Safety and efficacy of weekly somapacitan for growth hormone deficiency in children

A 72-week observational study

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ABSTRACT

الأهداف: في هذه الدراسة سوف نقيم مدى فعالية و سلامة استخدام هرمون النمو الأسبوعي للأطفال كعلاج جديد واعد لتحسين مدى التزام المصابين بنقص هرمون النمو من الأطفال بالعلاج .

المنهجية: هذه دراسة قائمة على الملاحظة تشمل 184 طفل مصاب بنقص هرمون النمو يزورون عيادة الغدد الصماء للأطفال في مستشفى جامعة الملك عبد العزيز بجدة، حيث استمرت على مدار 72 أسبوعا تلقى فيها المرضى على علاج هرمون النمو الأسبوعي ابتدأت بجرعة أولية تعادل 0.16 مغ/كغ ومن ثم معايرة الجرعة استنادا الى تحليل معامل هرمون النمو (IGF-1).

النتائج: متوسط أعمار الأطفال المشاركين في البحث 10.1 سنة تضمنت 67.4% بالمئة منهم ذكور، لوحظ خلال هذه الدراسة تحسن في تسارع الطوال بالإضافة الى معامل هرمون النمو خاصة في الأسبوع 72 من البحث، هرمون النمو الأسبوعي أظهر فعالية وتقبل المرضى مع وجود أعراض جانبية خفيفة.

الخلاصة: علاج هرمون النمو الأسبوعي آمن وذو فعالية عند استخدامه لنقص هرمون النمو في الأطفال.

Objectives: To assess the effectiveness and safety of somapacitan, a long-acting growth hormone analog, as a promising treatment to improve adherence in pediatric growth hormone deficiency (GHD) management.

Methods: The observational study included 184 children diagnosed with GHD. Carried out over 72 weeks at the Pediatric Endocrinology Outpatient Clinic in collaboration with King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Patients received weekly somapacitan doses, starting at 0.16 mg/kg and adjusted according to insulin-like growth factor 1 (IGF-1) levels. Key outcomes included changes in height velocity and IGF-1 levels, with statistical significance set at a *p*-value of <0.05.

Results: The cohort, with an average age of 10.1 years and 67.4% male, showed substantial improvements by week 72: IGF-1 levels increased from 166.97 to 363.74, and height velocity gains were most pronounced in children at Tanner Stage 1. Treatment-naive children exhibited greater initial height velocity improvements compared to those switching from daily GH therapy, although these differences leveled over time. Somapacitan was well-tolerated, with minimal side effects, supporting its long-term safety.

Conclusion: Weekly somapacitan offers an effective, safe pediatric GHD treatment, with individualized dosing based on IGF-1 levels. Routine IGF-1 monitoring is advised to maximize benefits and minimize risks. Further studies on diverse populations are recommended to validate these findings in pediatric endocrinology.

Keywords: growth hormone, children, weekly, effectiveness, safety

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Growth hormone deficiency (GHD) results in short stature in children due to the anterior pituitary gland's insufficient growth hormone (GH) production. This condition requires early diagnosis and effective treatment to prevent long-term complications such as persistent short stature, metabolic issues, and reduced quality of life that impact both physical and emotional well-being.[1] Addressing these challenges emphasizes the need for practical and manageable treatment options

to support optimal outcomes in children affected by GHD.

Since recombinant human GH (rhGH) therapy was introduced in 1985, the standard treatment for pediatric GHD has involved daily injections. Although effective in promoting growth and improving metabolic health, the daily injection regimen presents challenges that may hinder treatment success.[2] Children often experience discomfort and distress from frequent injections, and the daily scheduling can be challenging to maintain, particularly with the demands of everyday routines or travel.[3,4] Additionally, the psychological strain of adhering to a daily injection schedule impacts not only the children but also their families, frequently leading to reduced adherence and subsequently affecting the treatment's effectiveness.

Reducing the frequency of injections can alleviate these challenges, ultimately improving adherence and growth outcomes. Somapacitan, a long-acting humanized GH analog requiring only weekly administration, presents a promising alternative. Recently approved for pediatric GHD, somapacitan has demonstrated efficacy in increasing growth rates while maintaining therapeutic levels of insulin-like growth factor-1 (IGF-1), an important marker for GH therapy effectiveness.[5,6] Its sustained-release mechanism supports continuous metabolic and growth benefits with fewer injections than the daily therapy regimen.[7] This study aims to evaluate the advantages of weekly somapacitan, particularly regarding adherence, safety, and efficacy for children managing GHD.

Methods. This 72-week observational cohort study was carried out at the Pediatric Endocrinology Outpatient Clinic in collaboration with King Abdulaziz University Hospital in Jeddah, Saudi Arabia, from February 2023 until August 2024. The study aimed to evaluate the efficacy and safety of somapacitan, a long-acting rhGH, in 184 pediatric patients diagnosed with GHD. Patient selection and study design were carefully structured to ensure the results would be generalizable to pediatric GHD management.

Children aged 2-18 years with confirmed GHD were eligible, including those new to GH therapy (treatment-naive) and those switching from daily GH injections to weekly somapacitan (switch group). Exclusion criteria were defined to ensure reliable follow-up. They included children with genetic syndromes, active cancer, severe renal impairment, closed growth plates, recent major surgery or trauma, uncontrolled diabetes (hemoglobin A1C [HbA1c] of >9%), obesity (body mass index of >30 kg/m^2), respiratory conditions, GH hypersensitivity, or an elevated risk of intracranial pressure.

The study was approved by the institutional review board at King Abdulaziz University, Jeddah, Saudi Arabia (reference: 253-24) and adhered to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all participants or their legal guardians.

The diagnosis of GHD was established thorough clinical assessments and biochemical testing. Criteria for diagnosis included a height that was more than 2 standard deviations (SDs) below the mean for age, growth velocity in the lowest 25th percentile or a noticeable decline over the past year, and GH levels of 10 ng/mL or lower in 2 stimulation tests (glucagon and clonidine). Additionally, IGF-1 levels below age norms and signs of delayed bone maturation further supported the diagnosis. These criteria were rigorously applied to all patients, ensuring diagnostic accuracy throughout the study.

Participants received weekly subcutaneous injections marketed under the brand name Sogroya. Somapacitan, a once-weekly GH therapy developed and manufactured by Novo Nordisk A/S in Bagsværd, Denmark, starts at 0.16 mg/kg. The dose of weekly somapacitan therapy is adjusted based on growth velocity and IGF-1 levels to optimize efficacy and ensure safety. If growth is inadequate and IGF-1 is below target, the dose is increased by 10-20%, while elevated IGF-1 levels (±2 SD) or adverse effects warrant a similar dose reduction. Adjustments occur every 12 weeks, with stable doses maintained once growth and IGF-1 normalize.

Efficacy was evaluated by tracking height velocity (HV) and IGF-1 levels. Follow-up measurements occurred at 12, 24, 36, 48, 52, and 72 weeks. Height velocity was measured with standardized stadiometers, while IGF-1 levels were assessed 96 hours post-injection every 12 weeks. Height velocity was used as a key indicator of treatment effectiveness, with IGF-1 levels measuring GH's biological activity.

Several critical variables were monitored throughout the study to ensure comprehensive assessment and analysis. Mid-parental height (MPH) was estimated based on the parents' heights to predict the genetic growth potential of the children involved. Bone age was assessed annually through X-rays, which were

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compared with standardized references to evaluate growth progression. Pubertal maturation was evaluated using Tanner staging at each follow-up visit, providing insight into developmental milestones. Additionally, glucose metabolism was monitored by measuring fasting glucose and HbA1c levels every 6 months to assess any metabolic impacts. Thyroid function was also a key focus, with thyroid stimulating hormone and free T4 levels assessed at baseline and every 6 months to detect any potential GH-related hypothyroidism. Lastly, serum IGF-1 levels were monitored regularly to ensure they remained within the therapeutic range, facilitating effective management of the treatment regimen.

Adherence to the prescribed treatment regimen was systematically tracked using patient and caregiver logs, which were cross-referenced with prescription records to verify medication usage and ensure data accuracy. During the study, adverse medical events were classified and coded following the Medical Dictionary for Regulatory Activities guidelines. This approach ensured consistency in identifying, reporting, and analyzing safety-related events, adhering to standardized protocols for regulatory compliance, and enabling reliable safety monitoring throughout the study.

Statistical analysis. Data analysis was carried out using the Statistical Package for the Social Sciences statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarized categorical and continuous variables, and normality was assessed using the Shapiro-Wilk test. Categorical data were analyzed with Chi-square tests, while nonparametric data were evaluated using Mann-Whitney U tests. Multivariate logistic regression was used to identify significant predictors, with statistical significance set at a *p*-value of <0.05.

Results. The study enrolled 184 children aged 2-18 with a mean age of 10.14±3.01 years. The study population included 67% (n=124) males and 32% (n=60) females. Most patients were at Tanner stage 1 (75%, n=138). Stage 2 accounted for 19% (n=36), followed by stage 3 with 4% (n=9) and stage 4 with 1% (n=2). Baseline measurements revealed an average height of 127.92±17.69 cm and a mean weight of 29.42±13.26 kg. The MPH averaged 165.02±13.74 cm. Naïve comprised 72% (n=132), while 28% (n=52) were categorized as switching from a previous daily GH therapy regimen.

Height Velocity showed a positive response to somapacitan treatment. After 12 weeks of therapy, the average HV was 8.91±5.16 cm/year. By the end of the 72-week period, it was 8.03±3.21 cm/year. Boys had a marginally higher HV during the first 12 weeks (8.96 cm/year compared to 8.82 cm/year for girls), but by 72 weeks, HV had leveled out, with both genders showing similar results (boys: 7.88 cm/year, girls: 7.83 cm/year; **Table 1 & Figure 1**). Statistical analysis showed no significant gender-based differences in HV at any time point (*p*-values ranged from 0.499-0.831).

Patients who were new to somapacitan treatment (the naive group) initially showed significantly higher HV (p=0.018) compared to those switching from daily injections (the switch group, p=0.010), especially in the first 24 weeks. However, these differences evened out by 36 weeks and beyond, indicating similar long-term efficacy for both groups (**Table 2**).

As measured by HV, GH therapy response varied across Tanner stages. At the 12-week mark, Tanner stage 1 patients had the highest HV (9.39 cm/year), followed by stage 2 (8.20 cm/year), stage 4 (7.40 cm/year), and stage 3 (6.15 cm/year). By the end of the study, Tanner stage 1 patients continued to show the best response, with an HV of 10.50 cm/year, whereas stage 4 patients recorded the lowest HV (5.00 cm/year). This indicates that GH therapy is most effective in the earlier Tanner stages, tapering off as puberty progresses.

Most patients (96.6%) remained on the initial 0.16 mg/kg dose at the 12-week follow-up, with a mean HV of 8.94 cm/year. By 72 weeks, 22.2% of patients required dose increases, up to 0.24 mg/kg, to maintain

Table 1 - Height velocity by gender across various intervals in patients receiving somapacitan therapy.

Intervals	Female	Male	*P*-values
12 weeks	8.82±5.23	8.96±5.15	0.800
24 weeks	8.05±3.95	8.58±3.72	0.499
36 weeks	8.91±3.65	8.73±2.56	0.831
72 weeks	7.83±5.80	7.88±1.73	0.603

Values are presented as mean ± standard deviation (SD).

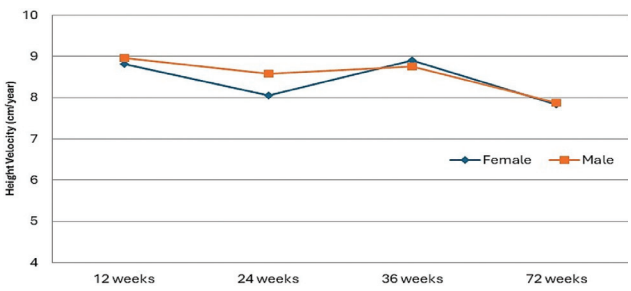

Figure 1 - Comparison of height velocity measurements by gender across sequential time intervals in patients receiving weekly somapacitan therapy.

Table 2 - Height velocity comparison between naive and switched patients across different intervals.

Intervals	Naive	Switched	*P*-values
12 weeks	9.52±5.18	7.64±4.95	0.018
24 weeks	9.06±3.84	7.33±3.47	0.010
36 weeks	8.76±3.09	8.88±2.78	0.950
72 weeks	8.33±3.45	7.00±2.83	0.883

Values are presented as mean ± standard deviation (SD).

growth rates. These findings suggested that the majority responded well to the initial dose, with only a minority needing adjustments to sustain growth.

Insulin-like growth factor-1 levels steadily increased throughout the study, rising from 166.97±94.39 ng/mL at baseline to 363.74±80.06 ng/mL by 72 weeks. The treatment-naive and switch groups experienced similar increases, highlighting somapacitan's efficacy in maintaining therapeutic IGF-1 levels across different patient types. Table 3 and Figure 2 show detailed data for IGF-1 changes at each follow-up point.

Out of 184 patients, 9 (4.89%) reported adverse events, with the most common being gastrointestinal discomfort (namely, emesis) in 4 (2.17%) patients. A total of 3 (1.63%) patients experienced localized allergic reactions; one allergic reaction manifested as evidenced by periorbital swelling, and one reported musculoskeletal pain and headaches (0.54%). Additionally, 3 cases of moderate lipoatrophy, which was not previously linked to somapacitan, were observed. No severe or life-threatening events occurred, indicating that somapacitan was tolerated well.

Adherence was impressive, with an overall rate of 99.58%. The treatment-naive group had a 99.43% adherence rate, whereas the switch group reached an even higher 99.92%. This high level of adherence underscores weekly somapacitan therapy's practicality and acceptance among pediatric patients and their caregivers.

Discussion. This study contributes to the growing evidence supporting the efficacy and safety of weekly somapacitan therapy for pediatric GHD. The predominance of male patients (67.4%) is consistent with international data showing a higher incidence of GHD among boys. Some studies, however, attribute this disparity to factors such as diagnosis rates or genetic predispositions rather than physiological differences.[8,9] The mean age of 10.14 years aligns with typical ages for GHD diagnosis, underscoring the importance of early intervention, particularly in younger children or those with delayed puberty, to optimize growth outcomes.[10,11]

Table 3 - Changes in insulin-like growth factor-1 levels between treatment-naive patients and patients switched from daily growth hormone therapy over specified intervals.

Time	Naive	Switched
Baseline	152.82±70.62	202.86±131.62
12 weeks	277.71±106.25	306.45±117.40
24 weeks	276.44±111.61	332.59±135.89
36 weeks	300.01±94.57	348.46±129.67
72 weeks	405.26±60.13	456.85±17.32

Values are presented as mean ± standard deviation (SD).

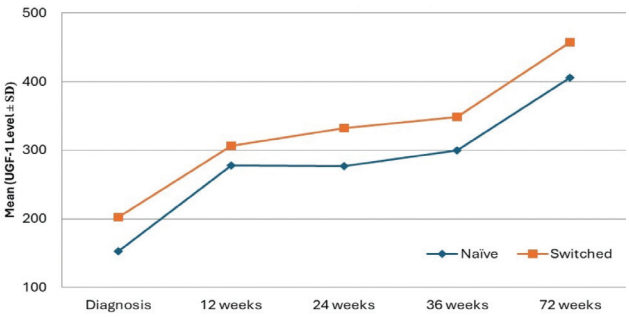

Figure 2 - Longitudinal changes in serum insulin-like growth factor-1 levels over 72 weeks for treatment-naive patients compared to patients switched from daily growth hormone therapy.

Height velocity increased significantly with somapacitan therapy, particularly in treatment-naive patients who exhibited a pronounced response during the initial 24 weeks. This early HV surge aligns with other studies that report heightened GH sensitivity in newly treated patients.[12,13] By the 72-week mark, however, differences between treatment-naive and switched patients diminished, indicating comparable long-term efficacy across groups. Additionally, serum IGF-1 levels rose consistently in both patient groups, confirming somapacitan's biological activity and sustained efficacy.[12,14]

Somapacitan's safety profile was favorable, with only mild to moderate adverse events reported, such as gastrointestinal discomfort and localized allergic reactions. Although not commonly associated with somapacitan, cases of lipoatrophy were moderate rather than severe, warranting further study to understand this side effect better.[15] High adherence rates, with 99.58% of doses administered as prescribed, suggest that weekly dosing schedules enhance treatment compliance compared to daily injections, alleviating the treatment burden on patients and caregivers.[16]

Study limitations. The observational design and relatively short follow-up period limit the study's capacity to capture long-term outcomes and rare side

effects. Future research should incorporate randomized controlled trials with extended follow-up periods to strengthen these findings.

In conclusion, weekly somapacitan offers a practical and effective alternative to daily GH injections. Early intervention may maximize growth potential, particularly in the earlier Tanner stages. Individualized dosing based on IGF-1 levels is essential to optimize results, and ongoing monitoring of side effects, including lipoatrophy, is crucial to ensure long-term safety. The observed high adherence rates highlight the benefits of a weekly dosing regimen in reducing the physical and emotional burden of daily injections, ultimately improving the quality of life for patients. Although the study provides valuable insights, the single-center, observational design limits the generalizability of the findings. Furthermore, reliance on self-reported adherence data introduces potential bias. Future studies should aim for multi-center trials with diverse populations to explore somapacitan's long-term efficacy and safety further. Despite these limitations, our results suggest that somapacitan is a promising option for managing pediatric GHD, particularly in enhancing treatment adherence and growth outcomes.

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