Drug Design, Development and Therapy

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REVIEW

# Developments in the Management of Growth Hormone Deficiency: Clinical Utility of Somapacitan

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**Abstract:** Growth hormone (GH) replacement therapy for growth hormone deficiency (GHD) in children and adults has for over 25 years, until recently, been administered as daily injections. This daily treatment regimen often incurs a burden to patients and caregivers, leading to high rates of non-adherence and, consequently, decreased treatment efficacy outcomes. To address this shortcoming, long-acting growth hormones (LAGHs) have been developed with the aim of reducing the burden of daily injections, thereby potentially improving treatment adherence and outcomes. Somapacitan (Sogroya®) (Novo Nordisk, Bagsværd, Denmark) is a LAGH currently approved for the treatment of adult and childhood GHD (AGHD and CGHD, respectively) in several countries. Other LAGHs, such as somatrogon (Ngenla®) (Pfizer, New York, United States) and lonapegsomatropin/TransCon GH (Skytrofa®) (Ascendis Pharma, Copenhagen, Denmark), are also currently approved and available for the treatment of CGHD in several countries. In this review, we will consider the method of protraction, pharmacokinetics (PK) and pharmacodynamics (PD), efficacy, and safety results of somapacitan in adult and pediatric trials and how these characteristics differ from those of the other aforementioned LAGHs. Additionally, the administration of somapacitan and timing of measurement of serum insulin-like growth factor-I (IGF-I) levels are summarized. Information on administration, advice on missed doses, and clinical guidelines are discussed, as well as identifying which patients are suitable for somapacitan therapy, and how to monitor and adjust dosing whilst on therapy.

**Keywords:** (3–6): growth hormone, long-acting growth hormone, adult growth hormone deficiency, pediatric growth hormone deficiency, adherence

## Introduction to Somapacitan and Long-Acting Growth Hormones

The long-term safety and efficacy of daily growth hormone (GH) have been well documented since its approval by the US Food and Drug Administration (FDA) in 1985 and by the European Medicines Agency (EMA) in 1987 for the treatment of growth hormone deficiency (GHD) in children.[1]

Adherence is the extent to which participants act in accordance with their prescribed dose regimen, while persistence is the accumulation of time from initiation to discontinuation of therapy.[2] It is known that adherence to GH treatment is related to treatment outcomes, such as height. In a real-world study, the association between adherence to daily GH and height outcomes among 201 children with GHD (CGHD) was investigated.[3] The results showed that participants who had good adherence to treatment gained an additional 1.8 cm in height compared with non-adherent participants over 1 year.[3] In another study, treatment adherence was investigated in 103 participants with CGHD,[4] and it was observed that

Received: 12 October 2023
Accepted: 11 January 2024
Published: 3 February 2024

adherence was lower ($p < 0.01$) in pubertal children compared to prepubertal children, and in children self-administering their medication compared with those whose treatment was administered by their parent/guardian.[4] Additionally, two retrospective studies investigating treatment adherence and persistence of children to daily GH were conducted in the USA and UK.[5,6] Both studies found that a high proportion of children discontinued treatment despite exhibiting early persistence.[5,6] For adults with GHD (AGHD), adherence to daily GH among 107 participants was investigated using a cross-sectional analysis,[7] and the results showed that older age was significantly associated with better adherence to daily GH ($p = 0.021$).[7] Given trends seen in other chronic conditions requiring long-term treatment, it is likely that the high injection frequency plays a role in the increasingly low adherence to daily GH.[4,8]

To address this shortcoming of sub-optimal adherence with daily GH administration, long-acting growth hormones (LAGHs) have been studied, most of which are administered once weekly (Table 1). Somapacitan (Sogroya®) (Novo Nordisk, Bagsværd, Denmark) is a LAGH that has been approved for the treatment of AGHD in the USA, Europe, Australia, and Japan, and for the treatment of CGHD in the USA, Europe, Japan, Saudi Arabia, and Canada.[9–13] Other LAGHs, such as somatrogon (Ngenla®) (Pfizer, New York, United States), lonapegsomatropin/TransCon GH (Skytrofa®) (Ascendis Pharma, Copenhagen, Denmark), LB 3002 (Eutropin Plus®) (LG Chem, Seoul, South Korea), and PEGylated recombinant human GH (Jintrolong®) (GeneScience, Beijing, China) are also currently approved and available for the treatment of CGHD in their respective manufacturing countries. In this review, we will summarize the method of protraction, pharmacology, efficacy, safety, pharmacokinetics (PK)/

**Table 1** Summary and Comparison of Approved Long-Acting Growth Hormones, Including Somapacitan

| | **Novo Nordisk** | **Ascendis** | **Pfizer/OPKO Health** |
|---|---|---|---|
| | **Somapacitan** | **Lonapegsomatropin, TransCon hGH** | **Somatrogon** |
| Molecular weight (g/mol) | 23,305.10[a] | 22,000[b] | 41,000[c] |
| Protraction technique | Reversible albumin binding[d] | Transient PEGylation[e] | CTP fusion[c] |
| Half-life, hours | | | |
| Adults | 48–72[d] | 18–43.4[f] | 20.8–23.6[c] |
| Children | 34[d] | 30.7[f] | 18.3–36.1[c] |
| Elimination technique | Metabolized by proteolytic degradation and cleavage of the linker sequence between the peptide and albumin binder[d] | Catabolized in the liver and kidney to its constitutive amino acids[g] | Primarily degraded by proteolytic catabolism[c] |
| Dosing interval | Once weekly[d] | Once weekly[e] | Once weekly[c] |
| $C_{max}$ | 0.02 mg/kg: 14.4 ng/mL<br>0.04 mg/kg: 19.8 ng/mL<br>0.08 mg/kg: 64.2 ng/mL<br>0.12 mg/kg: 142.5 ng/mL[h] | 0.24 mg/kg: 15.2 ng/mL[g] | 0.66 mg/kg: 690 ng/mL[c] |
| Formulation | Liquid, subcutaneous[d] | Freeze dried in dual chamber cartridge, subcutaneous[f] | Liquid, subcutaneous[c] |
| Development | AGHD: approved[d]<br>CGHD: approved[d] | AGHD: Phase 3 initiated[i]<br>CGHD: approved*[g] | AGHD: failed primary endpoint at phase 3[j]<br>CGHD: approved** |

**Notes**: *Approved in the USA and EU; **Approved in the EU and a complete response letter issued in the USA. [a]Sogroya® Novo-PI.2023. Available at: https://www.novo-pi.com/sogroya.pdf;[14] [b]Miller BS, Yuen KCJ. *Drug Des Devel Ther* 2022;16:2055–2066;[15] [c]Assessment report: Ngenla®:EMA, 2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/ngenla-epar-public-assessment-report_en.pdf;[16] [d]Sogroya® SmPC. EMA, 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/sogroya-epar-product-information_en.pdf;[17] [e]Lonapegsomatropin SmPC. EMA, 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/skytrofa-previously-lonapegsomatropin-ascendis-pharma-epar-product-information_en.pdf;[18] [f]Lonapegsomatropin PI. FDA 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761177s001lbl.pdf;[19] [g]Assessment report: Lonapegsomatropin® EMA, 2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/lonapegsomatropin-ascendis-pharma-epar-public-assessment-report_en.pdf;[20] [h]Højby Rasmussen et al *J Clin Endocrinol Metab* 2016;101(3):988–998;[21] [i]ClinialTrials.gov: NCT05171855. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05171855;[22] [j]ClinicalTrials.gov: NCT01909479. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT01909479.[23]

**Abbreviations**: AGHD, adult growth hormone deficiency; CGHD, childhood growth hormone deficiency; $C_{max}$, maximum serum concentration; CTP, carboxyl terminal peptide; hGH, human growth hormone; PEG, polyethylene glycol.

pharmacodynamics (PD), and administration of somapacitan. Additionally, we provide insight into several key factors that should be considered when reviewing clinical trial results of somapacitan or making the decision to initiate somapacitan.

## Method of Protraction

Somapacitan is a LAGH consisting of a human GH protein (22kDa) and a single amino acid substitution at position 101 (leucine to cysteine) where a side chain has been attached (Figure 1).[24] The side chain in somapacitan consists of a linker sequence and an attached small noncovalent albumin-binding moiety, which facilitates reversible binding to endogenous albumin, delaying the elimination and extending the half-life and duration of action.[24,25] This protraction technology has been successfully applied to other peptide drugs to prolong their half-lives, such as insulin detemir, liraglutide, and semaglutide.[26–28]

Somapacitan binds reversibly, but extensively (>90% of somapacitan molecules are bound in the circulation and tissues), to a specific site on endogenous circulating human serum albumin domain II.[25,29] In a Phase 1 dose-escalation trial, the ratio of the highest somapacitan dose of 0.12 mg/kg/week administered in the presence of the lowest normal albumin concentration was 88,000.[21] This suggests that albumin occupancy was around 0.001%; hence, displacement of circulating albumin that is bound to somapacitan is unlikely to be of clinical significance.[21] Somapacitan is cleared in the kidneys by glomerular filtration and subsequently degraded in the tubular cells or during the receptor-mediated internalization by the GH receptor in target tissues.[29]

In a study that investigated the tissue distribution and receptor activation of somapacitan in hypophysectomized rats with GHD, a dose- and time-dependent activation of phosphorylated STAT5 (P-STAT5) was observed for somapacitan in multiple tissues including the epiphyseal growth plates.[29] The level of activation was measured based on downstream tyrosine P-STAT5, as it is the primary mediator of insulin-like growth factor-I (IGF-I) transcription.[29] In addition, fluorescently tagged somapacitan administered to hypophysectomized rats with GHD was shown to distribute to the growth plate in living rats to bind specifically to the hypertrophic zone and primary spongiosa. These data demonstrate the ability of somapacitan to distribute to relevant tissues to promote growth and metabolic activities. However, somapacitan activity in adipose tissue was not assessed.

## Absorption, Metabolism, and Excretion

A study investigated the absorption, metabolism, and excretion, as well as the PK, of tritium-labelled somapacitan ([$^3$H]-somapacitan).[24] The participants were seven healthy males who received a single subcutaneous dose of 6 mg of tritium-labelled somapacitan containing [$^3$H]-somapacitan 20 MBq. The PK of plasma components was determined, and the radioactive peaks of the most abundant plasma metabolites and urine metabolites were selected for analysis.[24] After 28 days from dosing, 94.0% of the administered dose was recovered as [$^3$H]-somapacitan-related material, of which 80.9% was excreted in urine, 12.9% was excreted in feces, and 0.2% was exhaled in expired air.[24] Somapacitan was extensively degraded to small residual fragments that were excreted, which indicates that it is almost fully biodegradable.[24]

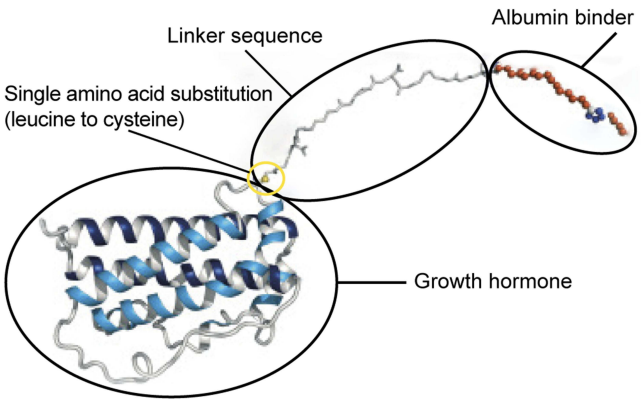


**Figure 1** Molecular structure of somapacitan.
**Notes**: Figure adapted from Petersen M, Gandhi PS, Buchardt J et al. Tissue distribution and receptor activation by somapacitan, a long acting growth hormone derivative. *Int J Mol Sci*. 2020;21(4):1181. Creative Attribution 4.0 International (CC BY 4.0).[29]

It has been suggested that recombinant GH, including somapacitan, is mainly eliminated by the kidneys and liver.[30] Two trials (ClinicalTrials.gov NCT03186495 and NCT03212131) were conducted to investigate the steady-state exposure of somapacitan in participants with kidney or hepatic impairment at varying degrees, compared with participants with normal kidney or hepatic function.[30] Each trial included participants aged 18–75 years with normal kidney and hepatic function matched with adults with impaired kidney or impaired hepatic function. Participants in both trials received three somapacitan injections (0.08 mg/kg/week) in the morning on days 1, 8, and 15, and their blood samples were collected before each dose, at 28 time-points throughout the 2 weeks after the last dose, as well as at follow-up, which was 3–4 days after the last dose. The primary endpoint of the trials was area under the somapacitan serum concentration–time curve from 0 to 168 hours after the last dosing (area under the curve $[AUC]_{(0–168)}$).

In the kidney impairment trial, somapacitan $AUC_{(0–168h)}$ was higher in the severe kidney impairment requiring hemodialysis group compared with the normal kidney function group (estimated ratio [ER] and 90% CI [confidence interval]: 1.75 [1.00;3.06] and 1.63 [1.01;2.61], respectively).[30] For the moderate kidney impairment group, somapacitan $AUC_{(0–168h)}$ was similar to the normal function group (ER [90% CI] 1.25 [0.74;2.11] and 1.27 [0.77;2.07], respectively).

In the hepatic impairment trial, somapacitan $AUC_{(0–168h)}$ was significantly higher in the moderate hepatic impairment group compared with the normal function group, with exposure more than four times higher (ER 4.69 [90% CI 2.92;7.52]).[30] For the mild hepatic impairment group, the exposure was similar to that of the normal hepatic function group (ER 1.08 [90% CI 0.66;1.75]). Specific dosing recommendations of somapacitan for individuals with moderate hepatic impairment include initiating treatment at a lower dose and using smaller dose increment increases when titrating the dosage. For individuals with severe hepatic impairment, somapacitan therapy is not recommended.[14] For individuals with renal impairment, specific dosing recommendations of somapacitan have not been provided.[10]

In terms of safety endpoints, in the kidney impairment trial, 24 participants (54.5%) experienced 65 adverse events (AEs), of which 50 were mild and 15 were moderate.[30] None of the AEs were serious and[30] all participants recovered from the AEs. Two participants reported five injection-site reactions, all of which were mild in severity. In the hepatic impairment group, nine AEs occurred in five participants, of which 6 were mild and 3 were moderate. The most common AE was injection-site reaction (four events in two participants), all of which were mild in severity.

# Clinical Trial Results

## AGHD

### Efficacy

The efficacy of somapacitan in adults with AGHD was investigated in REAL 1, a randomized, parallel-group, placebo- and active-controlled Phase 3 trial (NCT02229851).[31] The trial took place across 17 countries and investigated somapacitan versus daily GH and once-weekly placebo in treatment-naive participants with AGHD (n = 301). Participants were randomized in a 2:2:1 ratio to receive somapacitan (n = 121), daily GH (n = 119), or once-weekly placebo (n = 61) for a duration of 34 weeks that constituted the main period of the trial. Following the main period, a 52-week extension took place where participants continued treatment with somapacitan or daily GH. The results at 34 weeks showed that somapacitan significantly reduced truncal fat percentage (estimated treatment difference versus placebo [ETD] [95% CI] −1.53% [−2.68; −0.38], p = 0.0090) and improved visceral fat, lean body mass, and IGF-I standard deviation score (SDS) levels. Compared with daily GH, after 34 weeks, the truncal fat percentage decrease was lower (ETD versus daily GH [95% CI] 1.17 [0.23; 2.11]), while similar effects were observed for visceral fat, lean body mass, and IGF-I SDS. After 86 weeks of treatment, a reduction in visceral fat and increases in total lean body mass and appendicular skeletal muscle mass were maintained in both groups.

The efficacy of somapacitan compared with daily GH was also investigated in previously treated Japanese adults (n = 62) with AGHD over a 52-week period in the REAL Japan Phase 3 trial (NCT03075644).[32] Participants were randomized 3:1 to somapacitan (n = 46) or daily GH (n = 16) for a 20-week dose titration period and a 32-week fixed-dose treatment period. The results showed no significant differences between groups for changes from baseline to week 52 in visceral, subcutaneous, and total adipose tissue (ETD [95% CI] −1.74 [−18.13; 14.66], −11.53 [−35.54; 12.48], and −12.85 [−47.31; 21.62] $cm^2$, respectively).

## Safety

A dose-escalation trial for somapacitan was conducted in 105 healthy male subjects.[33] The results showed that somapacitan at all dose levels (0.01–0.32 mg/kg) was well tolerated, and no serious AEs were reported. In total, 20 of 79 participants reported transient injection-site reactions.

In a Phase 1 randomized trial, the safety, tolerability, PK, and PD of somapacitan (at doses of 0.02, 0.04, 0.08, and 0.12 mg/kg/week) were compared with those of daily GH in 34 adults with AGHD.[21] The number of AEs reported was similar at the dose levels of 0.02, 0.04, and 0.08 mg/kg/week somapacitan compared with daily GH, whereas the number of AEs reported was greater at the highest dose level of somapacitan 0.12 mg/kg/week compared with daily GH. $AUC_{(0–168h),}$ peak plasma concentrations of somapacitan and IGF-I levels increased in a dose-dependent manner.

The safety and tolerability of somapacitan versus daily GH were also evaluated in participants with AGHD in REAL 2, a 26-week Phase 3 trial (NCT02382939).[34] Participants were randomized 2:1 to receive somapacitan (n = 61) or daily GH (n = 31). The results showed that, throughout the trial, estimated mean IGF-I SDS remained between 0 and 2 in both groups. AEs were reported by 86.9% of participants in the somapacitan group and 67.7% of participants in the daily GH group. Most of the AEs reported were mild or moderate, and no clinically significant injection-site reactions were reported. The safety of somapacitan was also assessed in REAL 1 and REAL Japan.[31,32] In REAL 1, somapacitan was well tolerated, with a similar rate of AEs reported per 100 patient-years at risk in the group receiving somapacitan compared with the group receiving daily GH.[31] In REAL Japan, the rate of AEs reported per 100 patient-years was similar between groups, and the majority of AEs reported were of mild severity.[32] Additionally, in REAL Japan, a post hoc analysis of the AEs probably/possibly related to treatment was conducted and the results showed a nonsignificant rate difference of –33.4 (95% CI: –74.9; 8.0) between the somapacitan and daily GH arms.[32]

The effects of somapacitan, compared with daily GH and a once-weekly placebo, on glucose metabolism were investigated in post hoc defined analyses using data from three Phase 3 trials (REAL 1, REAL 2, and REAL Japan).[35] The investigations included assessments of fasting plasma glucose (FPG) levels, homeostasis model assessment of insulin resistance (HOMA-IR), glycated hemoglobin (HbA1c), and homeostasis model assessment of beta-cell function (HOMA-β). No new cases of diabetes mellitus were reported with somapacitan. Two participants in REAL 1 and one participant in REAL Japan, treated with daily GH, were diagnosed with diabetes mellitus (type not specified) during the trial. Among GH-naïve participants receiving somapacitan (n = 120) or daily GH (n = 119), transient changes from baseline in FPG, HOMA-IR, and fasting insulin levels were observed with daily GH versus somapacitan at 34 weeks, but not at 86 weeks. HbA1c and HOMA-β did not differ between groups at either timepoint. In previously treated participants (REAL 1 extension: n = 51 somapacitan, n = 52 daily GH; REAL 2: n = 61 and n = 31, respectively; REAL Japan: n = 46 and n = 16, respectively), the differences in changes from baseline were not statistically significant between somapacitan and daily GH for any glucose metabolism parameters, reinforcing the neutral effect of somapacitan on glycemia.

## Treatment Satisfaction

In REAL 2 and REAL Japan, treatment satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9).[32,34] In REAL 2, treatment satisfaction increased significantly with somapacitan versus daily GH (p = 0.0171).[34] In REAL Japan, the differences in change from baseline to the end of the trial in convenience, effectiveness, and global satisfaction scores were all numerically in favor of somapacitan, but not statistically different to daily GH (p = 0.0877, 0.2462, and 0.0890, respectively).[32]

## Adherence

In REAL 1, REAL 2, and REAL Japan, adherence to treatment was captured by site staff asking participants to record the date and time of each dose of trial product, as well as any missed doses.[31,32,34] In REAL 1, mean adherence was 95.5% to somapacitan, 90.6% to daily GH, and 93.9% to placebo.[31] In REAL 2, mean treatment adherence was 93.1% in the somapacitan group and 90.4% in the daily GH group.[34] In REAL Japan, mean adherence among participants receiving somapacitan was 98.7% and 92.2% for participants receiving daily GH.[32]

# CGHD

## Efficacy

The efficacy of somapacitan has been investigated in children with CGHD in REAL 3 and REAL 4.[36–39] REAL 3 is an ongoing Phase 2 trial (NCT02616562) investigating the safety and efficacy of three doses of somapacitan versus daily GH in children with CGHD.[36] The trial consisted of a main phase and an extension phase, each of which lasted 26 weeks, followed by a 104-week safety extension, comparing 0.16 mg/kg/week somapacitan with daily GH 0.034 mg/kg/day.[36] A further 208-week-long safety extension is currently taking place using somapacitan 0.16 mg/kg/week only.[36,37] Results from year 1, year 3, and year 4 (year 1 of the long-term safety extension) of the trial have been published.[36–38]

During the main phase of the REAL 3 trial, 59 prepubertal children were randomized 1:1:1:1 to 0.04, 0.08, or 0.16 mg/kg/week somapacitan or 0.034 mg/kg/day daily GH.[36] ETD in AHV at week 26 between the group receiving somapacitan 0.16 mg/kg/week and the daily GH group was 1.7 cm/year [95% CI: −0.2; 3.6]. The increase in HV at week 52 was significantly greater with somapacitan 0.16 mg/kg/week versus daily GH. Model-derived mean (standard deviation, SD) IGF-I SDS for the somapacitan groups 0.04, 0.08, and 0.16 mg/kg/week was −1.62 (0.86), −1.09 (0.78), and 0.31 (1.06), respectively, versus −0.40 (1.50) observed for daily GH.

Year 3 results from the REAL 3 trial showed similar improvements in height outcomes.[37] At year 3, all participants on somapacitan received 0.16 mg/kg/week somapacitan, while participants on daily GH continued with their treatment unchanged.[37] The ETD (95% CI) in HV for the somapacitan group receiving 0.16 mg/kg/week for 3 years versus the group receiving daily GH was 0.8 cm/year (−0.4; 2.1). Mean height SDS was similar for the pooled somapacitan groups and daily GH group. Additionally, change in mean IGF-I SDS from baseline to year 3 was similar across treatments.

At year 4 in the REAL 3 trial, children receiving daily GH for 3 years switched to somapacitan 0.16 mg/kg/week, while all children receiving somapacitan (0.16 mg/kg/week) were pooled into one group.[38] Changes from baseline in HV and HV SDS were similar and as expected in both groups. The number of children who had entered puberty at year 3, midway through year 4, and at the end of year 4 was two, four, and five in the pooled group, and two, three, and three in the switched group, respectively.

REAL 4 is a Phase 3, randomized, multinational, open-label, active-controlled, parallel-group trial (NCT03811535) taking place in 86 sites across 20 countries.[39] REAL 4 was designed to investigate the efficacy and safety of somapacitan versus daily GH in children with CGHD. Participants were randomized 2:1 to 0.16 mg/kg/week somapacitan or 0.034 mg/kg/day daily GH. The primary endpoint of the trial was annualized HV at week 52 and additional assessments included HV SDS, height SDS, bone age, IGF-I SDS, patient-reported outcomes, and safety measures. At week 52, estimated mean HV for the somapacitan group and daily GH group was 11.2 and 11.7 cm/year, respectively, which confirmed noninferiority of somapacitan to daily GH (Table 2). Changes in HV SDS, height SDS, bone age, and IGF-I SDS from baseline to week 52 were similar between treatment groups. At week 52, mean IGF-I SDS values were similar between treatment groups and within the normal range (−2 to +2). Results at year 2 of the REAL 4 trial showed sustained HV (SD) between weeks 52–104.[40] Mean (SD) HV between weeks 52–104 was 8.4 (1.5) cm/year for the group that received somapacitan and 8.7 (1.8) cm/year for the group that received daily GH for 1 year and followed by somapacitan for 1 year. Additionally, year 2 results for mean IGF-I SDS were comparable. For children in the somapacitan group, between groups and within the normal range (−2 to +2).[40]

A Phase 3 clinical trial in China is currently underway to investigate the safety and efficacy of somapacitan compared with daily GH in children with CGHD. The trial is expected to complete in January 2024.[43]

## Safety

In a Phase 1, randomized, dose-escalation trial (NCT01973244), the safety and tolerability of somapacitan was evaluated in 32 prepubertal children with CGHD.[42] Participants were sequentially randomized 3:1 to receive a single dose of somapacitan (0.02, 0.04, 0.08, and or 0.16 mg/kg/week, n = 6 each) or daily GH (n = 2 each) for 7 days. A total of 19 AEs were reported in 11 participants receiving somapacitan and two AEs were reported in one participant receiving daily GH. None of the reported AEs were serious, and no treatment-related patterns in the frequency of AEs reported were found. In total, three out of 24 participants receiving somapacitan reported four transient injection-site reactions. The PK results showed that mean serum concentrations of somapacitan increased in a dose-dependent, but nonlinear, manner.

**Table 2** Summary of the Efficacy Endpoints of Long-Acting Growth Hormones, Including Somapacitan, Investigated in Treatment-Naive Pediatric Populations Over a 12-Month Period

| Trial | Number of Participants (Age Range, Years) | Mean AHV of LAGH (cm/year) | Mean AHV of Daily GH (cm/year) | ETD in AHV at Week 52 Between LAGH and Daily GH Comparator (95% CI) | Change in HSDS from Baseline* | Change in IGF-I SDS | Mean IGF-I SDS at Week 52 |
|---|---|---|---|---|---|---|---|
| REAL 4[a]<br>Somapacitan | n = 200<br>Age range: girls 2.5–10 and boys 2.5–11 | 11.2 | 11.7 | −0.5 (−1.1 to 0.2) | 1.25 | 2.36 | 0.28 |
| NCT02968004[b]<br>Somatrogon | n = 228<br>Age range: girls 3–10 and boys 3–11 | 10.10 | 9.78 | 0.33 (−0.24 to 0.89) | | | |
| NCT03874013 (Japan)[c]<br>Somatrogon | n = 44<br>Age range: girls 3 to <10 and boys 3 to <11 | 9.65 | 7.87 | 1.79 (0.97 to 2.61) | 0.94 | | |
| HeiGHt[d]<br>Lonapegsomatropin | n = 161<br>Age range: girls 3–11 years and boys 3–12 years | 11.2 | 10.3 | 0.9 (0.2 to 1.5) | 1.10 | | 0.72 |

**Notes**: *Change in HSDS from baseline was for the following time period: REAL 4, 52 weeks; NCT03874013 (Japan), 12 months; HeiGHt, 52 weeks. The treatment product and the dose for each trial were as follows: REAL 4, somapacitan 0.16 mg/kg/week; NCT02968004 and NCT03874013 (Japan), somatrogon 0.66 mg/kg/week; HeiGHt, lonapegsomatropin 0.24 mg/kg/week. [a]Miller et al *J Clin Endocrinol Metab* 2022;107(12):3378–3388;[39] [b]Deal et al *J Clin Endocrinol Metab*. 2022;107(7): e2717-e2728;[43] [c]Horikawa et al *Horm Res Paediatr*. 2022;95(3):275–285;[44] [d]Thornton et al *J Clin Endocrinol Metab* 2021;106(11):3184–3195.[45]

**Abbreviations**: AHV, annualized height velocity; CI, confidence intervals; ETD, estimated treatment difference; GH, growth hormone; HSDS, height standard deviation score; IGF-I, insulin-like growth factor-I; LAGH, long-acting growth hormone; n, number of participants; SDS, standard deviation score.

Pharmacodynamic results showed that IGF-I and insulin-like growth factor binding protein-3 (IGFBP-3) levels increased in a dose-dependent manner for all doses investigated. Somapacitan administered to participants with CGHD was well tolerated at all doses investigated, and no clinically significant safety issues were identified.

Safety results at week 52 of the REAL 3 trial showed that the overall AE rate per 100 patient-years was similar between the somapacitan groups and daily GH group (364.8 and 364.1, respectively).[36] In the same time period, seven serious AEs collectively were reported in two participants in the somapacitan groups (0.08 and 0.16 mg/kg/week) and in one participant in the daily GH group. Additionally, three participants in the somapacitan groups experienced injection-site reactions: mild urticaria (n = 2), injection-site hematoma, and lipoatrophy (n = 1). The overall AE rate per 100 patient-years during Years 2 and 3 was again similar between the treatment arms: pooled somapacitan groups, 237.7; daily GH, 224.9.[37] Most AEs were mild and deemed unlikely to be related to treatment. After the first year of treatment, four participants experienced six injection site-related AEs, which were all considered mild in severity.

At year 4 of the REAL 3 trial, the safety profile of somapacitan was similar to that of daily GH; the rate of AEs per 100 patient-years for the group that switched treatment from daily GH to somapacitan was 270.8 before the switch, compared with 248.2 for the pooled somapacitan groups to the end of year 4.[38] In the same year, three participants in the somapacitan pooled group experienced a total of five injection-site reactions and three of the reported reactions included pain as a descriptor.

In REAL 4, AEs occurred in 94 (71.2%) participants in the somapacitan group and 41 (60.3%) participants in the daily GH group; most AEs were mild or moderate in severity (98%) and deemed unlikely to be related to trial products.[39] Additionally, low rates of injection-site reactions were reported for somapacitan (5.3%) and daily GH (5.9%), with 1.5% of those in each group reporting transient injection-site pain. At year 2 of the trial, somapacitan was well tolerated, with no safety issues identified.[40]

## Treatment Satisfaction

During the REAL 3 trial, a questionnaire was developed and validated to assess the burden that GH treatment can have on participants aged between 4 and <13 years and their parents/guardians.[38] For children in the somapacitan group,

overall treatment burden scores were lower at year 4 than years 2 or 3 (Figure 2A). For children in the daily GH group who switched to somapacitan at year 4, overall treatment burden scores at year 4 were lower than at year 3, but slightly higher than at year 2 (Figure 2A). This may be due to an overall general increase in treatment fatigue after 4 years of treatment, regardless of injection frequency. The slight decrease in treatment burden score from year 3 to 4 in the somapacitan group may also be due to increasing familiarity of treatment, whereas the larger decrease in the group who switched to somapacitan in year 4 may be related to reduced injection frequency. For parents/guardians of children in the somapacitan group, the overall treatment burden scores were similar at year 4 and year 2 (Figure 2B). For parents/guardians of children in the daily GH group who switched treatment, overall treatment burden scores at year 4 were lower than at years 2 or 3, but year 3 results were higher than at year 2 (Figure 2B). At year 4 of the trial, the parents/

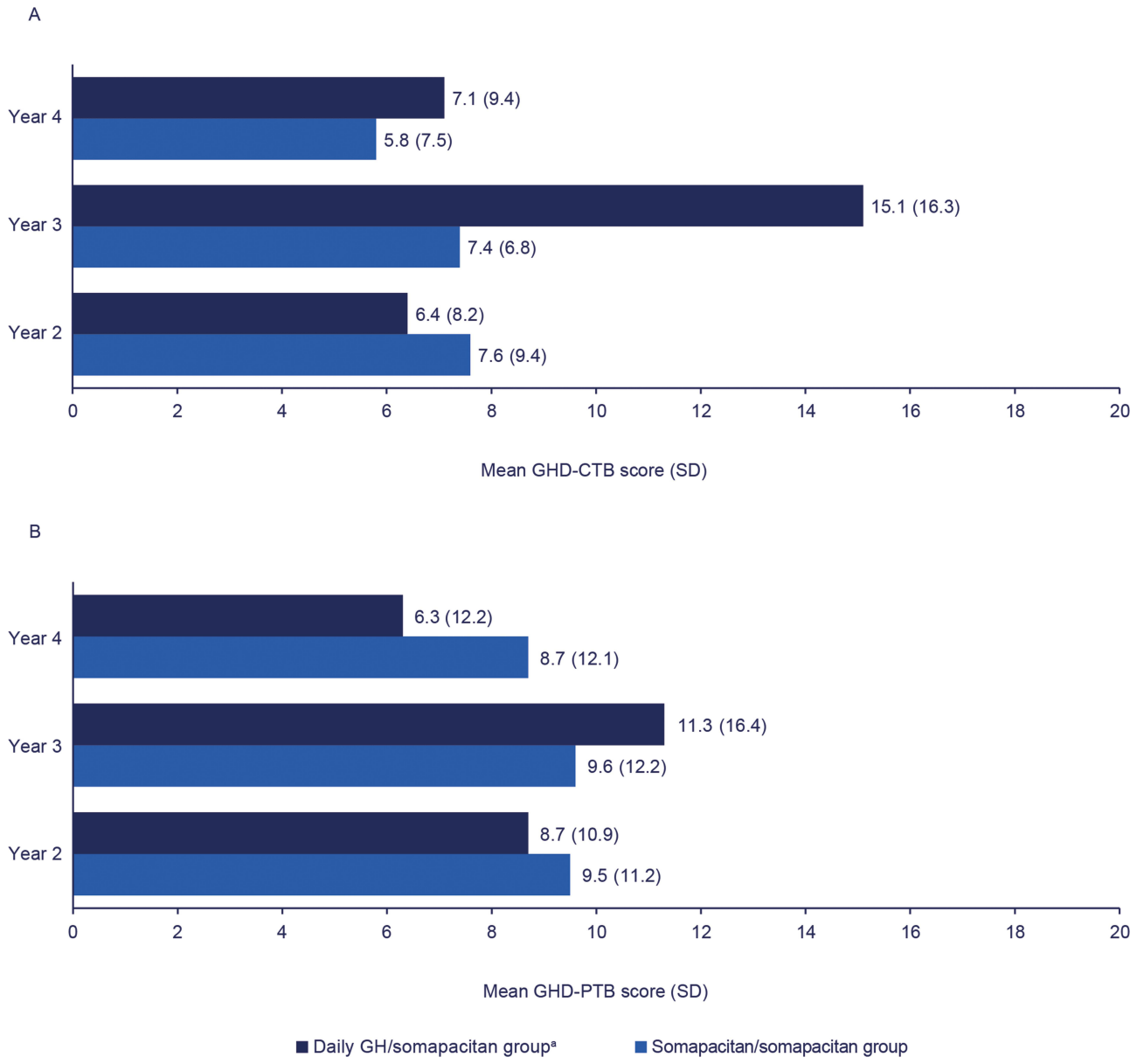


**Figure 2** Treatment burden scores for participants with CGHD and their parents/guardians in the REAL 3 trial. (**A**) Growth Hormone Deficiency–Child Treatment Burden (GHD-CTB) and (**B**) Growth Hormone Deficiency–Parent Treatment Burden (GHD-PTB) mean (SD) scores at years 2, 3, and 4.
**Note**: [a]The increase in GHD-CTB and GHD-PTB mean (SD) scores in the daily GH/somapacitan group between years 2 and 3 can largely be attributed to two patients, who may have experienced greater treatment fatigue compared with the rest of the cohort. Total scores range from 0 to 100. Data from Sävendahl et al.[38]
**Abbreviations**: CGHD, childhood growth hormone deficiency; GH, growth hormone; SD, standard deviation.

guardians of the participants were also given a GH patient-preference questionnaire.[38] The results showed that most parents/guardians of the participants who switched treatment at year 3 from daily GH to somapacitan preferred somapacitan. They also reported that they would be more adherent to somapacitan than daily GH.

In REAL 4, both somapacitan and daily GH treatments similarly reduced disease burden from baseline to week 52.[39] Treatment burden assessments favored somapacitan over daily GH, for both participants and their parents/guardians, and the difference being statistically significant for the latter group ($p = 0.0031$).[39] Year 2 results from the GH patient preference questionnaire in REAL 4 showed that 90% of participants and their caregivers in the group that switched treatment from daily GH to somapacitan preferred somapacitan treatment and most indicated that they would be more adherent to it.[40]

### Adherence

In REAL 4, mean adherence for somapacitan was 95.8% and mean adherence for the daily GH group was 88.3%.[39] In the REAL 3 trial, adherence over 52 weeks of treatment was >96% for the pooled somapacitan groups and 91.8% for the daily GH group.[36] For the same trial at year 3 of treatment, adherence was 92.2% for the pooled somapacitan groups and 87.2% for the daily GH group.[37]

## PK/PD of Somapacitan

The PK and PD profiles of somapacitan differ from those of daily GH. For example, PD profiles of LAGH demonstrate greater excursions when compared with daily GH.[46] IGF-I is currently the biomarker of choice for titration and monitoring of GH replacement.[47,48] One study simulated 39,200 IGF-I profiles from 26 adults and 23 children with GHD to develop and assess a model for predicting mean and peak IGF-I levels on different days after dosing with somapacitan.[49] A robust linear relationship was found between IGF-I sampled on any day after a somapacitan dose and the weekly mean IGF-I level, as well as the peak IGF-I level.[49]

### Participants with AGHD

A PK/PD modelling study using data from three Phase 3 clinical trials (REAL 1, REAL 2, and REAL Japan) was conducted with the aim of providing clinical guidance on dose–response titration of somapacitan for participants with AGHD.[47] A total of 4364 PK somapacitan concentration values and 4880 IGF-I values from 330 participants were included in the final somapacitan PK and PK/PD datasets, respectively. Modelling analysis was also used to predict the dose–IGF-I response for each patient by starting dose groups. The results showed that the somapacitan IGF-I SDS profile reached its maximum around 2 days after dosing; thus, sampling for IGF-I monitoring is recommended 3–4 days after dosing. Following on from that, in case of a missed dose, the generated modelling predictions indicated that administration with up to a 3-day delay is acceptable. The results also supported the clinical recommendations of higher starting doses for younger participants and women on oral estrogen replacement therapy.

### Participants with CGHD

A pooled modelling analysis from three Phase 1 clinical trials, including data from children with CGHD, was used to develop PK/PD models.[48] The results of the analysis showed that body weight was a significant predictor of the differences observed in the PK/PD levels between children and adults. Additionally, for both adults and children, the IGF-I level of once-weekly dosing of somapacitan was elevated, despite little or no accumulation of somapacitan. The study found that for children with CGHD, adjustments in dosage should be considered based on body weight or body surface area and growth response to treatment.[48] Another analysis used data from several clinical trials with participants.[50] The analysis involved 1473 PK samples from 210 participants with CGHD receiving somapacitan and 1381 IGF-I samples from 186 participants. All participants had CGHD and were receiving somapacitan in the respective trials. The results showed a relationship between somapacitan dose, exposure, change from baseline IGF-I SDS, and HV. Flexible dosing was also supported by the findings from the analysis, where dosing day changes can occur whilst maintaining at least four days between doses.

## Administration of Somapacitan

Somapacitan is indicated as a replacement treatment of endogenous GH for AGHD and children aged 2.5 (USA) or 3 years (Europe) and over with CGHD.[14,17] This drug is administered subcutaneously once per week via a pre-filled pen under the skin, with recommendations to alternate injections between the abdomen, thighs, buttocks, or upper arms.[14,17] There are three different prefilled pens of somapacitan: the Sogroya 5 mg/1.5 mL (3.3 mg/mL) pen delivers doses from 0.025 mg to 2 mg in increments of 0.025 mg, the Sogroya 10 mg/1.5 mL (6.7 mg/mL) pen delivers doses from 0.05 mg to 4 mg in increments of 0.05 mg, and the Sogroya 15 mg/1.5 mL (10 mg/mL) pen delivers doses from 0.1 mg to 8 mg in increments of 0.10 mg (Figure 3).[14,17] In case of a missed dose, it is recommended that the dose is administered as soon as possible and no later than 3 days after the original administration day.[14,17] Following that, the next once-weekly dose should be resumed at the regularly scheduled dosing day, regardless of whether the previous dose was caught up or not.[14,17] The shelf life of somapacitan is 2 years. After first opening, it must be stored in a refrigerator (2°C–8°C) and the shelf-life after opening is 6 weeks.[14,17] During travelling or if refrigeration is not possible, somapacitan may be kept at temperatures up to 30°C for up to a total of 72 hours. The pen should be stored with its cap on and protected from direct light.

### Adults with AGHD

For GH-naive patients and patients switching from daily GH, somapacitan dosage should be initiated at 1.5 mg per week.[14,17] The dosage must also be individually adjusted for each patient, and any increase is recommended to take place gradually with 2–4-week intervals in increments of 0.5 mg to 1.5 mg, based on the patient's clinical response, IGF-I level (aimed at the upper normal range and not exceeding SDS of +2) and occurrence of adverse reactions, up to a dose of 8 mg per week.[14,17] There are alternative recommendations for specific populations, such as patients aged 65 and over, patients with hepatic impairments and women receiving oral estrogen.[14,17] Although there is no evidence for increased risk of new primary cancers in adults receiving GH, patients receiving GH who have been treated for benign tumors or have achieved complete remission from malignant disease should be considered carefully for LAGH and followed closely.[14,17]

### Children with CGHD

The recommended starting dose of somapacitan for pediatric patients is 0.16 mg/kg body weight.[14] Thereafter, dosage should be individualized based on the growth response (US). Dosage may also be individualized and adjusted based on growth velocity, adverse reactions, body weight, and serum IGF-I concentrations (Europe). For pediatric patients switching from daily GH to somapacitan, the final daily GH dose should be administered the day before, or at least 8 hours before, the administration of the first somapacitan dose.[14] Somapacitan can be injected at any hour in the day. Higher doses of somapacitan may be needed for patients with moderate hepatic impairment; however, no further dose adjustment is required as doses are individually adjusted.[14]

## Discussion

LAGHs have been developed with the aim of reducing the treatment burden incurred by daily injections.[1,31,34,51–54] Somapacitan is a LAGH that is approved for the treatment of GHD for both adults and children.[10,14] Clinical recommendations for somapacitan are provided where appropriate in Table 3.

### Variation in GHD Severity in Pediatric Participants Included in REAL 3 and REAL 4

Positive results of treatment with somapacitan were observed in both REAL 3 and REAL 4. The results of REAL 4 met the primary endpoint of non-inferiority of somapacitan to daily GH. Participants were stratified based on GH peak level


**Figure 3** Somapacitan administration pens.

**Table 3** Summary of Main Recommendations for Clinicians About Adults and Children with GHD Receiving Somapacitan

| Recommendation Type | AGHD | CGHD |
|---|---|---|
| Dosing | Initiate somapacitan at a dose of 1.5 mg once weekly for treatment-naive participants and participants switching from daily GH<br>Initiate higher starting doses of 2 mg once weekly for younger participants and women on oral estrogen<br>Initiate lower starting doses of 1 mg once weekly for participants aged ≥65 years<br>Increase the weekly dosage every 2–4 weeks by approximately 0.5 mg to 1.5 mg until the desired response is achieved<br>Titrate the dose based on clinical response and serum IGF-I levels<br>Initiating a lower dose and using smaller dose increments for individuals with moderate hepatic impairment<br>Decrease the dosage as necessary on the basis of adverse reactions and/or serum IGF-I levels above the age and sex-specific normal range<br>The maximum recommended dosage is 8 mg once weekly<br>Administer a missed dose as soon as possible and no later than 3 days<br>If more than 3 days have passed since the missed dose, skip the dose and administer the next dose on the regular dosing day | Initiate somapacitan at a dose of 0.16 mg/kg body weight, individualizing the dose thereafter based on growth response<br>Administer a missed dose as soon as possible and no later than 3 days<br>If more than 3 days have passed since the missed dose, skip the dose and administer the next dose on the regular dosing day<br>Change the dosage in 10–20% increments<br>If possible, adjust the dose after 2 elevated IGF-I measures |
| Monitoring | Draw IGF-I samples 3–4 days after the prior dose | Draw IGF-I samples 3–4 days after the prior dose |
| Transition | | Participants who were treated with somapacitan for CGHD in whom the epiphyses are closed should be reevaluated before continuing<br>For participants switching from daily GH to somapacitan, the final daily dose should be administered the day before switching, or at least 8 hours before the administration of the first somapacitan dose<br>Carefully monitor height, weight, growth velocity, bone age, and IGF-I when transitioning a patient from daily GH to somapacitan |

**Abbreviations**: AGHD, adult growth hormone deficiency; CGHD, childhood growth hormone deficiency; GH, growth hormone; GHD, growth hormone deficiency; IGF-I, insulin growth factor-1.

(<7.0; ≥7.0 ng/mL) in REAL 4,[39] as a GH peak value of 7.0 ng/mL is sometimes taken as the lower cutoff for a normal level of GH. Participants in the group who initially received daily GH in REAL 4 had more severe GHD at baseline (GH peak (SD): 4.93 µg/L (2.5) for participants who initially received somapacitan and 4.10 µg/L (2.8) for participants who initially received daily GH) and more severe short stature at baseline (HSDS (SD): −2.99 (1.00) for participants who initially received somapacitan vs −3.47 (1.5) for participants who initially received daily GH).[39] This could have contributed to the finding that treatment with somapacitan only was not significantly superior to daily GH followed by somapacitan in terms of effect on HV at weeks 52 and 104 in REAL 4. In contrast, HV was significantly greater in participants treated with somapacitan 0.16 mg/kg/week compared with daily GH at week 52 in REAL 3.[36] The results of REAL 4 at year 2 showed that HV growth was sustained for both groups.[40]

## Factors to Be Considered When Switching from Daily to Weekly Injections

In clinical trials investigating somapacitan in pediatric populations, adherence was as high as can be expected in a clinical trial setting, and numerically slightly higher for somapacitan than daily GH.[36,37,39] Higher adherence to somapacitan compared with daily GH was also observed in the trial investigating somapacitan in adults with AGHD.[31,32] In both adult and pediatric trials, adherence was monitored using electronic diaries where participants were instructed to record the date, time, and injection dose as well as any missed doses.[31,32,36,37,39] In trials investigating other LAGHs, adherence was either not recorded or recorded and calculated using different measures.[43,45,55] It can be argued that not only is there a lack of standardized tool to measure adherence and compliance to GH treatment across trials but also persistence to treatment is unlikely to be captured in a clinical trial setting. GloBE-Reg is an international consortium-led registry project aimed at collecting real-world data on the safety and clinical parameters of several medicinal products, including LAGHs.[56] Analyses using data from this registry would shed more light on adherence and persistence of LAGH in a real-world setting.

Whether or not persistence with LAGH is improved compared with daily GH, participants with AGHD and children with CGHD enrolled in the aforementioned trials have indicated a preference for a once-weekly injection instead of a daily injection.[32,36,37,40,57] The reduced burden with weekly injections could encompass an improvement in physical functioning and emotional wellbeing, as well as a reduction in interference, for the patient and their parent/guardian if applicable. The ease of use of pen device of the LAGH is also an important consideration for participants switching from a once-daily to a once-weekly treatment regimen. Somapacitan is available in three different pre-filled pen devices (Figure 3).[9,17] Each device is color-coded based on the dose strength and the dose increase increments vary for each device.[9,10] For other LAGH such as lonapegsomatropin, although there are more dosage strengths available, the treatment is in a powder and solvent form and thus requires mixing prior to injection.[58] For somatrogon, similarly to somapacitan, the treatment is available in a pre-filled pen, but the strength of the dosage and the incremental increase are not fine-tuned.[59]

## When to Catch Up with a Missed Dose?

Regardless of the LAGH, the question of when to catch up with a missed dose becomes an important consideration when a single dose equates to seven injections as with daily GH. An analysis of missed doses with somapacitan showed that up to a 3-day delay catch-up with a missed dose is acceptable.[47] For somatrogon, this timeframe of when to catch-up with a missed dose is the same, while for lonapegsomatropin, it is recommended that a missed dose is administered no later than 2 days.[58,59]

## Cost-Effectiveness and Environmental Impact of LAGH

Another factor that should be considered is the cost-effectiveness of LAGHs compared with daily GH. While this has not yet been assessed in somapacitan, an analysis of cost-effectiveness has previously been conducted for somatrogon across five countries (the USA, Canada, Spain, Sweden, and Ireland) and the results showed a favorable cost-effectiveness for the LAGH versus daily GH in pediatric populations.[60] In contrast, for pediatric participants with CGHD in Germany and the UK, a similar analysis was conducted for somatrogon from a payor perspective, and the results showed that LAGH for pediatric populations is unlikely to be cost-effective.[61] Analyses are required on the cost-effectiveness of somapacitan in the countries where it is approved for the indication of GHD in pediatric participants and adults. Investigation of the environmental impact of LAGHs versus daily GH treatment should be considered as well. It can be speculated that fewer consumables, less frequent travel to collect prescriptions, and reduced pollution from manufacturing would be in favor of a once-weekly rather than a once-daily regimen.

## Who is Not Suitable for Weekly Injections?

Participants not suitable for GH treatment in general would also not be suitable for LAGHs. Historically, there have been questions regarding a potential link between GH treatment and cancer development. Reports of whether or not GH treatment increases the risk of second neoplasms are mixed, with some studies finding no statistical increase in the risk of developing second neoplasms with GH treatment and others reporting an increase dependent on factors such as gender and age.[62–65] However, it is generally regarded as appropriate to institute GH therapy in patients who survived childhood

cancer after clearly successful remission and a waiting period, provided that patients are closely followed up and monitored.[66] However, the effect of LAGH has not been studied in cancer survivors to date and any change in risk of cancer development remains theoretical. Patients with trypanophobia would also not be suitable for once-weekly injections. For children with chronic kidney disease, there are no clinical data available.

## Can Results from Prepubertal Children Be Extrapolated to Adolescents?

The trials investigating somapacitan in pediatric populations had either a cut-off of 11 years for boys or 10 years for girls, with the exception of REAL 3, where the cut-off was ages 10 and 9, respectively.[36,39] However, REAL 3 is a long-term safety and efficacy trial of somapacitan designed with a long-term safety extension of a total of 7 years.[36–38] The results from year 4 of the trial showed that a small number of children had entered puberty in each group.[38] Additionally, the protocol of the trial had been amended to include very young children (below 2 years) and children above the cut-off for boys and girls and below or equal to 17 years old. REAL 4, which is investigating somapacitan in children with CGHD, also has a long-term extension of a total of 4 years.[39,40,67] The results from these trials will provide insights into the long-term effects of a somapacitan in children and adolescents with CGHD.

Considering trials of other LAGHs, participants up to the age of 17 years were eligible for the phase 3 fliGHt trial of lonapegsomatropin, with 45.9% of enrolled participants being ≥11 or ≥12 years of age (girls and boys respectively). Results for AHV and change in HSDS were similar for this age group to younger patients, although the highest outcomes were observed for the youngest (<6 years of age) group. Proportion of participants who underwent puberty was not reported and safety results were not assessed by age group.[52] The phase 3 enliGHten trial was an extension of the fliGHt trial, and recruited participants had completed the prior trial; consequently, the age criteria were the same as fliGHt. Proportion of enrolled participants in each age group, proportion of participants who underwent puberty, and efficacy and safety results by age group were not reported.[55] However, the extent to which any observed results for other LAGHs will apply to somapacitan is unknown.

# Conclusion

Somapacitan demonstrated similar efficacy and safety to daily GH in Phase 3 trials in adults with AGHD and non-inferiority in children with CGHD. As a result, somapacitan has been approved for the treatment of GHD in adults and, more recently, in children. LAGHs have been developed with the aim of reducing the treatment burden and low adherence that daily injections can incur, thereby improving adherence and treatment outcomes. Adherence of patients to LAGHs, including somapacitan, is yet to be investigated in real-world studies. Additionally, the efficacy and safety of somapacitan in infants and adolescents with GHD are currently being investigated.

# Abbreviations

AGHD, adult growth hormone deficiency; AE, adverse event; AUC, area under the curve; CTP, carboxy-terminal; CGHD, childhood growth hormone deficiency; CI, confidence interval; ER, estimated ratio; EMA European Medicines Agency; ETD, estimated treatment difference; FDA, Food and Drug Administration; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; GH, growth hormone; GHD growth hormone deficiency; [$^3$H]-somapacitan, tritium-labelled somapacitan; HV, height velocity; HOMA-β, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IGFBP-2, insulin-like growth factor binding protein-2; IGFBP-3, insulin-like growth factor binding protein-3; IGF-I, insulin-like growth factor-I; LAGH, long-acting growth hormone; PD, pharmacodynamics; PK, pharmacokinetics; P-STAT5, phosphorylated STAT5; SD, standard deviationSDS, standard deviation score; TSQM-9, Treatment Satisfaction Questionnaire for Medication-9.

# Data Sharing Statement

The data for this review article were publicly sourced from the literature.

## Acknowledgments

The authors thank Novo Nordisk Health Care AG for reviewing the article for medical accuracy. Editorial support (in the form of writing assistance, collating author comments, assembling tables/figures, grammatical editing, and referencing) was provided by Emra Baker, Izabel James, and Helen Marshall of Ashfield Medcomms, and was funded by Novo Nordisk Health Care AG.

## 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; agreed on the journal to which the article was submitted; and agree to be accountable for all aspects of the work.

## Funding

Writing support for this review article was funded by Novo Nordisk Health Care AG.

## Disclosure

B.S.M.: Consulted for Ascendis Pharma, BioMarin, Bristol Myers Squibb, EMD Serono, Endo Pharmaceuticals, Eton Pharmaceuticals, GenSci, Novo Nordisk, Orchard Therapeutics, Pfizer, Provention Bio, and Tolmar; and received research support from Alexion, AbbVie, Ascendis Pharma, Aeterna Zentaris, Amgen, Amicus, Foresee Pharmaceuticals, Lumos Pharma, Lysogene, Novo Nordisk, OPKO Health, Pfizer, Prevail Therapeutics, and Sangamo Therapeutics. J.B.: Received honoraria for presentations at meetings sponsored by Novo Nordisk, Sandoz, and Ipsen; received sponsorship to attend scientific meetings from Novo Nordisk; and received payment for membership of the Publication Steering Committee of the International Outcomes Study, sponsored by Novo Nordisk. R.H: Advisory board member and lecturer for Novo Nordisk, Pfizer, Lumos Pharma, JCR, and Sandoz. A.L.: Consulted for/received research funding/honoraria from Novo Nordisk, Merck Serono, Alexion, AstraZeneca Rare Disease, and Pfizer Inc; and received honoraria from Ipsen and Sandoz. K.C.J.Y.: Received research grants to Barrow Neurological Institute from Crinetics, Ascendis, Corcept, Amryt, and Sparrow; served as an occasional advisory board member for Novo Nordisk, Ascendis, Ipsen, Amryt, Crinetics, Recordati, Neurocrine, and Xeris; lecture fees from Pfizer; and served as occasional speaker for Recordati and Novo Nordisk.

## References

1. Christiansen JS, Backeljauw PF, Bidlingmaier M, et al. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. *Eur J Endocrinol*. 2016;174(6):C1–C8. doi:10.1530/EJE-16-0111
2. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract*. 2008;62(1):76–87. doi:10.1111/j.1742-1241.2007.01630.x
3. 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
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. Miller BS, Rotenstein D, Deeb LC, Germak J, Wisniewski T. Persistence with growth hormone therapy in pediatric patients. *Am J Pharm Benefits*. 2014;6(1):e9–e17.
6. Loftus J, Wogen J, Oliveri D, et al. Persistence with daily growth hormone among children and adolescents with growth hormone deficiency in the UK. *Front Endocrinol*. 2022;13:1014743. doi:10.3389/fendo.2022.1014743
7. Kreitschmann-Andermahr I, Siegel S, Unger N, et al. Motivation for and adherence to growth hormone replacement therapy in adults with hypopituitarism: the patients' perspective. *Pituitary*. 2020;23(5):479–487. doi:10.1007/s11102-020-01046-y
8. Danielson E, Melin-Johansson C, Modanloo M. Adherence to treatment in patients with chronic diseases: from alertness to persistence. *Int J Community Based Nurs Midwifery*. 2019;7(4):248–257. doi:10.30476/IJCBNM.2019.81303.0
9. Food and Drug Administration. FDA approves weekly therapy for adult growth hormone deficiency. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-weekly-therapy-adult-growth-hormone-deficiency. Accessed March 24, 2023.
10. European Medicines Agency. Sogroya European public assessment report (EPAR). Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/sogroya. Accessed March 24, 2023.
11. Pharmaceutical and Medical Devices Agency. Report on investigation results. Available from: https://www.pmda.go.jp/files/000246397.pdf. Accessed 24, March 2023.

12. GlobalNewswire. Novo Nordisk A/S: Sogroya® data show potential as once-weekly treatment in children living with growth hormone deficiency. Available from: https://www.globenewswire.com/news-release/2022/06/12/2460802/0/en/Novo-Nordisk-A-S-Sogroya-data-show-potential-as-once-weekly-treatment-in-children-living-with-growth-hormone-deficiency.html. Accessed March 24, 2023.
13. Novo Nordisk. FDA approves once-weekly Sogroya® for the treatment of children living with growth hormone deficiency. Available from: https://www.novonordisk-us.com/content/nncorp/us/en_us/media/news-archive/news-details.html?id=166098. Accessed May 30, 2023.
14. Novo Nordisk. Sogroya(R) somapacitan-beco injection 10 mg pen. Available from: https://www.novo-pi.com/sogroya.pdf. Accessed April 13, 2023.
15. Miller BS, Yuen KCJ. Spotlight on lonapegsomatropin once-weekly injection and its potential in the treatment of growth hormone deficiency in pediatric patients. *Drug Des Devel Ther*. 2022;16:2055–2066. doi:10.2147/DDDT.S336285
16. European Medicines Agency. Ngenla(R) European public assessment report (EPAR). Available from: https://www.ema.europa.eu/en/documents/assessment-report/ngenla-epar-public-assessment-report_en.pdf. Accessed January 12, 2023.
17. European Medicines Agency. Sogroya SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/sogroya-epar-product-information_en.pdf. Accessed August 25, 2023.
18. European Medicines Agency. Lonapegsomatropin: SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/skytrofa-previously-lonapegsomatropin-ascendis-pharma-epar-product-information_en.pdf.Accessed January 12, 2023.
19. Food and Drug Administration. Highlights of prescribing information: Skytrofa. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761177s001lbl.pdf. Accessed January 12, 2023.
20. European Medicines Agency. Lonapegsomatropin(R) European public assessment report (EPAR). Available from: https://www.ema.europa.eu/en/documents/assessment-report/lonapegsomatropin-ascendis-pharma-epar-public-assessment-report_en.pdf.Accessed.Accessed January 12, 2023.
21. Højby Rasmussen M, Janukonyté J, Klose M, et al. Reversible albumin-binding GH possesses a potential once-weekly treatment profile in adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2016;101(3):988–998. doi:10.1210/jc.2015-1991
22. ClinicalTrials.gov. A trial to investigate long term efficacy and safety of lonapegsomatropin in adults with growth hormone deficiency: NCT05171855. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05171855. Accessed January 12, 2023.
23. ClinicalTrials.gov. A phase 3, multicenter study to evaluate The efficacy and safety of MOD-4023 in adults with growth hormone deficiency. Available from: https://clinicaltrials.gov/ct2/show/NCT01909479. Accessed May 30, 2023.
24. Helleberg H, Bjelke M, Damholt BB, Pedersen PJ, Rasmussen MH. Absorption, metabolism and excretion of once-weekly somapacitan, a long-acting growth hormone derivative, after single subcutaneous dosing in human subjects. *Eur J Pharm Sci*. 2021;167:106030. doi:10.1016/j.ejps.2021.106030
25. Johansson E, Nielsen AD, Demuth H, et al. Identification of binding sites on human serum albumin for somapacitan, a long-acting growth hormone derivative. *Biochemistry*. 2020;59(14):1410–1419. doi:10.1021/acs.biochem.0c00019
26. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. *Vasc Health Risk Manag*. 2009;5(1):199–211. doi:10.2147/VHRM.S4039
27. Havelund S, Plum A, Ribel U, et al. The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. *Pharm Res*. 2004;21(8):1498–1504. doi:10.1023/B:PHAM.0000036926.54824.37
28. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. *Front Endocrinol*. 2019;10:155. doi:10.3389/fendo.2019.00155
29. Petersen M, Gandhi PS, Buchardt J, et al. Tissue distribution and receptor activation by somapacitan, a long acting growth hormone derivative. *Int J Mol Sci*. 2020;21(4):1181. doi:10.3390/ijms21041181
30. Bentz Damholt B, Dombernowsky SL, Dahl Bendtsen M, Bisgaard C, Højby Rasmussen M. Effect of kidney or hepatic impairment on the pharmacokinetics and pharmacodynamics of somapacitan: two open-label, parallel-group trials. *Clin Pharmacokinet*. 2021;60(8):1015–1027. doi:10.1007/s40262-021-00990-7
31. Johannsson G, Gordon MB, Højby Rasmussen M, et al. Once-weekly somapacitan is effective and well tolerated in adults with GH deficiency: a randomized phase 3 trial. *J Clin Endocrinol Metab*. 2020;105(4):e1358–e1376. doi:10.1210/clinem/dgaa049
32. Otsuka F, Takahashi Y, Tahara S, Ogawa Y, Højby Rasmussen M, Takano K. Similar safety and efficacy in previously treated adults with growth hormone deficiency randomized to once-weekly somapacitan or daily growth hormone. *Clin Endocrinol*. 2020;93(5):620–628. doi:10.1111/cen.14273
33. Højby Rasmussen M, Brændholt Olsen MW, Alifrangis L, Klim S, Suntum M. A reversible albumin-binding growth hormone derivative is well tolerated and possesses a potential once-weekly treatment profile. *J Clin Endocrinol Metab*. 2014;99(10):E1819–E1829. doi:10.1210/jc.2014-1702
34. Johannsson G, Feldt-Rasmussen U, Håkonsson IH, et al. Safety and convenience of once-weekly somapacitan in adult GH deficiency: a 26-week randomized, controlled trial. *Eur J Endocrinol*. 2018;178(5):491–499. doi:10.1530/EJE-17-1073
35. Takahashi Y, Biller BMK, Fukuoka H, et al. Weekly somapacitan had no adverse effects on glucose metabolism in adults with growth hormone deficiency. *Pituitary*. 2023;26(1):57–72. doi:10.1007/s11102-022-01283-3
36. Sävendahl L, Battelino T, Brod M, et al. Once-weekly somapacitan vs daily GH in children with GH deficiency: results from a randomized phase 2 trial. *J Clin Endocrinol Metab*. 2020;105(4):e1847–e1861. doi:10.1210/clinem/dgz310
37. Sävendahl L, Battelino T, Højby Rasmussen M, Brod M, Saenger P, Horikawa R. Effective GH replacement with once-weekly somapacitan vs daily GH in children with GHD: 3-year results from REAL 3. *J Clin Endocrinol Metab*. 2022;107(5):1357–1367. doi:10.1210/clinem/dgab928
38. Sävendahl L, Battelino T, Højby Rasmussen M, et al. Weekly somapacitan in GH deficiency: 4-year efficacy, safety and treatment/disease burden results from REAL 3. *J Clin Endocrinol Metab*. 2023;108:2569–2578. doi:10.1210/clinem/dgad183
39. 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
40. Miller BS, Blair JC, Rasmussen MH, et al. Effective GH replacement with somapacitan in children with GHD: REAL4 2-year results and after switch from daily GH. *J Clin Endocrinol Metab*. 2023;108:3090–3099. doi:10.1210/clinem/dgad394
41. ClinicalTrials.gov. A research study in Chinese children with a low level of hormone to grow. Treatment is somapacitan once a week compared to Norditropin® once a day. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04970654. Accessed January 12, 2023.
42. Battelino T, Rasmussen MH, De Schepper J, Zuckerman-Levin N, Gucev Z, Sävendahl L. Somapacitan, a once-weekly reversible albumin-binding GH derivative, in children with GH deficiency: a randomized dose-escalation trial. *Clin Endocrinol*. 2017;87(4):350–358. doi:10.1111/cen.13409
43. Deal CL, Steelman J, Vlachopapadopoulou E, et al. Efficacy and safety of weekly somatrogon vs daily somatropin in children with growth hormone deficiency: a phase 3 study. *J Clin Endocrinol Metab*. 2022;107(7):e2717–e2728. doi:10.1210/clinem/dgac220

44. Horikawa R, Tanaka T, Hasegawa Y, et al. Efficacy and safety of once-weekly somatrogon compared with once-daily somatropin (Genotropin®) in Japanese children with pediatric growth hormone deficiency: results from a randomized phase 3 study. *Horm Res Paediatr*. 2022;95(3):275–285. doi:10.1159/000524600
45. Thornton PS, Maniatis AK, Aghajanova E, et al. Weekly lonapegsomatropin in treatment-naïve children with growth hormone deficiency: the phase 3 heiGHt trial. *J Clin Endocrinol Metab*. 2021;106(11):3184–3195. doi:10.1210/clinem/dgab529
46. Bidlingmaier M, Schilbach K. The use of IGF-I to monitor long-acting growth hormone therapy-timing is an art…. *J Clin Endocrinol Metab*. 2021;106(5):e2367–e2369. doi:10.1210/clinem/dgab016
47. Kildemoes RJ, Hollensen C, Biller BMK, Johannsson G, Takahashi Y, Rasmussen MH. Dose-exposure-IGF-I response of once-weekly somapacitan in adults with GH deficiency. *Eur J Endocrinol*. 2022;187(1):27–38. doi:10.1530/EJE-21-1167
48. Juul RV, Rasmussen MH, Agersø H, Overgaard RV. Pharmacokinetics and pharmacodynamics of once-weekly somapacitan in children and adults: supporting dosing rationales with a model-based analysis of three Phase I trials. *Clin Pharmacokinet*. 2019;58(1):63–75. doi:10.1007/s40262-018-0662-5
49. Juul Kildemoes R, Højby Rasmussen M, Agersø H, Overgaard RV. Optimal monitoring of weekly IGF-I levels during growth hormone therapy with once-weekly somapacitan. *J Clin Endocrinol Metab*. 2021;106(2):567–576. doi:10.1210/clinem/dgaa775
50. Kildemoes RJ, Backeljauw PF, Højby M, et al. Model-based analysis of IGF-I response, dosing, and monitoring for once-weekly somapacitan in children with GH deficiency. *J Endocr Soc*. 2023;7(11):bvad115. doi:10.1210/jendso/bvad115
51. 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
52. Maniatis AK, Nadgir U, Saenger P, et al. Switching to weekly lonapegsomatropin from daily somatropin in children with growth hormone deficiency: the fliGHt trial. *Horm Res Paediatr*. 2022;95(3):233–243. doi:10.1159/000524003
53. Miller BS. What do we do now that the long-acting growth hormone is here? *Front Endocrinol*. 2022;13:980979. doi:10.3389/fendo.2022.980979
54. Miller BS, Velazquez E, Yuen KCJ. Long-acting growth hormone preparations - current status and future considerations. *J Clin Endocrinol Metab*. 2020;105(6):e2121–e2133. doi:10.1210/clinem/dgz149
55. Maniatis AK, Casella SJ, Nadgir UM, et al. Safety and efficacy of lonapegsomatropin in children with growth hormone deficiency: enliGHten trial 2-year results. *J Clin Endocrinol Metab*. 2022;107(7):e2680–e2689. doi:10.1210/clinem/dgac217
56. Miller B, Savendahl L, Hickman K, et al. A long-acting growth hormone module for paediatric growth hormone deficiency in the Global Registry For Novel Therapies In Rare Bone & Endocrine Conditions – The GloBE-Reg LAGH Study. Available from: https://www.karger.com/Article/Pdf/525606. Accessed April 13, 2023.
57. McNamara M, Turner-Bowker D, Westhead H, et al. Factors driving patient preferences for growth hormone deficiency (GHD) injection regimen and injection device features: a discrete choice experiment. *Patient Prefer Adherence*. 2020;14:781–793. doi:10.2147/PPA.S239196
58. Food and Drug Administration. Highlights of prescribing information for Skytrofa. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761177lbl.pdf. Accessed May 04, 2023.
59. European Medicines Agency. Ngenla: SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/ngenla-epar-product-information_en.pdf. Accessed May 04, 2023.
60. Rivolo S, Loftus J, Peter B, et al. Cost-effectiveness and cost-utility analysis of somatrogon once-weekly injectable vs. daily growth hormones for treating pediatric growth hormone deficiency. Poster EE27. Poster presented at: Annual Meeting of ISPOR Europe; 2022. Vienna, Austria.
61. Mehl A, Goh A, Gupta S. Cost-effectiveness of once-daily somatropin from Sandoz versus once-weekly somatrogon for the treatment of growth hormone deficiency in children and adolescents. Poster EE589. Poster presented at: Annual Meeting of ISPOR Europe; 2022. Vienna, Austria.
62. Patterson BC, Chen Y, Sklar CA, et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. 2014;99(6):2030–2037. doi:10.1210/jc.2013-4159
63. Darzy KH, Shalet SM. Pathophysiology of radiation-induced growth hormone deficiency: efficacy and safety of GH replacement. *Growth Hormone IGF Res*. 2006;16:30–40. doi:10.1016/j.ghir.2006.03.002
64. He M, Deng X, Wang X, et al. Association between recombinant growth hormone therapy and all-cause mortality and cancer risk in childhood: systematic review and meta-analysis. *Front Pediatr*. 2022;10:866295. doi:10.3389/fped.2022.866295
65. Jenkins PJ, Mukherjee A, Shalet SM. Does growth hormone cause cancer? *Clin Endocrinol*. 2006;64(2):115–121. doi:10.1111/j.1365-2265.2005.02404.x
66. Boguszewski MCS, Boguszewski CL, Chemaitilly W, et al. Safety of growth hormone replacement in survivors of cancer and intracranial and pituitary tumours: a consensus statement. *Eur J Endocrinol*. 2022;186(6):P35–P52. doi:10.1530/EJE-21-1186
67. ClinicalTrials.gov. Investigating efficacy and safety of once-weekly NNC0195-0092 (somapacitan) treatment compared to daily growth hormone treatment (Norditropin® Flexpro®) in growth hormone treatment naïve pre-pubertal children with growth hormone deficiency. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02616562?draw=2. Accessed April 13, 2023.