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Patients with Growth-Related Disorders and Caregivers Prefer the Somapacitan Device to the Somatrogon Device: Results from a Randomized Crossover Study Assessing Device Preference and Ease of Use Following Simulated Injections

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Purpose: Adherence to growth hormone treatment is known to affect growth outcomes. Both device preference and ease of use have been shown to affect treatment adherence. In this study, we assessed device preference and ease of use with two long-acting growth hormones, somapacitan (Sogroya®, Novo Nordisk A/S) and somatrogon (Ngenla®, Pfizer).

Patients and Methods: In a randomized, crossover study conducted between September 20 and November 2, 2023, we recruited 33 adolescents with a growth-related disorder, and 37 caregivers, at six locations in the United States. Each participant was trained in the use of both devices and asked to perform a simulated injection. Device training time, preparation and injection time, and injection completeness were recorded. Participants also completed the Device Handling and Preference Questionnaire (DHPAQ) to indicate their device preference and ease of use opinions. Following conclusion of the "standard" visit, 10 adolescents and 10 caregivers were randomly selected to participate in a sub-study to validate the relevance, comprehensiveness, and comprehension of the DHPAQ.

Results: The majority of participants (84.3%; 95% confidence interval [CI]: 74;92) preferred the somapacitan device to the somatrogon device ($p < 0.0001$). Almost all (98.6%; 95% CI: 92;100) participants answered that the somapacitan device was easy or very easy to use, while three-quarters (74.3%; 95% CI: 62;84) answered the same for the somatrogon device. Average training and injection times were lower for the somapacitan device than for the somatrogon device. Also, more patients successfully completed the injection with the somapacitan device than with the somatrogon device (97.1% vs 92.9%). Cognitive debriefing interviews indicated the DHPAQ was relevant, comprehensive, and fully comprehended.

Conclusion: The somapacitan device was preferred to the somatrogon device by a majority of participants. More participants considered the somapacitan device to be easy or very easy to use than the somatrogon device.

Plain Language Summary:

- Children who grow slower in height than their peers often need growth hormone replacement treatment to reach normal height. This treatment involves daily or weekly injections for several years. Injecting treatment regularly is important for it to work properly, but the schedule can be difficult to adhere to.
- From previous research, we know injection devices can influence adherence to treatment. Researchers in this study aimed to compare two different pen injectors (once-weekly medicines called somapacitan and somatrogon) to see which one patients and caregivers prefer and find easier to use.

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• This USA-based study included 33 adolescents with growth problems who injected themselves, and 37 caregivers of younger patients. During one visit, they were trained in how to use each device, observed giving a practice injection, and asked to fill in a questionnaire with their experience. Half of the participants did this with the somapacitan pen injector first and the somatrogon one second, while the other half followed the opposite order.

• The researchers found that 84.3% of participants preferred the somapacitan pen-injector, while 12.9% preferred the somatrogon pen-injector, and this difference was statistically significant. Almost all (98.6%) participants found the somapacitan pen-injector easy or very easy to use, while three-quarters (74.3%) answered the same for somatrogon. On average, the participants learned to use the somapacitan device faster and more correctly than the somatrogon device.

• In conclusion, given the device preference and ease of use, patients may be more likely to adhere to treatment with somapacitan compared with those receiving somatrogon.

Keywords: growth hormone deficiency, long-acting growth hormone, device preference, ease of use, somapacitan, somatrogon

Introduction

Children with inadequate secretion of growth hormone (GH) or insensitivity to GH require exogenous GH replacement therapy to reach a normal adult height.[1] However, growth outcomes are directly affected by adherence to treatment. Children who are adherent to GH replacement therapy experience significantly improved height compared to non-adherent children.[2] Despite this, adherence to GH treatment, in terms of how closely participants comply to prescribed treatment, is known to be generally suboptimal.[3,4] Age, puberty onset, gender, ethnicity, and obesity have all previously been identified as factors that affect treatment adherence.[3,4] In addition to demographic factors, there is evidence that device preference and ease of use can also affect treatment adherence.[5–7]

Somapacitan (Sogroya®, Novo Nordisk A/S, Bagsvaerd, Denmark) and somatrogon (Ngenla®, Pfizer Europe MA EEIG, Brussels, Belgium) are newly developed long-acting GH therapies (LAGHs) that are administered once weekly in contrast to prior GH therapies that are usually administered once daily.[8–11] By reducing the number of required injections, patients are expected to be more likely to adhere to once-weekly treatment than once-daily treatment. Somapacitan is approved for once-weekly administration to treat growth hormone deficiency (GHD) in children and adults.[8,9]

Device preference and ease of use are likely to affect treatment adherence, which in turn affects growth outcomes.[12] Therefore, the primary objective of the present study was to compare device preference for and ease of use of two devices, the somapacitan pen-injector and the somatrogon pen-injector, in adolescents with growth-related disorders and caregivers of children with growth-related disorders in the United States. A Device Handling and Preference Questionnaire (DHPAQ) was used to collect participants' responses, and their interpretation of the DHPAQ was evaluated in a sub-study.

Material and Methods

Study Design

This was an open-label, multicenter, randomized, crossover study to compare the somapacitan pen-injector with the somatrogon pen-injector based on device preference and ease of use (Figure 1). Data collection was conducted between

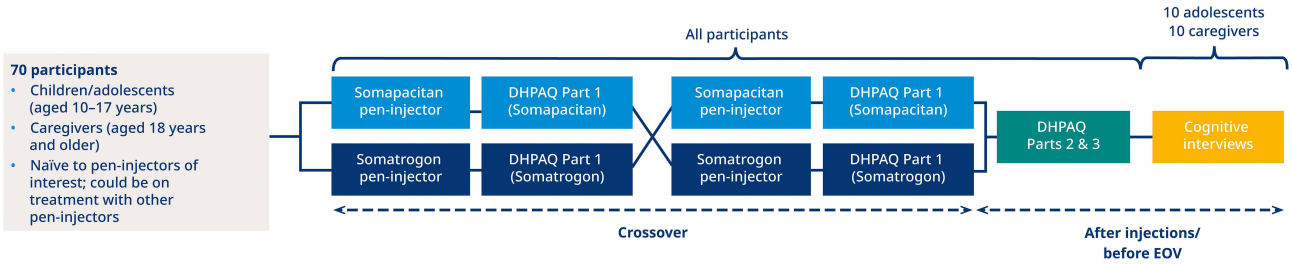

Figure 1 Study design.
Abbreviations: DHPAQ, Device Handling and Preference Assessment Questionnaire; EOV, end of visit.

September 20 and November 2, 2023. The study was carried out across five states in the United States. Testing sites included a usability lab operated by Research Collective in Tempe, AZ; market research facilities in Boston, MA, Raleigh, NC, and New York, NY; and private meeting spaces in Charlotte, NC and Columbus, OH. Photographs of all study environments are included in the Supplementary Figure S1. This study was conducted in accordance with the Declaration of Helsinki (2013 version), and the test plan was reviewed and approved by Castle IRB located in Chesterfield, MO, USA.

Inclusion and Exclusion Criteria

Seventy participants were recruited from two demographic groups: adolescents affected by short stature due to GHD or other causes who were prescribed recombinant human GH therapy, and caregivers of children with short stature due to GHD or other causes receiving recombinant human GH therapy. Eligible individuals were between 10 and 17 years of age in the adolescent group, and ≥18 years of age in the caregiver group. Adolescent participants had a self-reported diagnosis of GHD or a related disorder (Turner syndrome, Noonan syndrome, idiopathic short stature, or short for gestational age), and were capable of self-administering injections. Caregivers were required to have provided, or currently be providing, regular care for children with one of the previously listed conditions. Adolescent participants were required to be naïve to treatment with somapacitan and somatrogon, while caregiver participants were required to be naïve to administering treatment with somapacitan and somatrogon. Participants who were using pen-injectors from the PDS290 (Norditropin® FlexPro®, Novo Nordisk A/S, Bagsvaerd, Denmark) family of devices were excluded. Participants were required to be fluent in English or the local language of the investigators and be able to read and understand the study materials. Individuals were excluded if they had previously taken part in a similar study within 6 months, or if they had a diagnosis of a condition or disease that could interfere with their ability to participate. All participants were required to provide informed consent to take part in the study and allow any data collected to be processed.

Objective and Endpoints

The primary objective was to evaluate patient preference between the somapacitan pen-injector and the somatrogon pen-injector. The endpoint that measured this objective was a global preference item rating score (question 9) in the DHPAQ. Another objective was to compare the ease of use of the two devices, which was assessed using patient-reported outcomes via rating scores in the DHPAQ. Other endpoints included device training time, device preparation and injection time, and overall number of complete injections.

Devices

The devices used in this study were somapacitan and somatrogon pen-injectors (Figure 2). Both pen-injectors are prefilled, hold multiple doses, and can be disposed of after final usage. Both pen-injectors present dose units in mg on a scale drum. The somapacitan pen-injector contains either a 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL compact cartridge of somapacitan. The somapacitan injector does not depict trailing zeroes for dose units. The somatrogon pen-injector contains either a 24 mg/1.2 mL or 60 mg/1.2 mL compact cartridge of somatrogon. The somatrogon injector depicts trailing zeroes for dose units.

Visit Procedures

Participants each attended a single visit at one of the six testing sites. All testing sites were designed to mimic the home environment in which the two devices are intended to be used. Each testing site contained chairs and a table so the participant and test administrator could be seated. Each testing site also contained digital still and video cameras to record sessions and photograph participant actions of interest.

A test administrator was present for each participant visit. The test administrator was responsible for obtaining informed consent from the participant, conducting a background interview, guiding them through the visit's activities, facilitating the completion of the DHPAQ, and documenting the participants' handling and preference of the devices of interest during the visit. The test administrator was also responsible for observing for any distress in participants during the session.

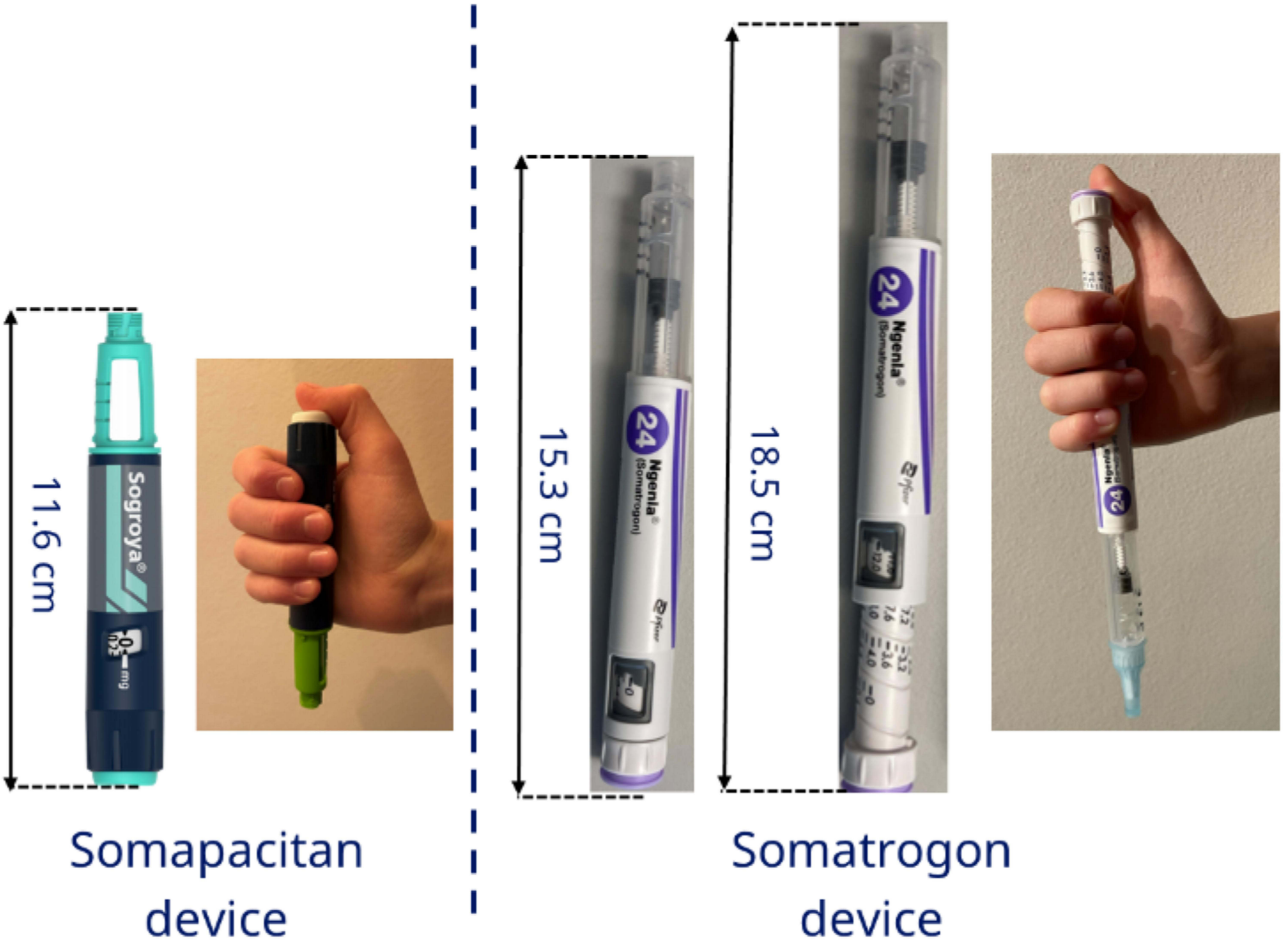

Figure 2 Scale photographs of the somapacitan device and somatrogon devices.

After a participants' arrival at the testing site and introduction by the study personnel, a registered nurse provided training in the use of one of the two pen-injectors (with training with the other device taking place after the first simulated injection). For each device, the nurse reviewed the instructions for use (IFU) with the participant, then demonstrated an injection using an injection pad. Afterwards, the participant had the opportunity to practice injecting with the device, as well as to ask the nurse any questions. Each training session was timed. Half of the participants received training with the somapacitan device first followed by the somatrogon device, while the other half received training in the reverse sequence.

After each training session, participants were required to perform a simulated injection. For both devices, this required removal of the pen cap, attaching the needle to the device, removing the inner and outer needle caps, setting the treatment dose, injecting the dose into a mannequin or injection pad, removing and disposing of the needle, and putting the pen cap back on. Each step, from attaching the needle to injecting the dose was evaluated to assess injection completeness.

Following the first simulated injection, the participant completed part 1 of the DHPAQ, for the relevant device. They then received training with the other device as before and were asked to complete a second simulated injection. After this, they completed part 1 of the DHPAQ for the other device. After completing both simulated injections and part 1 of the DHPAQ for both devices, the participants were shown both devices and completed parts 2 (comparison) and 3 (preference) of the questionnaire. At the end of the visit, participants were compensated at a rate commensurate with local market value.

DHPAQ Cognitive Debriefing Sub-Study

In addition to the main analysis, participants were randomly selected from the full study cohort and were asked to participate in a qualitative sub-study to gather information regarding their interpretation of the DHPAQ. Participants who agreed to participate in the sub-study took part in structured, one-to-one cognitive interviews following completion of the main portion of the study visit (before receiving compensation or leaving the test site).

The sub-study was conducted in accordance with the United States Food and Drug Administration (FDA) 2022 Principles for Patient Reported Outcome (PRO) Instruments and 2009 PRO Guidance for Industry.[13,14] The following factors from the FDA's 2022 Principles for PRO Instruments were considered when evaluating the DHPAQ:[13]

1. Relevance: were the concepts of interest being measured by the DHPAQ meaningful to adolescent patients with growth-related disorders and caregivers of children with growth-related disorders?
2. Comprehensiveness: did the DHPAQ reliably measure the concepts of interest?
3. Comprehension: were the elements of the DHPAQ (including questions, statements, tasks, and response options) understandable to adolescent patients with growth-related disorders and caregivers of children with growth-related disorders?

Each interview was recorded and lasted approximately 60 minutes. The interview questions were developed with the aim of evaluating participant comprehension of the DHPAQ components, and the perceived relevance and comprehensiveness of the DHPAQ components. The DHPAQ was developed based on the Haemophilia Device Handling and Preference Assessment Questionnaire,[15,16] but was modified for this study to account for differences in patient populations and applicable domains. The results from cognitive interviews for DHPAQ have been presented at ENDO 2024.[17]

Statistical Analyses

Required sample size was calculated using simulation based on Prescott's test.[18] To ensure the primary objective of demonstrating device preference (question 9) was met, the calculation considered the choice of "no preference" and the order of devices, with a 5% level of significance. Based on the assumption 10% report "no preference", with a preference of 63% for the somapacitan device, 27% for the somatrogon device (70% and 30%, respectively, among those who report a preference), 70 participants are needed to ensure ≥90% power to detect a true preference against the null hypothesis of equal preference. Demographic data and clinical characteristics reported by the study participants and their ranking results were managed in Microsoft Excel to generate tables of basic descriptive statistics (count, percent, mean and median). Endpoints were summarized using descriptive statistics. Any statistical tests conducted were two-sided with a 5% level of significance. Statistical analyses (Prescott's test) were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Results from the cognitive interviews were summarized by tabulating responses for each DHPAQ item. Responses were then qualitatively evaluated by the Research Collective team.

In a post hoc analysis, responses to the five-point scale of question 6, "overall, which device is easier to use?", were collapsed into three categories with "device much easier" and "device easier" options combined for each device. The resulting three categories were then analyzed using the Prescott test and a p-value was presented. Exploratory analyses of questions 5 A to H, questions 7 A and B, and question 8 followed the same procedure.

Results

Participant Demographics and Clinical Characteristics

Adolescents (n=33) and caregivers (n=37) were recruited across the six testing locations. Patient demographics and clinical characteristics are summarized in Table 1. In the adolescent group, 17 participants used the somapacitan device first and 16 participants used the somatrogon device first. In the caregiver group, 18 participants used the somapacitan device first and 19 participants used the somatrogon device first. All participants had self-reported good eyesight (although some participants used glasses or contact lenses). One adolescent participant was hard of hearing in both

Table 1 Participant Demographics and Clinical Characteristics

Characteristic	Adolescents (n=33)	Caregivers (n=37)
Mean (SD) age, years	13.8 (2.1)	47.0 (5.9)
Gender, n (%)		
Female	8 (24.2)	31 (83.8)
Male	25 (75.8)	6 (16.2)
Condition, n (%)*		
GHD	26 (78.8)	29 (78.4)
TS	2 (6.1)	3 (8.1)
NS	1 (3.0)	1 (2.7)
ISS	5 (15.2)	5 (13.5)
SGA	0 (0)	1 (2.7)
Current device type, n (%)		
Vial and syringe	2 (6.1)	2 (5.4)
Pen-injector	23 (69.7)	24 (64.9)
Autoinjector	0 (0)	1 (2.7)
N/A	8 (24.2)	10 (27.0)
Current treatment frequency, n (%)		
Daily	23 (69.7)	25 (67.6)
Weekly	1 (3.0)	1 (2.7)
Other†	2 (6.1)	2 (5.4)
N/A	7 (21.2)	9 (24.3)

Notes: *Some individuals were recorded with more than one condition. †Self-reported "other" frequencies were one instance each of 2x per month and 5x per week in both the adolescent and caregiver groups. All patient demographics and clinical characteristics were self-reported.
Abbreviations: GHD, growth hormone deficiency; ISS, idiopathic short stature; N/A, not applicable; NS, Noonan syndrome; SGA, short for gestational age; TS, Turner syndrome.

ears, and one caregiver participant had osteoarthritis, but remarked they had "plenty of dexterity". All other participants in both groups had self-reported good hearing and hand dexterity.

Device Preference

When asked to consider all factors, 59 (84.3%) participants (95% confidence interval [CI]: 74;92) from the total cohort answered that they preferred the somapacitan device to the somatrogon device ($p < 0.0001$). The somatrogon device was preferred by nine (12.9%) participants, and two (2.9%) had no preference between the devices. Over three-quarters of participants preferred the somapacitan device in the adolescent (78.8%; 95% CI: 61;91) and caregiver (89.2%; 95% CI: 75;97) groups.

Of the 84.3% of total participants who preferred the somapacitan device, 88.1% (95% CI: 77;95) indicated that their preference was strong or very strong. Again, similar results were observed in the adolescent (84.6%; 95% CI: 65;96) and caregiver (90.9%; 95% CI: 76;98) groups. Of the 12.9% of participants who preferred the somatrogon device, 55.6% (95% CI: 21;86) indicated that their preference was strong or very strong.

Ease of Use

When asked how difficult or easy it was to use each device, 98.6% (95% CI: 92;100) of participants in the total cohort answered that the somapacitan device was easy or very easy to use, while 74.3% (95% CI: 62;84) of participants answered the same way for the somatrogon device. Of the total cohort, 74.3% (95% CI: 62;84) of participants answered that the somapacitan device was very easy to use and 27.1% (95% CI: 17;39) of participants answered that the somatrogon device was very easy to use.

A summary of responses to questions in the DHPAQ relating to ease of use for each individual device is given in Table 2. A summary of responses to questions in the DHPAQ asking participants to directly compare aspects of ease of use between the two devices is given in Table 3. With regards to confidence using the device, 41.5% of participants were

Table 2 Results for Questions Relating to Ease of Use of Each Device in the DHPAQ

Question	Device	n	Response (%)				
1. How difficult or easy is it to			**Very Difficult**	**Difficult**	**Neither Difficult Nor Easy**	**Easy**	**Very Easy**
1a. Learn how to use the device?	Somapacitan	70	0.0	1.4	0.0	28.6	70.0
	Somatrogon	70	1.4	1.4	8.6	25.7	62.9
1b. Prepare the device for injection?	Somapacitan	70	0.0	0.0	2.9	30.0	67.1
	Somatrogon	70	1.4	0.0	8.6	27.1	62.9
1c. Select the dose?	Somapacitan	70	0.0	1.4	4.3	28.6	65.7
	Somatrogon	70	0.0	4.3	10.0	27.1	58.6
1d. Inject the dose?	Somapacitan	70	0.0	0.0	4.3	17.1	78.6
	Somatrogon	70	1.4	10.0	15.7	32.9	40.0
1e. Push the button to inject the dose?	Somapacitan	70	1.4	0.0	1.4	15.7	81.4
	Somatrogon	70	1.4	17.1	14.3	28.6	38.6
1f. Hold the device while injecting the dose?	Somapacitan	70	0.0	0.0	0.0	22.9	77.1
	Somatrogon	70	2.9	15.7	15.7	32.9	32.9
1g. Bring the device with you when you are out?	Somapacitan	70	0.0	5.7	7.1	21.4	65.7
	Somatrogon	70	7.1	21.4	20	24.3	27.1
1h. Use the device when you are outside your home?	Somapacitan	70	0.0	2.9	5.7	21.4	70.0
	Somatrogon	70	4.3	17.1	12.9	37.1	28.6
2. Overall, how difficult or easy is it to use the device?	Somapacitan	70	0.0	0.0	1.4	24.3	74.3
	Somatrogon	70	1.4	11.4	12.9	47.1	27.1
3. How confident are you that			**Not at all confident**	**A little confident**	**Somewhat confident**	**Very confident**	**Extremely confident**
3a. You can use the device correctly?	Somapacitan	70	1.4	0.0	2.9	25.7	70.0
	Somatrogon	70	0.0	2.9	12.9	35.7	48.6
3b. The device has delivered the correct full dose?	Somapacitan	70	0.0	1.4	5.7	28.6	64.3
	Somatrogon	70	0.0	1.4	11.4	42.9	44.3
4. Overall, how slow or fast is it to prepare and inject the medication with the device?			**Very slow**	**Slow**	**Neither slow nor fast**	**Fast**	**Very Fast**
	Somapacitan	70	0.0	1.4	14.3	31.4	52.9
	Somatrogon	70	1.4	1.4	25.7	42.9	28.6

Abbreviation: DHPAQ, Device Handling and Preference Assessment Questionnaire.

Table 3 Results for Questions Comparing Ease of Use Between the Devices in the DHPAQ

Question	n	Response (%)					P-value (Post Hoc Analysis)*
		Somapacitan Device Much Easier	**Somapacitan Device Easier**	**No Difference**	**Somatrogon Device Easier**	**Somatrogon Device Much Easier**	
5. Comparing the somapacitan device to the somatrogon device, which one is easier to							
5a. Learn how to use the device?	70	21.4	15.7	57.1	4.3	1.4	<0.0001
5b. Prepare the device for injection?	70	10.0	32.9	50.0	7.1	0.0	<0.0001
5c. Select the correct dose?	70	8.6	25.7	45.7	15.7	4.3	0.1261
5d. Inject the dose?	70	30.0	32.9	31.4	5.7	0.0	<0.0001
5e. Push the button to inject the dose?	70	44.3	15.7	32.9	4.3	2.9	<0.0001
5f. Hold the device while injecting the dose?	70	31.4	24.3	41.4	1.4	1.4	<0.0001
5g. Bring the device with you when you are out (eg travel or vacation)?	70	51.4	22.9	25.7	0.0	0.0	<0.0001

(*Continued*)

Table 3 (Continued).

Question	n	Response (%)					P-value (Post Hoc Analysis)*
		Somapacitan Device Much Easier	Somapacitan Device Easier	No Difference	Somatrogon Device Easier	Somatrogon Device Much Easier	
5h. Use the device when you are outside your home?	70	35.7	20.0	41.4	1.4	1.4	<0.0001
6. Overall, which device is easier to use?	70	44.3	34.3	15.7	5.7	0.0	<0.0001
7. Comparing the somapacitan device to the somatrogon device, with which one are you more confident that…		**Much more confident with somapacitan device**	**More confident with somapacitan device**	**No difference**	**More confident with somatrogon device**	**Much more confident with somatrogon device**	
7a. You can use the device correctly?	70	22.9	18.6	52.9	4.3	1.4	<0.0001
7b. The device has delivered the correctfull dose?	70	17.1	24.3	50.0	5.7	2.9	0.0001
8. Comparing the somapacitan device with the somatrogon device, which one is faster to prepare and inject the medication?		**Much faster with somapacitan device**	**Faster with somapacitan device**	**No difference**	**Faster with somatrogon device**	**Much faster with somatrogon device**	
9. All things considered, which device do you prefer?	70	22.9	32.9	35.7	5.7	2.9	<0.0001
		Somapacitan device		**No preference**		**Somatrogon device**	
	70	84.3		2.9		12.9	<0.0001

Notes: *P-value results are based on analysis of a collapsed set of three response categories for each question (for example, "much easier" and "easier" responses for each device were combined for questions 5 and 6. Exploratory analyses of questions 7 A and B, and question 8 followed the same procedure) using Prescott's test.
Abbreviation: DHPAQ, Device Handling and Preference Assessment Questionnaire.

either more or much more confident that they could use the somapacitan device correctly, compared with 5.7% of participants who answered the same for somatrogon (52.9% of participants reported no difference between the devices). In the post hoc analysis of questions asking participants to directly compare aspects of ease of use between the two devices, all but one of the responses were significantly ($p \leq 0.0001$) in favor of the somapacitan device. The exception was the response to question 5c, "comparing the somapacitan device to the somatrogon device, which one is easier to select the correct dose?", for which the difference between the two devices, while numerically in favor of the somapacitan device, was not statistically significant ($p=0.13$) (Table 3). Overall, all responses to the questions in the DHPAQ relating to ease-of-use favored the somapacitan device, indicating it was evaluated as easier to use than the somatrogon device by the participants.

Training Times and Injection Times

Average training time was lower for the somapacitan device than for the somatrogon device in the total cohort, the adolescent group, and the caregiver group (Figure 3). Average time required to prepare and inject with the device was also lower for the somapacitan device than for the somatrogon device across all three cohorts (Figure 3).

Injection Completeness

Of the total cohort, 97.1% of participants successfully completed the simulated injection with the somapacitan device. All participants successfully attached the needle, removed the outer and inner needle caps, and set the intended dose with the somapacitan device. One caregiver participant did not count to six after administering the injection with the somapacitan device, thus did not complete the dose-injection step correctly.

When conducting the simulated injection with the somatrogon device, 92.9% of participants successfully completed all steps. All participants successfully attached the needle, removed the outer and inner needle caps, inserted the needle, and injected the medicine. Five participants (three adolescents and two caregivers) did not complete at least one step in

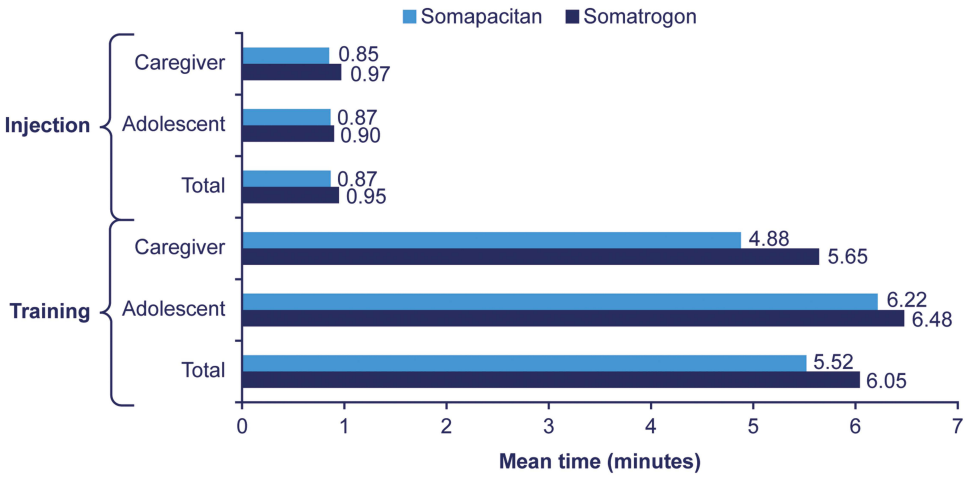

Figure 3 Average training times and times to prepare and inject for the somapacitan and somatrogon devices.

the somatrogon injection process. Three adolescents did not correctly set the intended dose, due to misunderstanding the dose indicator on the device. One adolescent and two caregivers did not count to 10 after injecting, with the root causes identified as confusion/misunderstanding of the procedure, insufficient emphasis in the IFU and training and patient-reported misleading content in the IFU and training, respectively.

Cognitive Interview Responses

Of the total cohort, 10 adolescent (six males and four females) and 10 caregiver (all female) participants were recruited to take part in cognitive interviews to evaluate the DHPAQ questionnaire.

When asked if any answer options were difficult to choose between, or did not need to be included, the participants generally indicated that the available response options were relevant to each DHPAQ item. Seven adolescents and five caregivers answered that certain response categories were too similar to each other, or unnecessary, across questions 1–8 of the DHPAQ; however, this did not affect the comprehension of the questionnaire. For example, most answers were in regard to the center response option "neither X nor Y" (eg neither difficult not easy) which was deemed unnecessary.

When asked if any particular items in the device-specific sections of the DHPAQ were not relevant to their experience with those specific devices during the test, all participants answered that there were no items that were not relevant in the device-specific sections of the questionnaire.

Participants were also asked to rank the importance of eight specific injection steps with each device included in the DHPAQ, from 1 (most important) to 8 (least important). All injection steps had a mean ranking of 6.3 or higher in importance, with "learning how to use the device" having the highest ranking of importance (mean ranking of 3.15). "Selecting the correct dose" and "injecting the dose" each had a mean ranking of 3.55.

To evaluate the comprehensiveness of the response options offered, participants were asked if anything was missing from the answer choices for each question. Generally, the participants answered that nothing was missing from the offered responses. Exceptions included the suggestion from one caregiver to add response options indicating uncertainty, and suggestions from two adolescents to add a "not strong at all" option for the preference-based questions.

The participants were also asked if they felt any questions were missing from the DHPAQ, specifically relating to their experience with each device. For both devices, it was suggested to include a question relating to the size of the device. Other suggestions included a question relating to the ease of reading the dose window and a question for adults relating to how easy or difficult it would be for a child to self-administer an injection with the device.

When asked if anything was missing from the list of eight specific injection steps with each device included in the DHPAQ, most participants indicated that nothing was missing. Suggested additional steps included convenience of using the device overall, how easy it would be to teach someone else to use and handle the device, and how easy it is to twist on the needle.

When asked to describe the meaning of each question in the DHPAQ in their own words, only one question (question 5H, Table 3) was deemed as not fully comprehended by all 20 participants by the study team (for this question, one participant did not fully comprehend and 19 participants fully comprehended the question).

When participants were asked if they had any difficulty understanding or answering each question, three questions did not receive exclusively "no difficulty" responses, relating to understanding the terms used, from all 20 participants. For two of these questions (questions 1D and 5H, Tables 2 and 3), 19 of the 20 participants answered "no difficulty". For the remaining question (question 10: "How strong is this preference (that you have indicated in question 9)?"), 18 of the 20 participants answered "no difficulty". Overall, the questionnaire was determined to be adequate and no changes were made.

Discussion

The somapacitan device was preferred to the somatrogon device by 84.3% of participants overall, and by 78.8% adolescents and 89.2% of caregivers, following simulated injections. Preference was strong or very strong in the majority of participants who expressed a preference for the somapacitan device. More participants found the somapacitan device easy or very easy to use compared to the somatrogon device.

Previous studies of children using daily or weekly injectable therapies (including those with GHD, multiple sclerosis, juvenile idiopathic arthritis, or inflammatory bowel disease) have demonstrated the influence of easier-to-use injection devices on improving adherence, which in turn has been linked to positive outcomes.[2,5–7] By demonstrating the relatively greater ease of use of the somapacitan device compared with the somatrogon device, the findings of this study suggest that patients who are prescribed somapacitan may be more likely to have higher treatment adherence and positive growth outcomes than those who are prescribed somatrogon. It is, however, important to note that, while 84.3% of participants preferred the somapacitan device, 12.9% of participants preferred the somatrogon device. Both devices scored highly in terms of ease of use, with almost all participants reporting that the somapacitan device is easy or very easy to use and three-quarters reporting the same for the somatrogon device. A small proportion of the cohort (2.9%) had no preference for either device; the reason for this is unclear.

Examining participant DHPAQ responses in detail, preference for the somapacitan device over the somatrogon device could be considered strongest in response to questions pertaining to injecting the dose, handling of the device, using the device outside the home, and efficiency of preparing and injecting the medication.

These results provide further data for clinicians and patients to consider when making an informed decision regarding GH therapy and reinforce the position that device preference should be factored into patient-centric care decisions. A longitudinal study comparing patients treated with GH therapy, with or without first being offered a choice of GH device, demonstrated that giving patients a choice of device can positively influence adherence and lead to improved therapeutic outcomes.[19] Offering patients a choice of device reduced the number of patients with low treatment adherence after 3 years of GH therapy. Additionally, patients who chose their device exhibited significantly improved height standard deviation scores (SDS) (p=0.020) and insulin-like growth factor-I SDS (p=0.038) compared to those who did not. Understanding patient preferences can also be valuable in improving the design and development of devices and selecting appropriate clinical endpoints to evaluate devices.[20]

To our knowledge, this study is the first comparison of device preference and ease of use between LAGHs conducted in adolescents and caregivers who are personally affected by growth-related disorders. The results for ease of use of the somapacitan device reported in this study are similar to those observed in the randomized Phase 3 REAL 4 clinical trial, in which 96% of 132 patients reported that somapacitan was easy or very easy to administer using devices of the FlexPro family of pen-injectors.[21] A prior study compared once-weekly somatrogon with once-daily somatropin using a Dyad Clinical Outcome Assessment (DCOA) questionnaire.[22] Although once-weekly somatrogon was associated with lower treatment burden compared with once-daily somatropin, when patients were asked to indicate treatment preference, only 1 of 4 favored the somatrogon device when considering pen ease of use elements ("preparation").

In the cognitive interviews, participants confirmed that the DHPAQ was comprehensive, relevant to their experiences, and fully comprehended. These findings support the content validity of the DHPAQ and thereby the findings concerning preferences in the current study. The cognitive interviews did not lead to any modifications of the DHPAQ. As treatment

adherence has been shown to affect growth outcomes in children receiving GH therapy,[2] it is important to support tools such as the DHPAQ with evidence to validity, to ensure that accurate patient feedback can be collected, which can in turn inform approaches to improve adherence.

Limitations

This study was conducted in participants in the US only. It was limited by a small sample size, and included two distinct groups of participants which may have reduced the statistical power of the findings for each population. Although current use of devices of the FlexPro family was an exclusion criteria, adolescents in the study were not required to be injection-naïve, which may have affected their perceptions with regard to device ease of use. This study did not assess device preference or ease of use in younger children, with no children younger than 10 years of age being included in the study. While it is likely that younger children may have similar preferences, this cannot be stated with any certainty. This study also did not assess treatment adherence with each device, so any benefits to the use of the somapacitan device in terms of adherence are theoretical at this stage. Moreover, due to the nature of the study, any adverse events, such as injection site reactions, associated with either device could not be assessed.

In addition, it should be noted that this study only assessed the somapacitan and somatrogon devices. As this was a usability study in a controlled setting, there is also the inherent limitation that participants may be more likely to read all instructions and remain within full compliance as they are being observed at all times. Furthermore, device use was assessed at a single time point, which may skew results based on first impressions and therefore not fully reflect usability over time as users become more accustomed to the device features.

Strengths

This study recruited participants diagnosed with or caring for children with GHD and other growth-related disorders, which offers consideration of different perspectives. Due to the crossover design of this study, there was no inter-subject variability between comparison groups, allowing for a direct comparison. The questionnaire used in this study, the DHPAQ, was confirmed to be comprehensive, relevant, and fully comprehended by a subset of 20 participants from the main study, suggesting that participant responses were reflections of their perceptions and preferences. In addition, the study included a mixture of adolescent participants who did or did not self-inject, allowing results to be collected from individuals who may or may not have previously considered ease of use.

Conclusions

In a randomized, multicenter, crossover study of device preference in adolescents with GHD or a related disorder and caregivers for children with GHD or a related disorder, a majority of participants preferred the somapacitan device to the somatrogon device following simulated injections. Both devices scored highly for ease of use, but the majority of participants considered the somapacitan device to be easier to use than the somatrogon device. Training, preparation, and injection times were faster with the somapacitan device than with the somatrogon device. These results suggest that participants treated with somapacitan may be more likely to have higher treatment adherence than participants treated with somatrogon. In a sub-study, adolescent and caregiver participants confirmed that the DHPAQ was a relevant, comprehensive, and well comprehended questionnaire.

Data Sharing Statement

The subject-level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The test plan for this Human Factors Comparative Preference and Handling study was reviewed and approved by Castle IRB located in Chesterfield, MO, USA.

All participants were required to provide informed consent to take part in the study and allow any data collected to be processed. All adolescent patients were accompanied by a parent or legal guardian who provided consent for participation in the study on their behalf.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Shahid Akhtar, Birgitte Berg, Johan Medina, Sophie Hamilton, Nicky Kelepouris, Jesper Skov Neergaard, Claus Sværke, Gitte Ter-Borch, and Niklas Kahr Rasmussen are employees of, and hold stocks in, Novo Nordisk. Maya Gonczi and Emily Hildebrand are employees of Research Collective, which received financial compensation from Novo Nordisk for performing the research reported in the manuscript. The authors report no other conflicts of interest in this work.

References

1. Ranke MB, Wit JM. Growth hormone - past, present and future. *Nat Rev Endocrinol*. 2018;14(5):285–300. doi:10.1038/nrendo.2018.22
2. Loftus J, Miller BS, Parzynski CS, et al. Association of daily growth hormone injection adherence and height among children with growth hormone deficiency. *Endocr Pract*. 2022;28(6):565–571. doi:10.1016/j.eprac.2022.02.013
3. Loftus J, Chen Y, Alvir JMJ, et al. Suboptimal adherence to daily growth hormone in a US real-world study: an unmet need in the treatment of pediatric growth hormone deficiency. *Curr Med Res Opin*. 2021;37(12):2141–2150. doi:10.1080/03007995.2021.1982682
4. Lass N, Reinehr T. Low treatment adherence in pubertal children treated with thyroxin or growth hormone. *Horm Res Paediatr*. 2015;84 (4):240–247. doi:10.1159/000437305
5. Graham S, Auyeung V, Weinman J. Exploring potentially modifiable factors that influence treatment non-adherence amongst pediatric growth hormone deficiency: a qualitative study. *Patient Prefer Adherence*. 2020;14:1889–1899. doi:10.2147/PPA.S268972
6. Tanaka T, Sato T, Yuasa A, Akiyama T, Tawseef A. Patient preferences for growth hormone treatment in Japanese children. *Pediatr Int*. 2021;63 (10):1185–1191. doi:10.1111/ped.14760
7. Gomez R, Ahmed SF, Maghnie M, Li D, Tanaka T, Miller BS. Treatment adherence to injectable treatments in pediatric growth hormone deficiency compared with injectable treatments in other chronic pediatric conditions: a systematic literature review. *Front Endocrinol*. 2022;13:795224. doi:10.3389/fendo.2022.795224
8. Novo Nordisk. SOGROYA® (somapacitan-beco) injection, for subcutaneous use: highlights of prescribing information. 2023. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761156s005lbl.pdf. Accessed April 24, 2024.
9. Novo Nordisk. Sogroya solution for injection in pre-filled pen: summary of product characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/sogroya-epar-product-information_en.pdf. 2023. Accessed April 24, 2024.
10. Pfizer. NGENLA (somatrogon-ghla) injection, for subcutaneous use: highlights of prescribing information. 2023. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761184Orig1s000Corrected_lbl.pdf. Accessed April 24, 2024.
11. Pfizer. Ngenla solution for injection in pre-filled pen: summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/ngenla-epar-product-information_en.pdf. Accessed April 24, 2024.
12. Aydın BK, Aycan Z, Sıklar Z, et al. Adherence to growth hormone therapy: results of a multicenter study. *Endocr Pract*. 2014;20(1):46–51. doi:10.4158/EP13194.OR
13. United States Food and Drug Administration. Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation. 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use. Accessed April 24, 2024.

14. United States Food and Drug Administration. Guidance for Industry - Patient-Reported Outcome Measures: use in Medical Product Development to Support Labeling Claims. Available from: https://www.fda.gov/media/77832/download. 2009. Accessed April 24, 2024.
15. Rasmussen NK, Berg B, Neergaard JS, et al. A usability study assessing handling and preference of the concizumab pen-injector in patients with haemophilia and caregivers. *Hematol Transfus Cell Ther*. 2023;45:S457–S458. doi:10.1016/j.htct.2023.09.852
16. Kahr Rasmussen N, Berg B, Christiansen ASL, et al. The Concizumab Pen-Injector is Easy to Use and Preferred by Hemophilia Patients and Caregivers: a Usability Study Assessing Pen-Injector Handling and Preference. *Patient Prefer Adherence*. 2024;18:1713–1727. doi:10.2147/PPA.S470091
17. Neergaard JAS, Berg B, Hamilton S, et al. Evaluating the Device Handling and Preference Assessment Questionnaire for Growth Hormone Deficiency: results from Content Validation Interviews. *ENDO*. 2024;8:bvae163–1441.
18. Prescott RJ. The Comparison of Success Rates in Cross-Over Trials in the Presence of an Order Effect. *J R Stat Soc*. 1981;30(1):9–15.
19. Gau M, Takasawa K. Initial patient choice of a growth hormone device improves child and adolescent adherence to and therapeutic effects of growth hormone replacement therapy. *J Pediatr Endocrinol Metab*. 2017;30(9):989–993. doi:10.1515/jpem-2017-0146
20. Lewis A, Douka D, Koukoura A, et al. Preference testing in medical devices: current framework and regulatory gaps. *Med Dev*. 2022;15:199–213. doi:10.2147/MDER.S368420
21. Miller BS, Blair JC, Rasmussen MH, et al. Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: the Randomized Phase 3 REAL4 Trial. *J Clin Endocrinol Metab*. 2022;107(12):3378–3388. doi:10.1210/clinem/dgac513
22. Maniatis AK, Carakushansky M, Galcheva S, et al. Treatment burden of weekly somatrogon vs daily somatropin in children with growth hormone deficiency: a randomized study. *J Endocr Soc*. 2022;6(10):bvac117. doi:10.1210/jendso/bvac117