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RESEARCH ARTICLE



Health-related quality of life in pre-pubertal children with pediatric growth hormone deficiency: 12-month results from a phase 3 clinical trial of once-weekly somatrogen versus once-daily somatropin

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ABSTRACT

Objective: Treatment of pediatric growth hormone deficiency (pGHD) with daily injection of recombinant human growth hormone (somatropin) aims to increase height velocity and improve health-related quality of life (HRQoL). The Quality of Life in Short Stature Youth (QoLISSY) questionnaire was administered in a phase 3 clinical trial that evaluated efficacy and safety of once-weekly somatrogen versus once-daily somatropin in children with pGHD (ClinicalTrials.gov no NCT02968004).

Methods: Treatment-naïve prepubertal children with pGHD received once-weekly somatrogen or once-daily somatropin for 12 months. The QoLISSY core module (physical/social/emotional subscales) was administered at baseline and 12 months after treatment initiation. QoLISSY-Parent was completed by parents/caregivers of children <7 years old and some parents/caregivers of children ≥7 years old; children ≥7 years old self-completed QoLISSY-Child.

Results: Baseline characteristics were similar between treatment groups ($N=117$). Among children <7 years old, QoLISSY-Parent total and subscale scores showed similarly improved HRQoL at 12 months relative to baseline in both treatment groups. Self-reported QoLISSY-Child total and subscale scores in children ≥7 years old indicated HRQoL improvements at 12 months that were numerically better with somatrogen than somatropin (similar results with QoLISSY-Parent in this age group). At both time points, children reported better HRQoL than perceived by their parents/caregivers.

Conclusion: Treatment for 12 months with once-weekly somatrogen or once-daily somatropin resulted in comparable improvements in HRQoL among children with pGHD. Lower HRQoL perceived by parents/caregivers possibly reflect children's tendency to emphasize adaptation. These results suggest that evaluation of HRQoL could help support treatment decisions in children with pGHD treated with growth hormone.

PLAIN LANGUAGE SUMMARY

Pediatric growth hormone deficiency is a condition that causes slow growth. Children with this condition have height that is lower than normal unless the condition is treated. The slow growth and short height may have bad effects on the emotional and social well-being of these children. Treatment usually consists of a growth hormone that is administered by daily injection under the skin over a period of years. However, children and their parents may not like these daily injections and often stop treatment. A newer treatment is available that can be injected once weekly. This newer treatment increases growth the same as daily injections. We looked at whether 12 months of treatment given once a week has the same positive effects on the physical, social, and emotional health of children as the daily treatment. Children and their parents answered questions that asked how being short affects the physical, social, and emotional parts of their life. These questions were asked before starting treatment and 12 months after starting treatment. In children younger than 7 years old, improvements at 12 months in their physical, social, and emotional health were similar between the treatments. In children 7 years old or older, those who received the once-weekly injections had slightly better improvements than those who received the daily injections. These results can help parents and doctors make decisions about treating children with pediatric growth hormone deficiency.

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Health-related quality of life; long-acting growth hormone; pediatric growth hormone deficiency; QoLISSY; somatrogen; somatropin

Introduction

Pediatric growth hormone deficiency (pGHD) is caused by insufficient production or release of pituitary growth hormone and manifests as reduced age-related height velocity that limits growth from early to late childhood. In addition

to the physical outcome of short stature, pGHD may be associated with other metabolic alterations that potentially result in dyslipidemia, insulin resistance, and risk of cardiovascular disease¹. Although short stature has also been suggested to impact health-related quality of life (HRQoL), the evidence

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for an association between pGHD and poorer HRQoL relative to children with normal stature has been equivocal^{2,3}. However, some studies have shown that the presence of pGHD negatively impacts specific domains that contribute to HRQoL including emotional and social well-being^{2,4,5}.

Administration of daily subcutaneous injections of recombinant human growth hormone (r-hGH) has become the standard of care for treatment of children with pGHD. Such treatment promotes linear height velocity with additional physiologic benefits by maintaining normal blood glucose levels and a favorable lipid profile⁶. Studies have also reported that children treated with r-hGH achieve significant gains in HRQoL, especially in emotional and social domains^{7,8}. Furthermore, results from a recent real-world study of children and adolescents with pGHD who were treated with growth hormone suggested that generic HRQoL was high and generally similar to a healthy reference population⁵; the disease-specific HRQoL was also reported to be good. However, adherence to daily r-hGH varies and has been generally considered to be suboptimal^{9–11}. Several studies indicated decreased adherence with increasing treatment duration^{11–14}, and a systematic review reported that up to 71% of children may be non-adherent to prescribed treatment¹⁰. The practical implications of non-adherence were suggested in one study that observed significantly higher growth among the 34% of children who were treatment adherent relative to those who were non-adherent, defined as missing >1 injection/week¹⁵, and in other studies that showed adherence significantly correlated with height velocity and 1-year change in height standard deviation score^{12,16}.

Although a variety of factors have been suggested to be associated with suboptimal adherence including injection-associated pain/discomfort, sociodemographic variables, family dynamics, and insufficient knowledge/understanding of pGHD and the benefits of treatment, the inconvenience and burden of a daily injection regimen and its interference on the day to day activities of a patient and caregiver have consistently been found to be major challenges to maintaining optimal adherence^{11,17–21}. An evaluation of treatment preferences of children with pGHD and their parents/caregivers indicated a clear preference for a less frequent injection schedule²². Such a schedule may be expected to reduce the treatment burden, thereby enhancing patient adherence and satisfaction with treatment, as has been observed in the treatment of other chronic conditions²³, and potentially leading to improved outcomes including height gain.

Over more than a decade, long-acting formulations of r-hGH have been in development and some are now approved for use in many countries, with efficacy that is comparable to short-acting formulations²⁴. Somatogon is a r-hGH that was developed with carboxy terminal peptides to extend the half-life and allow a longer interval between doses²⁵. The pivotal clinical trial was powered for non-inferiority and found that once-weekly somatogon was as effective as once-daily somatropin for the primary endpoint of height velocity at 12 months, with both treatments having similar safety and tolerability profiles²⁶. To evaluate HRQoL following

12 months of once-weekly somatogon and once-daily somatropin treatment, the Quality of Life in Short Stature Youth (QoLISSY) questionnaire²⁷ was included in the trial as an exploratory endpoint, and these results are reported here. The QoLISSY, which was developed in accordance with US Food and Drug Administration guidance on patient-reported outcome measures (PROMs)²⁸, is a condition-specific PROM that assesses HRQoL in children with short stature.

Materials and methods

Study design and population

This was a phase 3, 12-month, open-label, randomized, non-inferiority study that compared the safety and efficacy of once-daily somatropin with once-weekly somatogon in pre-pubertal children with pGHD who were growth hormone-treatment naïve (ClinicalTrials.gov no. NCT02968004). The study was conducted between April 2017 and August 2019 in 21 countries. The protocol, informed consent forms, and other study-related documents were approved by the institutional review board or independent ethics committee at each of the participating investigational centers, and followed the ethical principles outlined in the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent from each child's parents/guardians and written assent from the pediatric subjects (where applicable based on age and country-specific regulations) were obtained prior to initiating any study-specific activity.

Details of the study design and inclusion/exclusion criteria have been previously reported²⁶, but in brief, the study population consisted of prepubertal children (boys 3–11 years old and girls 3–10 years old) diagnosed with isolated GHD or growth hormone insufficiency as part of multiple pituitary hormone deficiency who did not receive prior r-hGH therapy. Other inclusion criteria were peak plasma growth hormone ≤ 10 ng/ml confirmed by 2 tests; bone age $\leq$ chronological age and not older than 10 and 11 years for girls and boys, respectively; impaired height and height velocity; and baseline insulin-like growth factor 1 (IGF-1) at least 1 standard deviation (SD) below the mean level standardized for age and sex. A history of radiation therapy or chemotherapy was a reason for exclusion, as were psychosocial dwarfism or born small for gestational age; the presence of anti-hGH antibodies at screening; any clinically significant abnormality likely to affect growth or the ability to evaluate growth; and closed epiphyses. The included subjects were randomized to receive subcutaneous doses of somatogon (NgenlaTM) administered once weekly (0.66 mg/kg/week) or SC doses of somatropin (Genotropin®) administered once daily (0.24 mg/kg/week) for 12 months as previously described²⁶.

The current analysis reflects data from a targeted sample of participants ($N=117$) recruited from 8 countries (United States [$n=41$], Spain [$n=19$], UK [$n=3$], Belarus [$n=2$], Russia [$n=20$], Ukraine [$n=24$], Australia [$n=4$], and New Zealand [$n=4$]) who were invited to complete the QoLISSY for assessment of HRQoL.

Outcomes

Health-related quality of life was an exploratory endpoint that was measured using a pen and paper version of the condition-specific QoLISSY questionnaire, a validated PROM that can be used to assess the impact of short stature on children from the perspectives of both the subjects and their parents/caregivers^{27,29}. The QoLISSY has also been specifically validated for use in clinical trials of, and during clinical treatment with, human growth hormone³⁰. The core questionnaire consists of 22 items assigned to three subscales that reflect physical, social, and emotional domains. Responses are on a 5-point Likert scale (“not at all/never” to “extremely/always”), and the combined QoLISSY total score is calculated by adding the means of the core subscales and dividing by 3; higher scores are indicative of better HRQoL. Scores were transformed from raw scores to a 0 to 100 scale before performing the analyses. Although QoLISSY also assesses domains of “coping”, “beliefs” and “treatment” plus two additional domains for the QoLISSY-Parent (“future” and “effects on parent”), these are not used to derive the total score and were not administered in the current study.

The QoLISSY was translated into the specific languages required for this study in accordance with the principles for translation set forth by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)³¹. Children and parents/caregivers were administered the questionnaire at baseline and 12 months after initiation of treatment. Parents/caregivers completed the questionnaire for children <7 years old, and children ≥7 years old were encouraged to complete the version of the QoLISSY core questionnaire for children and adolescents (“QoLISSY-Child”) on their own. The QoLISSY-Parent was also completed by parents/caregivers for a proportion of the children aged ≥7 years.

Statistical analysis

Results are reported using descriptive statistics based on the full analysis set, defined as all randomized subjects who

received at least 1 dose of the study drug. Demographic and clinical characteristics of the populations are presented using means and standard deviations (SDs) for continuous variables and number and frequency for categorical variables. All QoLISSY values, including baseline and 12-months are presented as means with their estimated 95% confidence intervals (95% CI). Mean change from baseline was also reported along with the 95% CI's for total QoLISSY score and each of the domains. It should be noted that a hypothesis-based statistical analysis was not planned, since the QoLISSY questionnaire was included in the pivotal clinical trial as an exploratory endpoint. In addition, approximately 50% of recruited patients completed it, hence the small sample sizes limited the analyses which could be undertaken.

Results

Response and population characteristics

Data were available for all of the 117 subjects who were invited to respond to the QoLISSY questionnaire, including 47 children <7 years old (somatogon $n=19$, somatropin $n=28$) whose parents/caregivers completed the QoLISSY-Parent, and 70 children ($n=35$ in each treatment group) who completed the QoLISSY-Child. Additionally, 54 parents/caregivers of subjects ≥7 years old (somatogon $n=26$, somatropin $n=28$) completed the QoLISSY-Parent. In each age cohort, baseline demographic and clinical characteristics were similar in both treatment groups for subjects who completed the QoLISSY (Table 1); the populations were predominantly male (71.4–85.7%), white (88.6–94.7%), with mean ages of 5.2–5.3 years and 9.3–9.7 years in the younger and older cohorts, respectively.

Quality of life

Results for children <7 years old

Among the children <7 years old, QoLISSY-Parent total scores showed that in both treatment groups, parents/

Table 1. Baseline demographic and clinical characteristics.

Variable	<7 years old		≥7 years old	
	Somatogon $n=19$	Somatropin $n=28$	Somatogon $n=35$	Somatropin $n=35$
Age, years	5.2 (1.2)	5.3 (1.0)	9.7 (1.5)	9.3 (1.4)
Sex, n (%)				
Male	16 (84.2)	24 (85.7)	28 (80.0)	25 (71.4)
Female	3 (15.8)	4 (14.3)	7 (20.0)	10 (28.6)
Race, n (%)				
White	18 (94.7)	27 (96.4)	32 (91.4)	31 (88.6)
Black or African-American	0	0	0	2 (5.7)
Asian	1 (5.3)	1 (3.6)	3 (8.6)	0
Other	0	0	0	2 (5.8)
Height	97.4 (8.0)	99.1 (6.4)	120.9 (10.1)	119.1 (8.2)
Weight	14.6 (2.9)	15.3 (2.0)	23.6 (5.6)	22.6 (4.5)
BMI	15.3 (1.9)	15.6 (1.4)	15.9 (1.9)	15.8 (1.6)
Height SDS	−2.8 (0.8)	−2.6 (0.7)	−2.7 (0.9)	−2.7 (0.7)
BMI SDS	−0.1 (1.0)	0.2 (0.9)	−0.5 (0.9)	−0.3 (0.8)
Peak GH, ng/dL	5.9 (2.6)	5.9 (2.3)	6.0 (2.7)	5.6 (2.7)
Bone age, years	3.0 (1.1)	3.1 (1.0)	7.0 (2.5)	6.7 (2.2)
Bone maturation	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	0.7 (0.2)

Data are mean (SD), unless otherwise indicated.

Abbreviations. BMI, body mass index; GH, growth hormone; SD, standard deviation; SDS, standard deviation score.

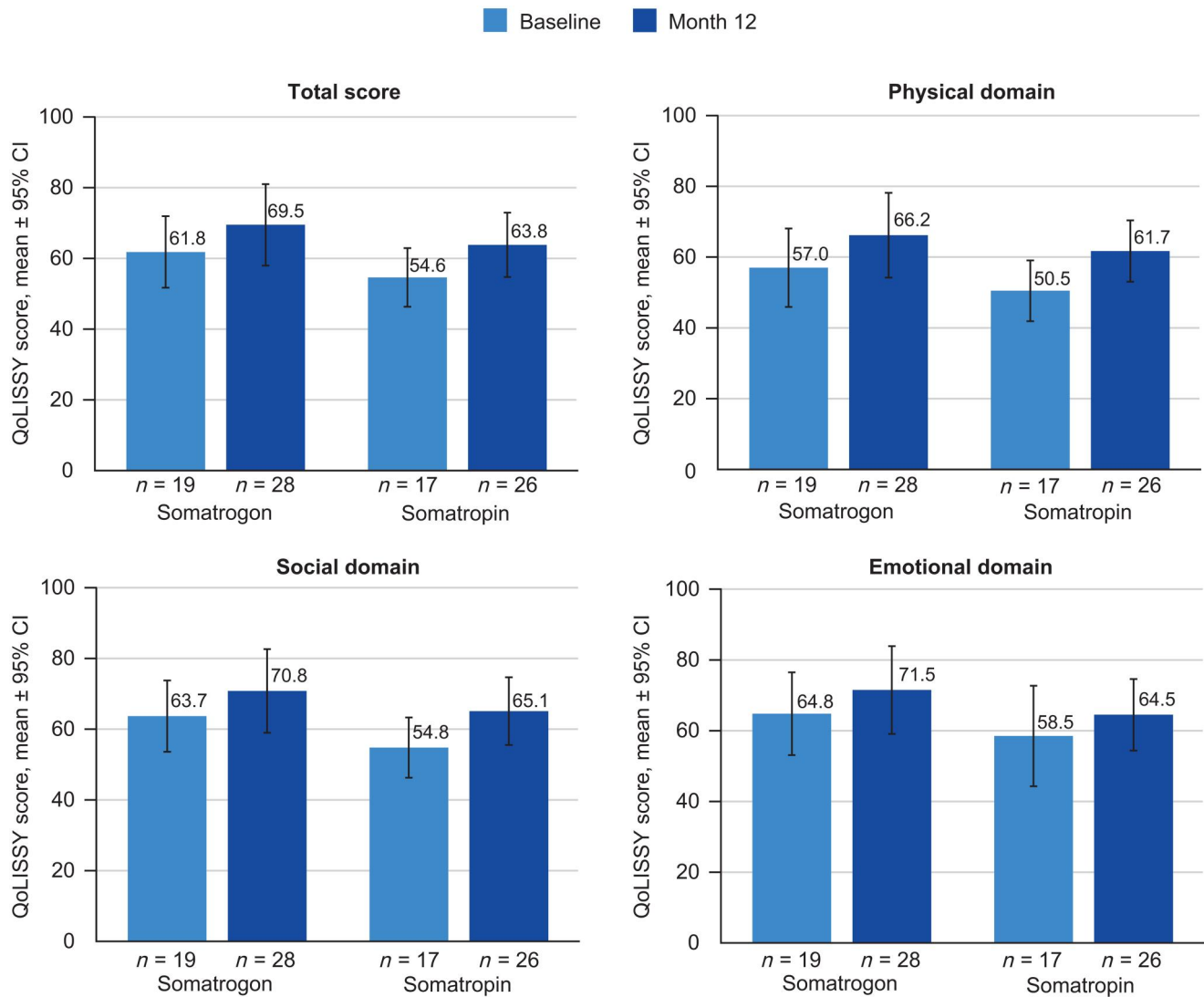


Figure 1. Baseline and 12-month QoLISSY-Parent scores for subjects <7 years old. Abbreviations. CI, confidence interval; QoLISSY, Quality of Life in Short Stature Youth.

caregivers reported higher scores (i.e. better HRQoL) after 12 months of treatment than at baseline (Figure 1). Higher scores at 12 months relative to baseline were also reported on the physical, social, and emotional subscales (Figure 1), suggesting improvement in these domains after treatment. The mean (95% CI) change from baseline in QoLISSY-Parent total score for children treated with somatrogen, 8.5 (1.1, 15.9), was comparable to that of somatropin, 8.5 (2.3, 14.7) (Figure 2). Mean changes from baseline were also similar between treatment groups on all subscales, and the greatest improvement was reported for the physical domain (Figure 2).

Results for children ≥ 7 years old

Children ≥ 7 years old in both treatment groups self-reported scores on the QoLISSY-Child that were higher at 12 months than at baseline for total score and on all subscales (Figure 3). The available QoLISSY-Parent scores that were reported by parents/caregivers for these children were also higher at the 12-month timepoint than at baseline in both treatment

groups (Figure 4). However, all scores reported by the children at the two timepoints were consistently higher than those reported by their parents/caregivers, suggesting that the children report HRQoL that is incrementally better than perceived by their parents/caregivers.

The mean (95% CI) changes from baseline in total score showed improvement in both treatment groups and was numerically higher among children treated with somatrogen (13.0 [5.8, 20.2]) relative to somatropin (7.8 [2.7, 13.0]) (Figure 5(a)). These changes were of comparable magnitude to those assessed on the QoLISSY-Parent (13.0 [4.0, 22.0] and 6.6 [-0.2, 13.4] for somatrogen and somatropin, respectively) (Figure 5(b)). A similar pattern of numerically higher changes from baseline with somatrogen relative to somatropin were observed on each of the subscales, and the changes with somatrogen were comparable for QoLISSY-Child and QoLISSY-Parent. However, for somatropin, parents/caregivers appeared to underestimate improvements on the physical and emotional domains relative to the children's perspective, and overestimate improvement on the social domain (Figure 5). The largest change from baseline in children treated with somatrogen was

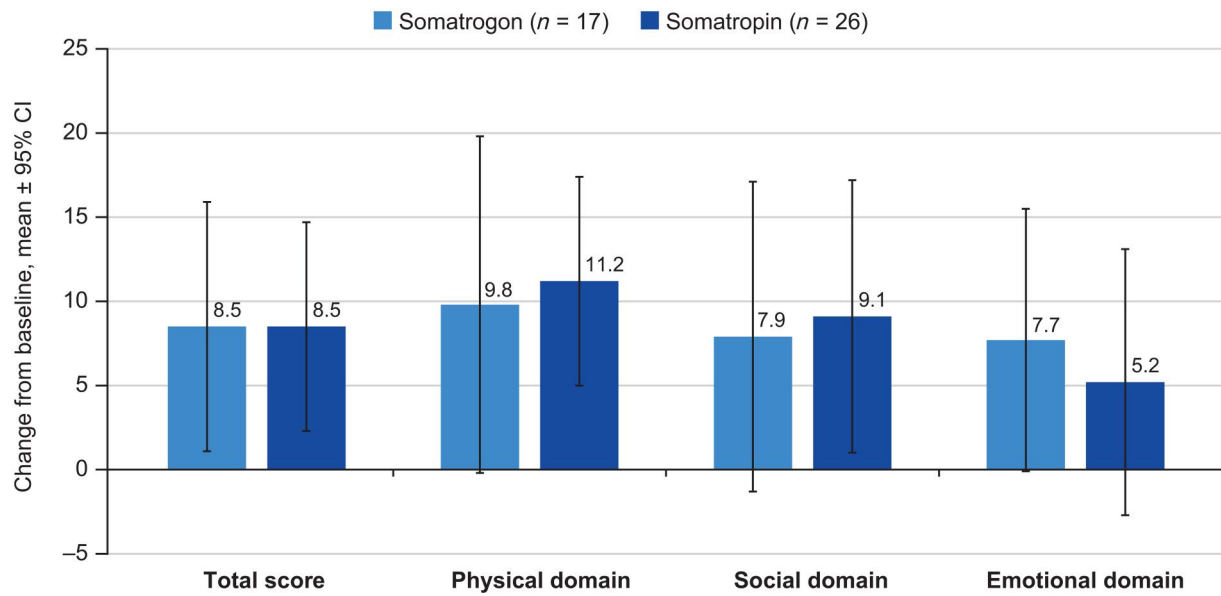


Figure 2. Change from baseline at month 12 in QoLISSY-Parent scores for subjects <7 years old. Abbreviations. CI, confidence interval; QoLISSY, Quality of Life in Short Stature Youth.

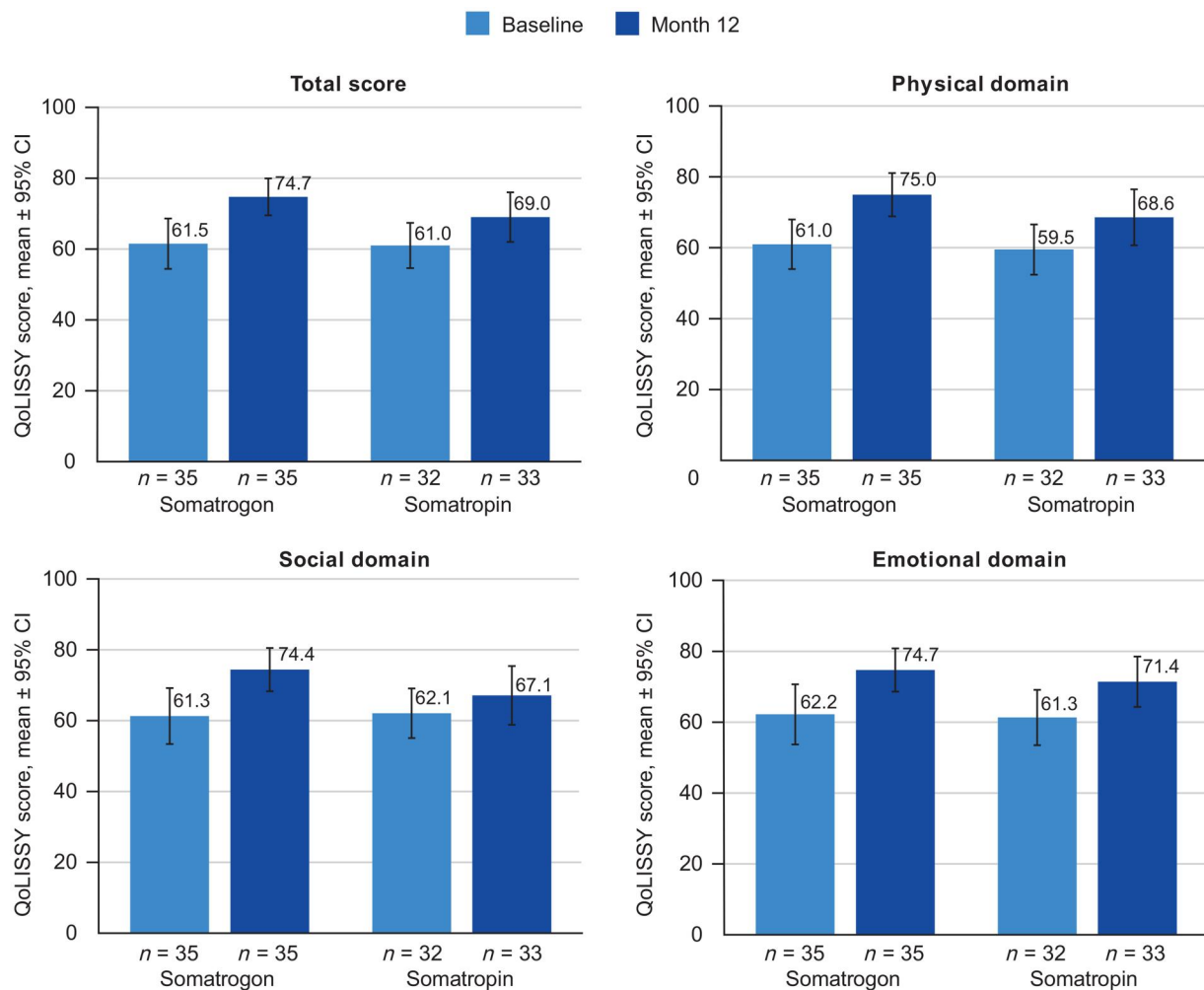


Figure 3. Self-reported baseline and 12-month QoLISSY-Child scores among subjects ≥7 years old. Abbreviations. CI, confidence interval; QoLISSY, Quality of Life in Short Stature Youth.

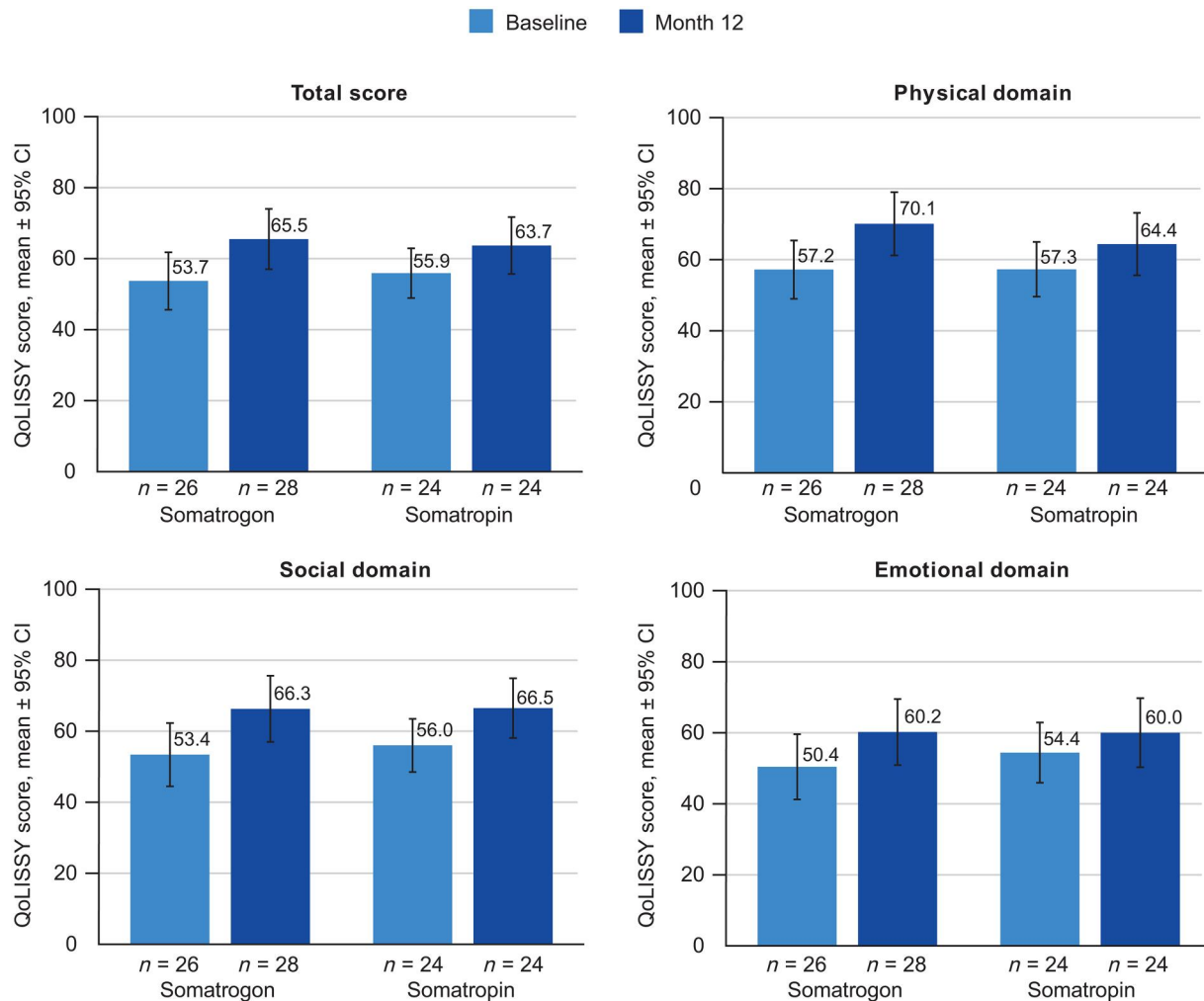


Figure 4. Parent/caregiver-reported baseline and 12-month QoLISSY-Parent scores among subjects ≥ 7 years old. Abbreviations. CI, confidence interval; QoLISSY, Quality of Life in Short Stature Youth.

on the physical subscale for both QoLISSY-Child (14.5; 95% CI 7.1, 21.8) and QoLISSY-Parent (14.9; 95% CI 6.0, 23.9), and the largest changes with somatropin treatment were on the emotional subscale for QoLISSY-Child and social subscale for QoLISSY-Parent (Figure 5).

Discussion

The observed improvements in HRQoL in this analysis extend the results of a clinical trial that showed comparable efficacy between once-weekly somatrogen and once daily somatropin for increasing height velocity at 12 months in prepubertal children with pGHD²⁶. When evaluating HRQoL in interventional studies, the responsiveness (i.e. ability to detect change) of the instrument used to measure HRQoL is an important characteristic. The psychometric properties of the QoLISSY questionnaire were demonstrated in cross-sectional studies and its use in randomized, open label, comparator trials during active growth-promoting therapy administration have also confirmed its validity^{32–34}. Accordingly, the QoLISSY is a useful measure to track HRQoL changes over time in clinical studies.

The clinical improvements previously described were, as expected, paralleled by gains in HRQoL from the perspectives

of both the children and their parents/caregivers among the subjects >7 years old and increases in HRQoL reported by parents/caregivers of children <7 years old. All improvements were reflected not only by the increase in QoLISSY total score at the 12-month assessment, but also in the scores for the physical, social, and emotional domains that contribute to HRQoL. These improvements were generally consistent with other studies that also demonstrated better HRQoL among children after 12 months of treatment with r-hGH relative to baseline^{7,8}. However, one of those studies reported no change in the physical domain⁷, and this contrast with the current analysis may relate to differences in the populations including a wider age range and more heterogeneous diagnoses in that study. The total QoLISSY and domain scores were also consistent with those reported in the real-world study⁵, albeit the treatment period varied over the evaluated population and had a longer treatment duration (mean [SD]) of 4.4 [3.3] years than the current study.

As the clinical trial was powered for non-inferiority between the two treatments for the primary endpoint, the gain in HRQoL would also be expected to be comparable between somatrogen and somatropin. Such comparability was more clearly observed among the children <7 years old

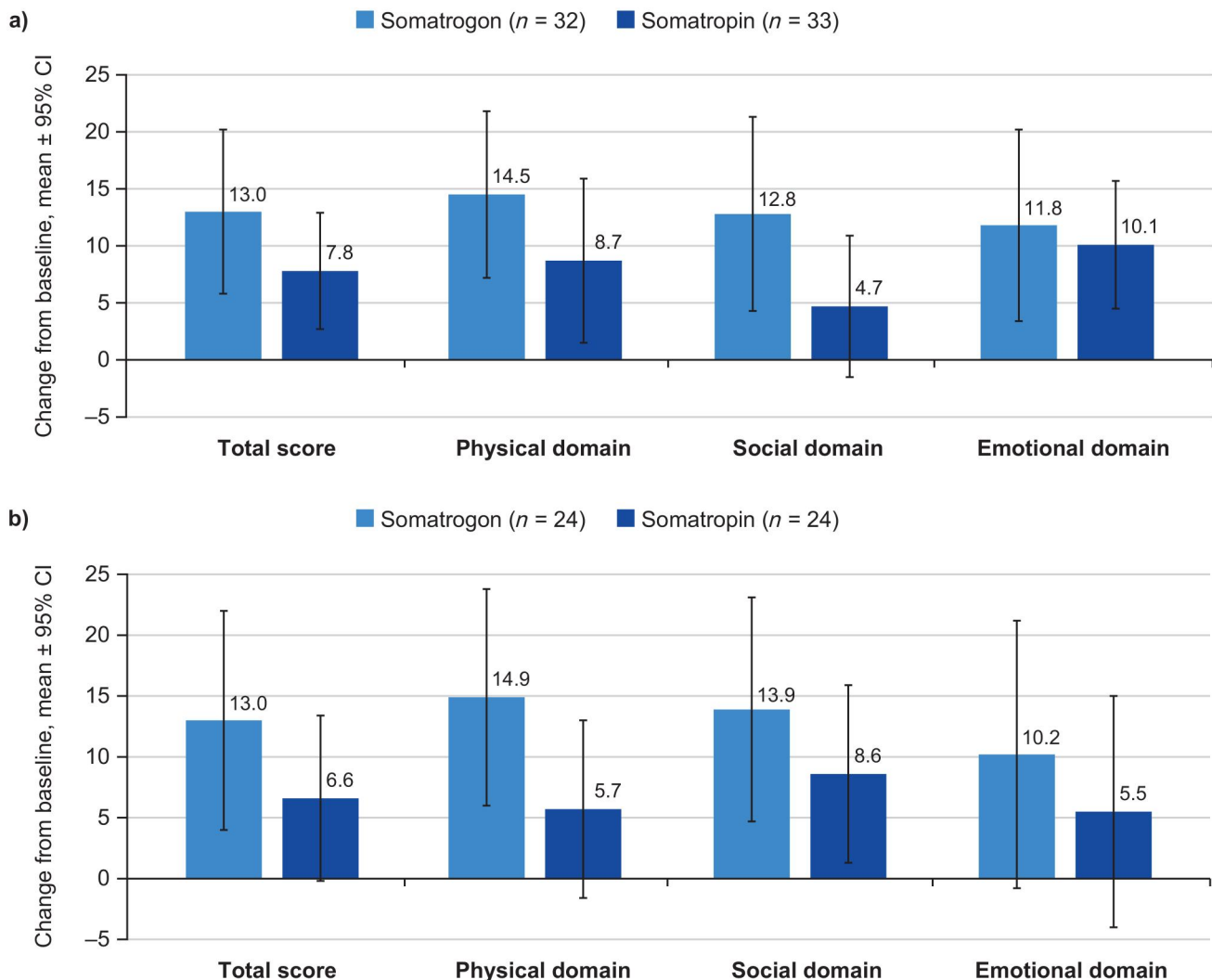


Figure 5. Change from baseline at month 12 in QoLISSY scores for subjects ≥ 7 years old. (a) Subject self-report on QoLISSY-Child. (b) Parent/caregiver report on QoLISSY-Parent. Abbreviations. CI, confidence interval; QoLISSY, Quality of Life in Short Stature Youth.

than among those ≥ 7 years old. In the older group, the changes from baseline in any of the QoLISSY scores were comparable between the two treatment groups, but the magnitude of the change in scores was consistently numerically higher with somatrogon regardless of whether assessed by the children themselves or their parents/caregivers.

It is important to not only acknowledge the improvement in HRQoL from the QoLISSY data in this population, but to place these results within the context provided by a separate phase 3 clinical trial that compared the treatment burden of a once-weekly injection schedule with that of a once-daily injection schedule³⁵. That study, which evaluated several endpoints specifically related to the impact of the injection schedule including on life interference, demonstrated that once-weekly somatrogon was associated with significantly lower interference with life activities (i.e. daily activities, social activities, recreation/leisure activities, travel, spending the night away from home, making changes to life routine and bother from injections) compared with somatropin. Patient preference and intention to adhere to therapy also favored somatrogon over somatropin³⁵. Taken together with

results of the current study, the overall clinical relevance is that the reduced treatment burden represented by weekly dosing may potentially lead to greater adherence to therapy, thus maintaining not only the clinical benefits associated with somatrogon treatment but also improvements in HRQoL. These outcomes are important to patients in the medium and longer term, as growth hormone therapy may be prescribed for a number of years to treat pGHD.

Improvements in HRQoL by end of month 12 were demonstrated from the perspective of both the children and their parents/caregivers. However, the baseline and 12-month scores in both treatment groups were numerically lower when reported by the parents/caregivers than those self-reported by the children. This discordance is consistent with the literature in which the parents/caregivers reported lower QoLISSY scores on behalf of the child³⁶. A similar pattern of discrepancy between child self-report and parent proxy report of HRQoL has been recognized in children/adolescents with chronic health conditions, most often in the social and emotional domains³⁷, which also appear to be domains that are especially affected in children with pGHD^{2,4}. The

difference in perspectives may reflect on one hand, the children's tendency to emphasize the positive aspects of adaptation, especially with treatment, and on the other hand, the parents' reliability in identifying the most strongly affected areas of their child's functioning. Nevertheless, these results highlight the importance of regularly evaluating HRQoL in children being treated for pGHD, which can provide a more holistic approach to evaluating the effects of treatment on the lives of children with this condition and may facilitate treatment decisions during long-term therapy.

Limitations

An important limitation of this analysis is that since it relied on a clinical trial population and collected HRQoL data from only approximately 50% of the enrolled patients, the results may not necessarily be generalizable to the real-world setting. Additionally, a larger sample size would have enabled formal statistical comparison that could have resulted in more robust inferences, but there was minimal missingness of responses despite the small sample size. Although use of a condition-specific measure of HRQoL may be considered a strength of this study, it should also be noted that the change in QoLISSY score that represents a clinically meaningful change has not been determined. Thus, the relevance of the observed changes in each treatment arm is not known, representing a further limitation. Future studies using QoLISSY should also include an appropriate anchor PROM (e.g. Patient Global Impression of Change) that can enable estimation of the clinically meaningful within-patient change^{38,39}. As mentioned previously, the lower burden associated with weekly dosing may be expected to result in greater adherence to therapy, thus maintaining the clinical benefits that are likely to be associated with the observed improvements in HRQoL. In this regard, the lack of long-term data represents another limitation, as children with pGHD require treatment that extends beyond 12 months. Therefore, it can be recommended that HRQoL data be collected at regular intervals over the treatment duration. A final limitation is that due to study constraints, not all QoLISSY modules were administered; QoLISSY includes modules on the impact of treatment on daily function and on parent/caregiver burden, which has been recently recognized as a component of the treatment and care of children with pGHD⁴⁰. Administration of these modules in future studies can provide a more comprehensive understanding of HRQoL in patients and their families.

Conclusion

In this cohort of children with pGHD and their parents/caregivers, comparable improvements in HRQoL as measured on QoLISSY-Child and QoLISSY-Parent, respectively, were reported by the end of Month 12 for children who received once-weekly somatogon or once-daily somatropin treatment. These results parallel demonstration of non-inferiority of somatogon for the clinical trial primary efficacy endpoint of height velocity at 12 months, suggesting that increased

growth also likely results in better HRQoL. Thus, the reduced administration burden of somatogon may be expected to result in higher adherence with treatment and provide benefits in clinical and patient-reported outcomes that are comparable to somatropin. Assessment of HRQoL in clinical practice during treatment with growth hormone to identify positive and negative aspects from the perspectives of patients and caregivers further enhances the patient-centric approach to evaluating treatment effects and can help support decisions for managing pGHD in this pediatric population, which in turn are important for improving treatment adherence.

Transparency

Declaration of funding

This study was sponsored by OPKO Health and Pfizer Inc.

Declaration of financial/other relationships

Jane Loftus and Srinivas Rao Valluri are employees and stockholders of Pfizer Inc. Julia Quitmann is involved in an ongoing QoLISSY-related study that is funded by Pfizer.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors participated in the interpretation and analysis of the study data, and in the drafting, critical revision, and approval of the final version of the manuscript.

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Data availability statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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