periods at 24 weeks, a large proportion of patients/caregivers preferred once-weekly somatogron injections to once-daily Somatropin injections on almost every domain of the DCOA 2 (Fig. 4). Although the pen ease of use domain did not clearly favor somatogron over Somatropin, these data suggest that, in general, somatogron administration was found to be no more difficult than Somatropin administration, an important consideration for choosing a treatment, particularly with regards to long-term adherence. The majority of patients/caregivers reported that once-weekly somatogron had less interference with daily/social activities, leisure/recreation, night away, and travel, when compared with once-daily Somatropin; this trend was observed across the 3 perspectives considered: patient, caregiver, and family (Fig. 4).

As might be expected from a treatment regimen that results in reduced life interference, most patients/caregivers in the study preferred the somatogron injection schedule, reporting it as being more convenient and easier to follow compared with the Somatropin injection schedule. Similar sentiments have been reported from patient preference studies in the United States [12] and Japan [18], in which patients showed a strong hypothetical preference for a treatment schedule with less frequent injections compared with once-daily regimens. The importance of the injection schedule to patients was also highlighted in both studies, which found it to be the most important treatment-related factor assessed [12, 18]. However, it should be noted that these previous hypothetical studies involved patients and caregivers who had only experienced daily rhGH injections. One of the strengths of this crossover study was that it enabled patients, for the first time, to make a comparison of both the weekly and daily injection schedules that they actually experienced in this study. Compared with the Somatropin injection schedule, a larger proportion of patients/caregivers in this study also indicated they were more likely or better able to follow the somatogron injection

schedule for a longer time. However, whether greater intention to comply with the once-weekly regimen translates to improved adherence remains to be seen and should be explored using longer term studies of real-world experience. Since adherence rates for daily rhGH treatments reported by observational studies are often much lower [9], treatments that can improve adherence may help address a range of issues associated with suboptimal adherence to daily rhGH injections. Studies have shown that poor treatment adherence is associated with suboptimal treatment response as well as economic cost (from unused injections) [6, 19, 20]. Studies of injectable treatments for type 2 diabetes [21] and relapsing–remitting multiple sclerosis [21–23] that compared a once-daily treatment regimen with a less-frequent treatment regimen showed that patients who had less-frequent injections had higher treatment adherence, fewer AEs, and higher levels of satisfaction [24]. Patients with relapsing–remitting multiple sclerosis who switched from once-daily injections to 3-times-weekly injections exhibited improved treatment adherence [23].

Once-weekly somatogron was generally well tolerated by patients with GHD and had a similar safety profile to once-daily Somatropin. No SAEs or severe TEAEs were reported during either treatment, and all AEs were mild to moderate in severity and of comparable incidence for both injection schedules, except for injection site hematoma, which was higher for patients receiving once-daily Somatropin, and injection site reactions, which was higher for patients receiving once-weekly somatogron. The most common TEAE observed in both treatment groups was injection site pain, and all but 2 events of injection site pain were mild. One patient discontinued the study while receiving somatogron due to a nonserious TEAE of injection site pain. Five patients tested positive for hGH antidrug antibodies at screening and 4 patients tested positive for somatogron antidrug antibodies after 12 weeks of treatment, but none developed neutralizing antibodies. The safety findings in this study were similar to those reported in the Phase 2 and global Phase 3 studies of somatogron, which found that once-weekly somatogron and once-daily Somatropin had similar safety and tolerability profiles. No severe AEs, SAEs, or withdrawals due to AEs were reported for any treatment group in the Phase 2 study [15]. The incidence of severe TEAEs and serious AEs for the somatogron group in the Phase 3 study was 8.3% and 2.8%, respectively, with 1 patient discontinued due to an AE [16].

This was the first study to assess the treatment burden of the once-weekly somatogron injection schedule in patients and caregivers across a wide pediatric age range. In line with the growing recognition of the importance of patient involvement in drug development [25, 26], this study addresses one of the key tenets of patient centricity [25], namely, understanding the real-world experiences and priorities of patients. In addition to the patient perspective, this study also seeks to understand the impact of the treatment regimens on the caregiver. This is particularly important given the high level of caregiver involvement required to support GH treatment in children and adolescents, meaning that caregivers have a key role in maintaining adherence [27]. Another strength of this study is that it enrolled subjects with prior experience of daily rhGH therapy, as they are the most qualified individuals to assess a “real-world” treatment difference when switching to weekly injections. In order to minimize bias from becoming acclimated to once-daily therapy, we utilized a crossover

study design with 12 weeks of each treatment (considered to be an appropriate time period) [27].

One potential limitation of the study was that the majority of patients were White and male. Although this reflects the demographics of the real-world population of patients with GHD who are undergoing treatment with rhGH [28, 29], expanding the study to include patients from other ethnicities, countries, or geographies could have increased the applicability of the findings. The study might have also been improved by the inclusion of an open-label extension period following the main study.

Conclusion

Compared with once-daily Somatropin, once-weekly somatropin has a lower treatment burden (as shown by less life interference) and is associated with a more favorable treatment experience in patients with pediatric GHD. The safety and tolerability profile of once-weekly somatropin appears to be similar to that of once-daily Somatropin. The reduction in life interference and treatment burden for patients and caregivers, combined with their preference for the somatropin weekly injection schedule and a higher intention to comply with treatment suggests real-world adherence to once-weekly somatropin might be higher than for once-daily Somatropin. This improved adherence would potentially have positive implications for both treatment response and clinical outcomes.

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Disclosure summary

A.K.M. has participated in advisory boards and served on a speakers bureau for Ascendis Pharma, Novo Nordisk, OPKO, and Pfizer, and has received research funding from Ascendis Pharma, Novo Nordisk, OPKO, and Pfizer. A.D. has received research funding from Pfizer and served on a speakers bureau for Pfizer, Novo Nordisk, and Merck. M.T.D. has participated in advisory boards for Novo Nordisk, is a consultant for Pfizer and Ipsen, and has served on a speakers bureau for Pfizer, Novo Nordisk, Sandoz, and Ipsen. J.L. has received research funding from Pfizer and Rare Thyroid Therapeutics, and served on a speakers bureau for Pfizer, Novo Nordisk, Merck, and Sandoz. J.L., A.A.P., M.A.R., and C.T.T. are employees and stockholders of Pfizer. M.C., S.G., G.P., and L.A.F. have no conflicts of interest to declare.

Prior Presentation

Data from this study were first presented at the Annual Meeting of the Endocrine Society (ENDO 2021), March 20-23, 2021, Virtual Meeting.

Clinical Trial Information

Clinicaltrials.gov ID: [NCT03831880](https://clinicaltrials.gov/ct2/show/study/NCT03831880).

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References

- Raben MS. Treatment of a pituitary dwarf with human growth hormone. *J Clin Endocrinol Metab*. 1958;18(8):901-903.
- Reh CS, Geffner ME. Somatotropin in the treatment of growth hormone deficiency and Turner syndrome in pediatric patients: a review. *Clin Pharmacol*. 2010;2:111-122
- Albertsson-Wikland K, Westphal O, Westgren U. Daily subcutaneous administration of human growth hormone in growth hormone deficient children. *Acta Paediatr Scand*. 1986;75(1):89-97.
- Ranke MB. Clinical experience with authentic recombinant human growth hormone. *Acta Paediatr Scand Suppl*. 1986;75(s325):90-92.
- Takano K, Shizume K, Hibi I, et al. Clinical trial with authentic recombinant somatropin in Japan. *Acta Paediatr Scand Suppl*. 1987;76(s331):18-24.
- Cutfield WS, Derraik JGB, Gunn AJ, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. *PLoS One*. 2011;6(1):e16223-e16223.
- Kapoor RR, Burke SA, Sparrow SE, et al. Monitoring of concordance in growth hormone therapy. *Arch Dis Child*. 2008;93(2):147-148.
- Miller BS, Velazquez E, Yuen KCJ. Long-acting growth hormone preparations - current status and future considerations. *J Clin Endocrinol Metab*. 2020;105(6):e2121-e2133.
- Graham S, Weinman J, Auyeung V. Identifying potentially modifiable factors associated with treatment non-adherence in paediatric growth hormone deficiency: a systematic review. *Horm Res Paediatr*. 2018;90(4):221-227.
- Brod M, Hojbjerre L, Alolga SL, Beck JF, Wilkinson L, Rasmussen MH. Understanding treatment burden for children treated for growth hormone deficiency. *Patient*. 2017;10(5):653-666.
- Kremidas D, Wisniewski T, Divino VM, et al. Administration burden associated with recombinant human growth hormone treatment: perspectives of patients and caregivers. *J Pediatr Nurs*. 2013;28(1):55-63.
- McNamara M, Turner-Bowker DM, Westhead H, et al. Factors driving patient preferences for growth hormone deficiency (GHD) injection regimen and injection device features: a discrete choice experiment. *Patient Prefer Adherence*. 2020;2020(14):781-793.
- Turner-Bowker DM, Yaworsky A, Palladino A, et al. Development and psychometric evaluation of the Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD) to assess growth hormone injection burden in children and adults. *Patient*. 2020;13(3):289-306.
- Hershkovitz O, Bar-Ilan A, Guy R, et al. In vitro and in vivo characterization of MOD-4023, a long-acting carboxy-terminal peptide (CTP)-modified human growth hormone. *Mol Pharm*. 2016;13(2):631-639.
- Zelinska N, Iotova V, Skorodok J, et al. Long-acting C-terminal peptide-modified hGH (MOD-4023): results of a safety and dose-finding study in GHD children. *J Clin Endocrinol Metab*. 2017;102(5):1578-1587.
- Deal C, Steelman J, Vlachopapadopoulou E, et al. Efficacy and safety of weekly somatropin vs daily somatropin in children with growth hormone deficiency: a phase 3 study. *J Clin Endocrinol Metab*. 2022;107(7):e2717-e2728. Doi: [10.1210/clinem/dgac220](https://doi.org/10.1210/clinem/dgac220)

17. Graham S, Auyeung V, Weinman J. Exploring potentially modifiable factors that influence treatment non-adherence amongst paediatric growth hormone deficiency: a qualitative study. *Patient Prefer Adherence*. 2020;14:1889-1899.
18. Tanaka T, Sato T, Yuasa A, Akiyama T, Tawseef A. Patient preferences for growth hormone treatment in Japanese children. *Pediatr Int*. 2021;63:1185-1191. Doi: [10.1111/ped.14760](https://doi.org/10.1111/ped.14760)
19. Hughes IP, Choong C, Rath S, et al. Early cessation and non-response are important and possibly related problems in growth hormone therapy: an OZGROW analysis. *Growth Horm IGF Res*. 2016;29:63-70.
20. Wit JM, Deeb A, Bin-Abbas B, Al Mutair A, Koledova E, Savage MO. Achieving optimal short- and long-term responses to paediatric growth hormone therapy. *J Clin Res Pediatr Endocrinol*. 2019;11(4):329-340.
21. Qiao Q, Ouwens MJ, Grandy S, Johnsson K, Kostev K. Adherence to GLP-1 receptor agonist therapy administered by once-daily or once-weekly injection in patients with type 2 diabetes in Germany. *Diabetes Metab Syndr Obes*. 2016;(9):201-205.
22. Cutter G, Veneziano A, Grinspan A, et al. Higher satisfaction and adherence with glatiramer acetate 40mg/mL TIW vs 20mg/mL QD in RRMS. *Mult Scler Relat Disord*. 2019;33:13-21.
23. Cutter G, Veneziano A, Grinspan A, et al. Satisfaction and adherence with glatiramer acetate 40mg/mL TIW in RRMS after 12 months, and the effect of switching from 20mg/mL QD. *Mult Scler Relat Disord*. 2020;40:101957.
24. Loftus J, Yaworsky A, Roland C, et al. Systematic review of patient experience with a less frequent injection schedule for growth hormone deficiency. *JMCP*. 2021;27(4-a Suppl).
25. Hoos A, Anderson J, Boutin M, et al. Partnering with patients in the development and lifecycle of medicines: a call for action. *Ther Innov Regul Sci*. 2015;49(6):929-939.
26. Yeoman G, Furlong P, Seres M, et al. Defining patient centricity with patients for patients and caregivers: a collaborative endeavour. *BMJ Innov*. 2017;3(2):76-83.
27. Hey-Hadavi J, Pleil A, Deeb LC, et al. Ease of use and preference for a new disposable self-injection pen compared with a reusable pen for administering recombinant human growth hormone: a multicenter, 2-Month, single-arm, open-label clinical trial in patient-caregiver dyads. *Clin Ther*. 2010;32(12):2036-2047.
28. Grimberg A, Lindberg A, Wajnrajch M, Cucchiara AJ, Camacho-Hubner C. Racial/ethnic disparities in US pediatric growth hormone treatment. *Horm Res Paediatr*. 2018;90(2):102-108.
29. Ranke MB, Lindberg A, Tanaka T, Camacho-Hubner C, Dunger DB, Geffner ME. Baseline characteristics and gender differences in prepubertal children treated with growth hormone in Europe, USA, and Japan: 25 Years' KIGS(R) experience (1987-2012) and review. *Horm Res Paediatr*. 2017;87(1):30-41.