Somapacitan, a once-weekly reversible albumin-binding growth hormone (GH) derivative, is well tolerated and convenient in adults with GH deficiency: results from a 26-week randomised, controlled phase 3 trial

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Objectives

To investigate the safety and tolerability of, and treatment satisfaction with, once-weekly somapacitan versus once-daily growth hormone (GH; Norditropin®, Novo Nordisk A/S, Denmark) in adult GH deficiency (AGHD) over 26 weeks.

Methods

- This was a multinational, multicentre, randomised, open-label, active-controlled trial (NCT02382939; REAL 2).
- Patients aged 18–79 years, who had been diagnosed with AGHD and treated with once-daily GH for ≥6 months, were randomised 2:1 to receive once-weekly somapacitan (starting dose 1.0–1.5 mg/week; 2.0 mg/week for women on oral oestrogen treatment) or once-daily Norditropin® (starting dose 0.1–0.3 mg/day).
- During the first 8 weeks, somapacitan and Norditropin® doses were titrated according to serum insulin-like growth factor-I (IGF-I) standard deviation score (SDS) in order to achieve IGF-I levels within the normal range and preferably between 0 and 2 SDS; a fixed dose was received for the remaining 18-week period. The maximum doses were somapacitan 8.0 mg/week or Norditropin® 0.7 mg/day.

Endpoints

- The primary endpoint was the incidence of adverse events (AEs), including injection site reactions.
- Secondary safety endpoints included the occurrence of anti-somapacitan or anti-GH antibodies, physical examination, body weight, vital signs, electrocardiograms and clinical laboratory tests.
- The key secondary efficacy endpoint was change from randomisation to Week 26 in treatment satisfaction, assessed using the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9). Items on the TSQM-9 are rated on a 7-point scale, with an increase in scores signifying an increase in treatment satisfaction.

Statistical analysis

- The safety analysis set and full analysis set both included all randomised subjects who received at least one dose of treatment.
- Estimated treatment differences in TSQM-9 scores were derived from a mixed model for repeated measurements, with treatment, GHD onset type, sex, region and sex by region interaction term as factors, and baseline as a covariate, all nested within week as a factor.

Introduction

- GH replacement in adults has been shown to be effective, with a favourable safety profile; however, daily subcutaneous injections in AGHD can be cumbersome.
- Somapacitan (NNC0195-0092, Novo Nordisk), a once-weekly, reversible albumin-binding GH derivative, has been shown in short-term trials to be well tolerated in healthy adults,[1] in children with GH deficiency (GHD)[2] and in AGHD.[3]

Results

Patient disposition

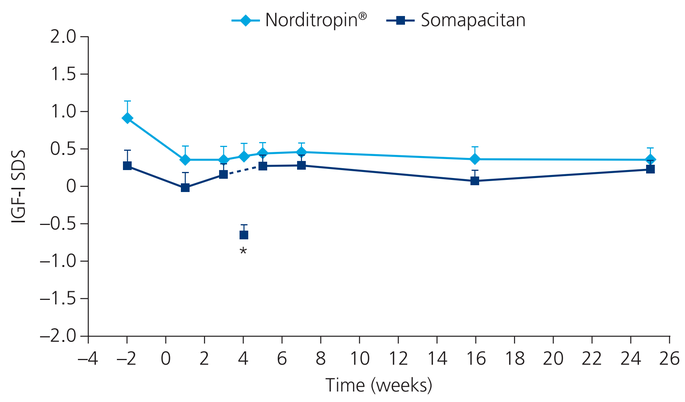
- Of 98 patients screened, 92 were randomised to receive once-weekly somapacitan (n=61) or once-daily Norditropin® (n=31).
- Characteristics of the randomised participants were well matched at baseline (**Table 1**).
- All randomised patients were exposed to the relevant trial treatment.
- After dose titration, IGF-I SDS was maintained in both treatment groups (**Figure 1**).
- The trial was completed by 95.1% (somapacitan) and 90.3% (Norditropin®) of patients.

Table 1. Baseline characteristics.

	Norditropin® once daily (n=31)	*Somapacitan once weekly (n=61)*
Age (years), mean (SD)	51.7 (17.1)	48.1 (16.2)
Female, N (%)	14 (45.2)	28 (45.9)
Ethnicity, N (%)		
Not Hispanic or Latino	24 (77.4)	48 (78.7)
Not available	7 (22.6)	13 (21.3)
Race, N (%)		
Asian	6 (19.4)	12 (19.7)
White	18 (58.1)	36 (59.0)
Not available	7 (22.6)	13 (21.3)
Body weight (kg), mean (SD)	81.0 (21.8)	82.1 (17.6)
BMI (kg/m^2), mean (SD)	28.5 (5.6)	28.6 (5.0)
GHD onset, N (%)		
Childhood – idiopathic	3 (9.7)	6 (9.8)
Childhood – organic	7 (22.6)	18 (29.5)
Adulthood	21 (67.7)	37 (60.7)
Somatropin dose level at screening (mg/day), mean (SD)	0.5 (0.9)	0.5 (0.3)

BMI, body mass index; GHD, growth hormone deficiency; SD, standard deviation.

Figure 1 IGF-I SDS levels (mean + SEM) versus time.



IGF-I, insulin-like growth factor-I; SDS, standard deviation score; SEM, standard error of the mean.
*Week 4 is the trough value, measured before administration of somapacitan.

- Three patients in each treatment group withdrew from the trial (somapacitan 4.9%; Norditropin® 9.7%). In each arm, two patients withdrew consent to participate in the trial and one patient withdrew due to AEs. One participant discontinued somapacitan treatment without withdrawing from the trial.

Safety

- AEs were reported by 86.9% of patients (somapacitan) and 67.7% (Norditropin®). Rates per 100 patient-years of exposure were 514.2 (somapacitan) and 530.8 (Norditropin®) (**Table 2**).
- The most frequently occurring AEs for both somapacitan and Norditropin® were nasopharyngitis, headache and fatigue (**Table 3**). The most frequent AEs had a greater frequency and event rate following Norditropin® than following somapacitan.

Table 2. Adverse events.

	Norditropin® once daily (n=31)			*Somapacitan once weekly (n=61)*		
	N (%)	*E*	*Rate*	*N (%)*	*E*	*Rate*
Adverse events	21 (67.7)	81	530.8	53 (86.9)	159	514.2
Serious adverse events	2 (6.5)	3	19.7	4 (6.6)	4	12.9
Severity						
Mild	18 (58.1)	58	380.1	44 (72.1)	119	384.8
Moderate	8 (25.8)	19	124.5	16 (26.2)	32	103.5
Severe	2 (6.5)	4	26.2	5 (8.2)	8	25.9
Relationship to trial drug						
Unlikely related	21 (67.7)	68	445.6	46 (75.4)	130	420.4
Possibly related	3 (9.7)	5	32.8	9 (14.8)	15	48.5
Probably related	4 (12.9)	8	52.4	8 (13.1)	14	45.3

E, number of adverse events; Rate, adverse event rate/100 patient-years of exposure.

Table 3. Adverse events occurring in ≥5% of patients in either treatment group.

	Norditropin®		*Somapacitan*	
	%	*Rate*	*%*	*Rate*
Nasopharyngitis	25.8	72.1	19.7	42.0
Headache	19.4	65.5	11.5	35.6
Fatigue	16.1	32.8	9.8	22.6
Dizziness	9.7	19.7	1.6	3.2
Arthralgia	6.5	13.1	8.2	16.2
Abdominal pain	0.0	0.0	6.6	12.9
Asthenia	3.2	6.6	6.6	16.2
Sciatica	0.0	0.0	6.6	12.9
Depression	6.5	13.1	0.0	0.0
Gamma-glutamyltransferase increased	6.5	13.1	0.0	0.0
Hypothyroidism	6.5	13.1	1.6	3.2

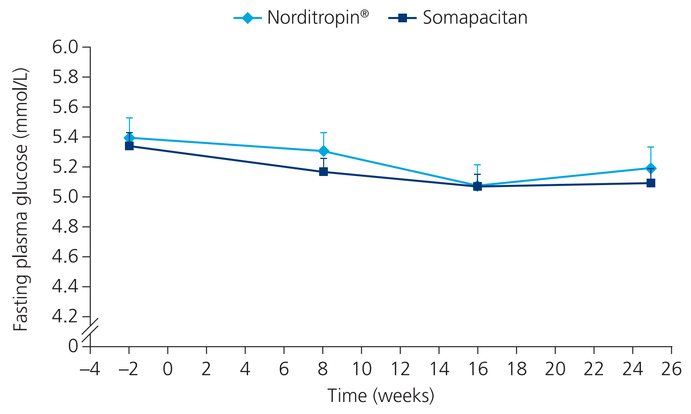
Rate, event rate/100 patient-years of exposure.

Conclusions

- Somapacitan was well tolerated and no safety issues were identified in this 26-week trial in patients with AGHD.
- Somapacitan was reported to be more convenient than once-daily GH injections.

- The serious AEs reported with somapacitan were cholelithiasis, procedural complication, mammoplasty and patella fracture (all n=1 event). Those reported with Norditropin® were intestinal ischaemia, short-bowel syndrome and nephrolithiasis (all n=1 event).
- Most AEs (**Table 2**), and all seven serious AEs reported, were judged by the investigator to be unlikely to be related to trial product.
- Two mild and transient injection site reactions were observed in patients treated with somapacitan: haematoma in one patient after the third dose and bruising in one patient after the second dose. No injection site reactions were reported with Norditropin®.
- No anti-somapacitan or anti-GH antibodies were detected.
- Fasting plasma glucose remained stable throughout the trial (**Figure 2**).
- No clinically relevant changes were observed upon physical examination, or in body weight, vital signs, electrocardiograms, or clinical laboratory measurements.

Figure 2 Fasting plasma glucose values (mean + SEM) versus time.

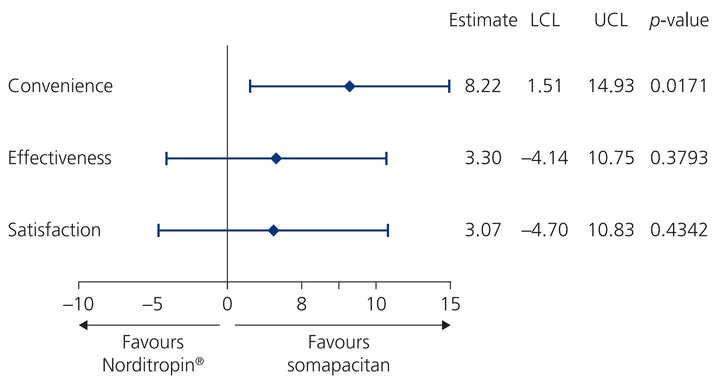


SEM, standard error of the mean.

Treatment satisfaction

- The change in the TSQM-9 convenience score from randomisation to Week 26 was statistically significantly greater with somapacitan than with Norditropin® (**Figure 3**).
- The differences in changes in effectiveness and overall satisfaction scores at Week 26 between somapacitan and Norditropin® did not reach statistical significance (**Figure 3**).

Figure 3 Estimated treatment difference in change in TSQM-9 scores at Week 26.



Full analysis set. Estimates are from a mixed model for repeated measurements.
LCL, lower confidence limit; TSQM-9, Treatment Satisfaction Questionnaire for Medication-9; UCL, upper confidence limit.

References

1. *J Clin Endocrinol Metab* 2014;99:E1819–29.
2. *Horm Res Paediatr* 2015;84(Suppl 1):FC7.4.
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†Deceased

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