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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Geanina Roman-Popoveniuc, MD
BLA 761156
SOGROYA/somapacitan-beco

CLINICAL REVIEW

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Reviewer Name(s)	Geanina Roman-Popoveniuc, MD
Review Completion Date	07/23/2020
Established/Proper Name	somapacitan-beco
(Proposed) Trade Name	Sogroya
Applicant	Novo Nordisk Inc.
Dosage Form(s)	6.7 mg/mL as a 1.5 mL single patient use prefilled pen
Applicant Proposed Dosing Regimen(s)	-starting dose: 1.5 mg/week; 1.0 mg/week (patients > ^(b) ₍₄₎ yrs. of age); 2.0 mg/week (women receiving oral estrogen). -dose should be titrated by increments of approximately 0.5 mg to 1.5 mg, based on clinical response, adverse reactions and serum insulin-like growth factor 1 (IGF-1) concentrations. - maximum dose: 8 mg/week
Applicant Proposed Indication(s)/Population(s)	replacement of endogenous GH in adults with Growth Hormone Deficiency (GHD)
Recommendation on Regulatory Action	approval
Recommended Indication(s)/Population(s) (if applicable)	replacement of endogenous GH in adults with GHD

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

The Applicant (Novo Nordisk Inc.) submitted a Biologic License Application (BLA) for somapacitan injection under section 351 of the Public Health Act seeking an approval of somapacitan injection for the treatment of adult growth hormone deficiency (AGHD). Somapacitan is a long-acting recombinant human growth hormone (rhGH) (somatropin) with a single amino acid substitution in the amino acid backbone (leucine [L] at position 101 substituted with cysteine [C]) to which an albumin binding side-chain is attached. The side-chain reversibly binds to endogenous albumin delaying the elimination of somapacitan in vivo and thus prolonging the drug half-life ($t_{1/2}$) and duration of action. The rhGH, somatropin, is a protein that is manufactured to be nearly identical to the main form of the naturally occurring human growth hormone (hGH), somatotropin. Somapacitan is a device-biologic combination. The drug product is supplied as a sterile solution for subcutaneous (s.c.) use as 10 mg/1.5 mL ready-to-administer pre-filled pen. The frequency and route of administration are once-weekly s.c. administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The current submission provided substantial evidence of effectiveness of somapacitan for the treatment of AGHD, based on demonstrated superiority to placebo in change in the truncal fat percentage (TFP) (adipose tissue compartment), as well as improvement in other body composition parameters [i.e. truncal lean body mass, total lean body mass, appendicular skeletal muscle mass (ASMM)] compared to placebo after 6 months of therapy, normalization of insulin-like growth factor-1 (IGF-1) levels and evidence of durability of the effect up to 18 months of therapy in treatment-naïve patients with AGHD, in the pivotal trial NN8640-4054 (herein referred to as trial 4054).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Somapacitan is a long-acting rhGH (somatropin) for once-weekly subcutaneous (s.c.) administration, indicated for replacement therapy in adults with growth hormone deficiency (GHD). Somapacitan reversibly binds to endogenous albumin, thus delaying the elimination of somapacitan in vivo and thus prolonging the drug half-life and duration of action.

The clinical manifestations of GHD in adults are non-specific and include truncal obesity, increased fat mass, decreased lean body mass, decreased bone mass with an associated increased fracture risk, decreased exercise capacity, dyslipidemia, insulin resistance, increased inflammatory markers and decreased quality of life (QoL).¹ Untreated AGHD in hypopituitary patients has been associated with premature cardiovascular morbidity and mortality.^{2, 3, 4}

The 2011 Endocrine Society Guidelines on treatment of GHD in adults⁵ recommends growth hormone (GH) replacement therapy to reverse the abnormalities in body composition, with potential additional benefit on several cardiovascular surrogate markers (i.e. lipoprotein metabolism, endothelial function, C-reactive protein, etc.) and exercise capacity. Although there are no data from prospective clinical trials directly demonstrating that the beneficial effect of GH replacement therapy on the body composition parameters and other cardiovascular markers in AGHD patients is associated with improved clinical outcomes (i.e. improved cardiovascular morbidity and mortality), most clinicians regard a composite of decrease in fat mass, and improvement in lean body mass parameters, accompanied by a normalization in IGF-1 levels, as meaningful clinical benefit.

Recombinant hGH therapy via daily subcutaneous injection is the only treatment available for AGHD patients. There are several daily rhGH products approved in US. Improvement in body composition parameters as surrogate efficacy endpoints has been used for all FDA-

¹ Cuneo RC et al. The growth hormone deficiency syndrome in adults. Clin Endocrinol (Oxf). 1992; 37: 387-397

² Jørgensen JOL, Juul A. THERAPY OF ENDOCRINE DISEASE: Growth hormone replacement therapy in adults: 30 years of personal clinical experience. Eur J Endocrinol. 2018; 179: R47-R56

³ Stockholm K, et al. Mortality and GH deficiency: a nationwide study. Eur J Endocrinol. 2007; 157:9-18

⁴ Pappachan JM, et al. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. J Clin Endocrinol Metab. 2015; 100:1405-1411

⁵ Molitch ME, et al. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. 2011. J Clin Endocrinol Metab. 2011; 96: 1587-1609

approved GH products, with primary and secondary endpoints varying among the GH products, without a specific body composition parameter being used on a consistent basis. Examples of surrogate efficacy endpoints previously used include, but are not limited to changes in: total body fat mass, total lean mass, truncal or total body fat percentage (%), and total lean mass %. Absent new scientific data informing the benefit-risk profile of improvement in body composition parameters as a result of GH replacement therapy in adult GHD patients, the Division continues to accept improvement in various body composition parameters as surrogate markers to determine efficacy of rhGH for the adult GHD indication.

The clinical development program of somapacitan to support approval for treatment of AGHD patients was comprised of 3 phase 3 trials investigating the efficacy and safety of somapacitan in AGHD patients and 5 clinical pharmacology studies. The substantial evidence of effectiveness of somapacitan in the proposed indication and pivotal safety data were provided from study 4054. Trial 4054 represents the pivotal global efficacy and safety trial in GH-treatment-naïve patients, which compares somapacitan to placebo and Norditropin® FlexPro® (herein referred to as Norditropin), as the active comparator. Trials NN8640-4244 and NN8640-4043 (herein referred to as trials 4244 and 4043) provided supportive evidence of safety and effectiveness (only trial 4244) of the drug in the intended population comparing somapacitan to Norditropin only. These trials were conducted in previously GH-treated patients.

The Applicant demonstrated that somapacitan was effective in improving the abnormalities in body composition parameters in treatment-naïve AGHD patients as demonstrated in the pivotal trial 4054, which was a multi-center, randomized, parallel-group, placebo-controlled (double-blind) and active-controlled (open label) trial in 300 patients with AGHD. The trial met its primary endpoint by demonstrating superiority to placebo in change in TFP after 6 months of therapy, with an estimated mean treatment difference (ETD) in TFP reduction between somapacitan and placebo of -1.53% [95% confidence interval (CI): -2.68; -0.38, $p = 0.009$].

Secondary supportive efficacy endpoints assessments showed that the changes in lean body mass parameters (truncal lean body mass, total lean body mass, and ASMM, respectively) between somapacitan and placebo were all in favor of somapacitan as well [ETD: 454 gm (95% CI: 25; 880, $p = 0.038$), 1144 gm (95% CI: 459; 1829, $p = 0.0011$), and 679 gm (95% CI: 340; 1019, $p = 0.0001$), respectively], while the changes from baseline in all lean body mass parameters between somapacitan and Norditropin were similar (804 gm vs 843 gm, 1394 gm vs 1345 gm, and 558 gm vs 462 gm, respectively).

Although the secondary comparison between somapacitan and Norditropin of the primary endpoint showed a greater effect of Norditropin on the TFP reduction compared to somapacitan, with an ETD of 1.17% [95% CI: 0.23; 2.11], the analysis seems to be

confounded by use of oral estrogen in female patients; oral estrogen therapy has a known attenuating effect on the metabolic actions of rhGH therapy. A post-hoc subgroup analysis showed a higher reduction in TFP in females on oral estrogen in Norditropin group compared to somapacitan [ETD: 2.21% (95%CI: 0.29; 4.141)], as opposed to the rest of the trial population excluding female patients on oral estrogen [ETD: 0.84% (95% CI: -0.28; 1.96)], which most likely explain the observed treatment differences between somapacitan and Norditropin groups for the entire trial population. Having said that, a beneficial effect was still noted in the reduction in TFP in females on oral estrogen in somapacitan group compared to placebo and was similar to the effect seen for the entire population [ETD: -1.44% (95%CI: -3.97; 1.09) vs -1.53% (95%CI: -2.68; -0.38)]. The observed treatment difference in the subgroup of females on oral estrogen between somapacitan and Norditropin was likely due to a suboptimal titration of somapacitan in this subgroup of patients [IGF-I standard deviation score (SDS) post-titration levels in females on oral estrogen were in general lower than in the other gender subgroups in both somapacitan and Norditropin groups, but the difference appeared to be most pronounced for somapacitan-treated females on oral estrogen, with 42% of them not reaching the IGF-1 SDS post-titration target of -0.5 IGF-1 SDS) and was further augmented by a random higher distribution of females on oral estrogen in somapacitan group compared to the other 2 treatment groups (31.7% in somapacitan group, 19.3% in Norditropin group and 16.4% in placebo group).

The improvement in the body composition parameters positively correlated with normalization in IGF-1 SDS for both somapacitan and Norditropin groups, demonstrating that the effect of somapacitan on the body composition endpoints was attributable to the drug, and not to other factors (i.e. lifestyle interventions).

In addition, the durability of the response of somapacitan treatment was demonstrated after 86 weeks of treatment through continued changes in all body composition parameters and maintained IGF-1 SDS levels.

The pattern of adverse events (AEs) emerging from somapacitan clinical development program (CDP) was similar to the AEs associated with hGH therapy class and are mechanistically anticipated pharmacodynamic effects. The most common ($\geq 5\%$) AEs that occurred with higher frequency in somapacitan group compared to placebo in pivotal trial 4054 were back pain (9.2.% vs 3.2%), arthralgia (6.7% vs 1.6%) and abdominal pain (5.8% vs 3.2%). Other important AEs that occurred more commonly in somapacitan group and are known adverse reactions of GH therapy class include peripheral edema, adrenal insufficiency, and weight increased (each occurring with an incidence of 3.3%), and lipohypertrophy (1.6%). The AEs of headache, allergic reactions (non-anaphylactic), injection site reactions, fatigue/asthenia, and paresthesia, also known important hGH class effects, occurred with lower frequency than placebo (8.3% vs 16.4%, 6.7% vs 14.8%, 6.7% vs 9.8%, 4.2 % vs

6.6%, 2.5% vs 3.3%, respectively), conferring somapacitan a reassuring safety profile. In general, all these class related AEs occurred with similar frequency between somapacitan and Norditropin groups.

Other potential GH related class effects (i.e. neoplasms, hyperglycemia/diabetes mellitus, hypothyroidism, carpal tunnel syndrome, intracranial hypertension, pancreatitis, severe hypersensitivity, lipoatrophy, stroke) occurred with very low incidence (< 1%), or did not occur at all in the overall CDP of somapacitan. A higher percentage of patients shifted from normal to high phosphate and creatine phosphokinase levels in somapacitan group compared to placebo and Norditropin groups from baseline to end of main trial period (17.5% vs 4.9% vs 6.7%, and 9.2% vs 6.6% vs 5.0%, respectively); although these laboratory changes were overall small, intermittent, and non-progressive during the trial, they should be labeled in Section 6. Adverse Reactions, for healthcare providers awareness. No new safety signals, including no immunogenicity findings, were detected during the CDP of somapacitan.

In summary, the Applicant demonstrated in pivotal trial 4054 that the drug is effective in treatment of AGHD based on the improvement of a spectrum of body composition parameters (i.e. TFP, truncal lean body mass, total lean body mass, ASMM), normalization of IGF-1 levels and demonstrated durability of the effect up to 18 months of therapy in treatment-naive patients with AGHD. The lower efficacy profile of somapacitan compared to Norditropin in the reduction of TFP was due to a lower effect of somapacitan in the subgroup of female patients on oral estrogen, which was likely driven by a suboptimal somapacitan dose titration during the trial and augmented by a higher representation of this subgroup of patients in somapacitan arm, compared to Norditropin and placebo arms. The antagonizing effects of oral estrogen on GH therapy in hypogonadal females with AGHD are well recognized in the literature, the effect is adequately mitigated through labeling [i.e. need for higher starting and maintenance doses of somapacitan in females on oral estrogen than general population (Sections 2. Dosage and Administration and Section 7. Drug Interactions)], while mitigation strategies in clinical practice include proper somapacitan dose titration to optimal IGF-1 levels, as well as potential alternate route (i.e. transdermal) for estrogen therapy administration to maximize GH effects in this patient population.

The Applicant also provided sufficient safety data that the drug has a reassuring safety profile with AEs that are recognized hGH class effects, are predictable, and can be adequately identified and managed by health care providers.

In conclusion, based on totality of the evidence, somapacitan represents another treatment option in the armamentarium of hGH therapies of demonstrated clinical safety and effectiveness. Thus, I recommend approval of somapacitan as replacement therapy in adults with GHD.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• GHD is a condition caused by insufficient production of GH from pituitary gland and most of the time is associated with other pituitary hormone deficiencies (hypopituitarism) • AGHD is associated with alterations in body composition (increased abdominal and visceral fat, decreased lean muscle mass and decreased bone density) and other comorbidities, such as insulin resistance, dyslipidemia, decreased exercise capacity and decreased QoL ⁵ • Untreated AGHD in hypopituitary patients has been associated with premature cardiovascular morbidity and mortality ² • The 2011 Endocrine Society Guidelines on treatment of GHD in adults⁵ recommends GH replacement therapy to reverse the abnormalities in body composition, with potential additional benefit on several cardiovascular surrogate markers (i.e. lipoprotein metabolism, endothelial function, C-reactive protein, etc.) and exercise capacity • Prospective, controlled data establishing that intervention with hGH therapy in AGHD patients that improves body composition parameters and other surrogate cardiovascular markers reduce the risk of cardiovascular complications in this patient population are not available	• AGHD in patients with hypopituitarism is associated with increased cardiovascular morbidity and mortality • GH replacement therapy reverses the body composition abnormalities and potentially other cardiovascular surrogate endpoints, but the beneficial effect on cardiovascular morbidity and mortality remains unknown

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Current Treatment Options</u>	- rhGH therapy via daily subcutaneous injection is the current available replacement treatment for AGHD patients - There are several rhGH formulations approved in US based on their beneficial effect on various body composition parameters (i.e. lean body mass, total fat body mass, truncal fat mass, percent total fat, etc.)	Daily rhGH replacement therapy via subcutaneous injections is the only available therapy for AGHD patients in US
<u>Benefit</u>	- Somapacitan is effective in improving the body composition abnormalities in AGHD patients as demonstrated in the single pivotal, multi-center, double-blind, placebo- and active controlled trial in treatment-naïve AGHD patients (trial 4054) - Somapacitan was superior to placebo in reducing the TFP after 6 months of therapy [ETD: -1.53% (95% CI: -2.68; -0.38, p= 0.009)], but had lower efficacy than Norditropin in reducing the TFP at 6 months [ETD: 1.17% (95% CI: 0.23; 2.11)] - Supportive secondary efficacy endpoints demonstrated statistically significant changes in lean body mass parameters (truncal lean body mass, total lean body mass, ASMM) in somapacitan-treated patients compared to placebo [ETDs: 454 (95% CI: 25; 880; p= 0.038), 1144 (95% CI: 459; 1829, p=0.0011), and 679 (95% CI: 340; 1019, p=0.0001), respectively]; observed changes in these body composition parameters were similar when compared to Norditropin-treated patients; adjustment for multiplicity testing was not done for the secondary endpoints - The improvement in body composition parameters in somapacitan was associated with normalization of IGF-1 SDS, demonstrating that the effect of somapacitan on the body composition endpoints was	- Improvement in body composition parameters are surrogate efficacy endpoints previously used by FDA to establish efficacy of GH products in AGHD patients, while there is no established treatment effect size that would define clinical benefit. - Somapacitan demonstrated clinical effectiveness in the treatment of AGHD, based on its effect on improvement of a spectrum of body composition parameters (i.e. TFP, truncal lean body mass, total lean body mass, ASMM) and normalization of IGF-1 levels in treatment-naïve AGHD patients. - The overall lower efficacy profile of somapacitan compared to Norditropin during current somapacitan CDP was due to a lower effect of somapacitan in the subgroup of female patients on oral estrogen, which was likely driven by a suboptimal somapacitan dose titration and augmented by a higher

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	attributable to the drug, and not to other factors (i.e. lifestyle interventions) • Subgroup analysis demonstrated a lower efficacy of somapacitan on TFP reduction in females with GHD compared to males with GHD [ETD -0.92% (females) vs -2.49% (males)], consistent with literature data • Post-hoc analysis demonstrated a lower efficacy of somapacitan compared to Norditropin on TFP reduction in females on oral estrogen, compared to rest of the study population [ETD: 2.21% (95% CI: 0.29; 4.14), vs 0.84% (95% CI: -0.28; 1.96)], which could explain the overall lower efficacy of somapacitan compared to Norditropin on the primary efficacy endpoint; the lower efficacy of somapacitan on TFP reduction in females on oral estrogen was likely driven by a suboptimal titration of somapacitan in females on oral estrogen (42% of females on oral estrogen did not reach the pre-defined IGF-1 SDS titration target vs 17% of females not on oral estrogen) and an uneven random distribution of females on oral estrogen (somapacitan: 31.7%, Norditropin: 19.3%; placebo: 16.4%) in trial 4054 • The durability of somapacitan effect was demonstrated after 86 weeks of treatment in trial 4054, through continued changes in all body composition parameters and maintained normalization in IGF-1 SDS levels • Somapacitan was also effective in maintaining the body fat parameters [total adipose tissue (TAT), subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT)] after 12 months of treatment in AGHD patients previously exposed to daily hGH therapy, with no statistically significant difference observed between somapacitan and	representation of this subgroup of patients in somapacitan arm, compared to Norditropin and placebo arms. The antagonizing effects of oral estrogen on GH therapy in hypogonadal females with AGHD are well recognized in the literature. The mitigation strategies for this patient population will be proposed in the label, including need for higher starting and maintenance doses of somapacitan in females on oral estrogen. The newness of somapacitan as a hGH replacement therapy is represented by its less frequent (i.e. weekly) administration schedule compared to current available therapy (i.e. daily), which may be of clinical importance to patients from a convenience and potentially compliance point of view.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the active comparator arm (Norditropin) (supportive, secondary efficacy endpoints, trial 4244)	
Risk and Risk Management	• The safety profile of somapacitan in AGHD patients was well characterized in the CDP • The overall incidence of deaths, serious adverse events (SAEs), severe AEs and discontinuations due to AEs was low, and similar, or lower in somapacitan group, compared to placebo, and Norditropin groups • The most common ($\geq 5\%$) AEs that occurred with higher frequency in somapacitan group compared to placebo in pivotal trial 4054 were back pain (9.2.% vs 3.2%), arthralgia (6.7% vs 1.6%) and abdominal pain (5.8% vs 3.2%). • Most of the AEs observed during somapacitan CDP are known adverse reactions of GH therapy class and include clinical manifestations of fluid retention (i.e. peripheral edema, arthralgia, nerve compression syndromes such as paresthesia, myalgia), back pain, headache, fatigue/asthenia, adrenal insufficiency, injection site reactions, lipohypertrophy, weight increased. These AEs occurred with relatively low frequency ($< 10\%$) in somapacitan group, and generally with similar, or lower frequency compared to Norditropin group, while many of them (i.e. paresthesia, myalgia, headache, fatigue/asthenia, injection site reactions) occurred with lower frequency in somapacitan group compared to placebo. • Other potential GH related class effects (i.e. neoplasms, hyperglycemia/diabetes mellitus, hypothyroidism, carpal tunnel	• The pattern of AEs emerging from somapacitan CDP was similar to the AEs associated with hGH therapy class and are mechanistically anticipated pharmacodynamic effects. • No new safety signals were detected during the non-clinical, and clinical development program of somapacitan, including no immunogenicity findings. • The AEs observed during somapacitan CDP (i.e. back pain, peripheral edema, arthralgia, adrenal insufficiency, lipohypertrophy/lipoatrophy, etc.) are predictable, monitorable AE, and will be mitigated through appropriate labeling. Other AE (i.e. neoplasia, glucose intolerance/diabetes, intracranial hypertension, severe hypersensitivity, hypothyroidism, pancreatitis, etc.) although observed with very low frequency (or not at all) during somapacitan CDP, they are mechanistically anticipated serious AE

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	syndrome, intracranial hypertension, pancreatitis, severe hypersensitivity, lipoatrophy, stroke) occurred with very low incidence (< 1%), or not at all in pivotal trial 4054, and in the overall CDP of somapacitan. • A higher percentage of patients shifted from normal to high phosphate and creatine phosphokinase levels in somapacitan group compared to placebo and Norditropin groups from baseline to end of main trial period (17.5% vs 4.9% vs 6.7%, and 9.2% vs 6.6% vs 5.0%, respectively); the changes were overall small, intermittent, non-progressive during the trial and of unknown clinical significance.	related to hGH therapy class and will be adequately mitigated through labeling as well

2. Therapeutic Context

2.1. Analysis of Condition

GHD is a condition caused by insufficient production of GH from pituitary gland, and most of the time is associated with other pituitary hormone deficiencies (hypopituitarism). The incidence of AGHD is about 1.90 for males and 1.42 for females, per 100.000.⁶

AGHD is generally classified as childhood onset (CO) and adult onset (AO). In CO GHD, the etiology is divided into congenital causes (i.e. genetic abnormalities in GH related genes, or associated with brain structural defects), acquired (i.e. due to trauma, mass effect from various CNS tumors, brain radiation, or surgery) and idiopathic. The etiology of AO GHD is most of the time due to organic causes, such as structural hypothalamo-pituitary disease (i.e. pituitary tumors, craniopharyngioma, Rathke's cleft cyst, metastasis, infiltrative/granulomatous lesions), local vascular compromise (i.e. as a result of surgery, radiation therapy, or head trauma), or rarely idiopathic. GHD is commonly associated with multiple pituitary hormone deficiencies, although isolated GHD in both CO and AO GHD can occur.

The diagnosis of AGHD typically requires demonstration of a blunted maximal GH response to various GH stimulation tests, according to specific diagnostic criteria, genetic test(s), or severe hypopituitarism.^{5,7} The reference standard GH stimulation test is insulin tolerance test (ITT), which elicits GH response to insulin-induced hypoglycemia, while additional tests include as stimuli GHRH-arginine, glucagon, and ghrelin receptor agonist (i.e. macimorelin). While low IGF-1 level is a biochemical marker of GHD, isolated IGF-1 level measurements are not of significant diagnostic value, due to low sensitivity and specificity, as patients with GHD may still have normal IGF-1 levels, while isolated low IGF-1 levels are more commonly encountered in the setting of aging and catabolic illness, rather than AGHD patients.⁸

The clinical manifestations of AGHD are non-specific and include truncal obesity, increased fat mass, decreased lean body mass, decreased bone mass with an associated increased fracture risk, decreased exercise capacity, dyslipidemia, insulin resistance, increased inflammatory markers and decreased quality of life.¹

⁶ Stockholm K, et al. Incidence GH deficiency - a nationwide study. Eur J Endocrinol. 2006;155:61-71

⁷ Cook DM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients – 2009 update. Endocr. Pract. 2009; 15:1–29

⁸ Melmed S. Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. N Engl. J Med. 2019. 380: 2551-2562

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The most consistent responses to GH replacement therapy have been observed on body composition parameters, such as decrease in total body fat content^{9, 10}, visceral fat mass¹¹, and increased muscle mass^{10, 12}. The long-term effect (after 3 years) of GH on body composition parameters suggests that similar effects are seen in both males and females with GHD on lean body mass, whereas the effects on fat mass are larger in males with AGHD than females, and the effects on lean body mass improve over time.¹⁰ There is also supportive evidence that improvement in muscle strength and exercise capacity may occur as a result of the increased muscle mass associated with GH therapy.^{13, 14}

In addition, it has been demonstrated that GH therapy improves several cardiovascular surrogate markers, such as: 1) endothelial function, via increase in flow-mediated dilatation and reduction of arterial stiffness¹⁵; 2) inflammatory markers (i.e. C-reactive protein and apolipoprotein B)¹⁶; 3) lipoprotein metabolism, via increase in HDL and decrease in LDL and total cholesterol^{10, 17, 18}. GH therapy improves insulin sensitivity indirectly via IGF-1 actions and decreases fat mass, but at the same time it has direct insulin antagonistic effects in the liver and other tissues. Therefore, although the overall effect of GH therapy on insulin resistance may seem to be neutral, a meta-analysis of placebo-controlled studies showed a slight increase in fasting glucose and fasting insulin levels.¹⁷

However, despite the beneficial effects on body composition parameters and cardiovascular markers, GH therapy has not been shown to have a mortality benefit, as it has not been studied in an adequately designed, prospective, long-term, placebo-controlled trial to properly address

⁹ Maiter D, et al. Baseline characteristics and response to GH replacement of hypopituitary patients previously irradiated for pituitary adenoma or craniopharyngioma: data from the Pfizer International Metabolic Database. *Eur J Endocrinol*. 2006; 155: 253–260

¹⁰ Attanasio AF, et al. Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status—3- year results from the HypoCCS Database. *J Clin Endocrinol Metab*. 2002; 87: 1600–1606

¹¹ Franco C, et al. The reduction in visceral fat mass in response to growth hormone is more marked in men than in estrogen deficient women. *Growth Horm IGF Res*. 2009; 19: 112–120

¹² Hoffman AR, et al. Growth hormone (GH) replacement therapy in adult-onset GH deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004; 89: 2048–2056

¹³ Götherström G, et al. Ten years of growth hormone (GH) replacement normalizes muscle strength in GH deficient adults. *J Clin Endocrinol Metab*. 2009; 94: 809–816

¹⁴ Widdowson WM, et al. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. *J Clin Endocrinol Metab*. 2008; 93: 4413–4417

¹⁵ Smith JC, et al. Effects of GH replacement on endothelial function and large-artery stiffness in GH-deficient adults: a randomized, double-blind, placebo-controlled study. *Clin Endocrinol (Oxf)*. 2002; 56:493–501

¹⁶ Bollerslev J, et al. Positive effects of a physiological dose of GH on markers of atherogenesis: a placebo-controlled study in patients with adult-onset GH deficiency. *Eur J Endocrinol*. 2006; 154: 537–543

¹⁷ Maison P, et al. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a meta-analysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab*. 2004; 89: 2192–2199

¹⁸ Abs R, et al. Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults—a KIMS database analysis. *Eur J Endocrinol*. 2006; 155: 79–90

this issue. Epidemiological studies have shown that adults with hypopituitarism from pituitary disease have increased mortality risk due to cardiovascular and cerebrovascular disease, however, multiple other risk factors for cardiovascular mortality were present in these studies, such as inadequate adrenal, thyroid and sex hormone replacement therapies, history of cranial irradiation, and possibly inadequate treatment for hyperlipidemia and hypertension.⁵ Therefore, ascribing increased mortality risk in hypopituitary patients solely to GHD would be inappropriate.

The reported impact of GHD on QoL has been extensively investigated, with findings showing wide variability, ranging on a spectrum from definitive benefit, to limited, or no benefit^{19, 20, 21}, and is largely dependent on the deviation from normality at the outset (i.e. if the QoL was normal at baseline, most likely no improvement will be seen with GH replacement therapy)²¹. Females and patients with AO GHD are more commonly affected¹⁹, while most commonly reported beneficial effects were noted on energy and vitality dimensions²⁰. However, it remains unclear whether GH therapy improves QoL, as most of the studies could not provide definitive evidence, largely because it is difficult to document positive GH effects on QoL in placebo-controlled trials, whereas improvements in open-label trials are prone to bias.

2.2. Analysis of Current Treatment Options

GH replacement therapy for AGHD was first approved by FDA in 1996. Since then, a number of rhGH formulations have been developed, all of them requiring daily s.c. administration (Table 1). All rhGH demonstrated efficacy in the treatment of AGHD and were approved based on the improvement in various body composition parameters; the examples of the body composition parameters and changes used for the approval are provided in Table 1.

¹⁹ Rosilio M, et al. Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H). J Clin Endocrinol Metab. 2004; 89: 1684–1693

²⁰ Koltowska-Haggstrom M, et al. Assessment of quality of life in adult patients with GH deficiency: KIMS contribution to clinical practice and pharmacoeconomic evaluations. Eur J Endocrinol. 2009. 161: S51–S64

²¹ Murray RD, et al. Influences on quality of life in GH deficient adults and their effect on response to treatment. Clin Endocrinol (Oxf). 199; 51: 565–573

Table 1: FDA-approved GH therapies in adults with GHD

GH product (Company)	Duration of studies, number of patients and endpoints
Humatrope (Lilly) 8.01.96*	• 6-month, PBO controlled; 165 pts • primary: lean body mass by bioelectric impedance (+2.81 kg relative to PBO) and body fat (-3.83 kg relative to PBO) HDL (after 18 months) and QOL (Nottingham Health Profile Score) • exercise capacity (V)2 max) and work performance (Watts) • bone mineral content (BMC) and bone mineral density (BMD)
Genotropin (Pharmacia) 10.31.97 *	• 6 month, PBO controlled, 172 pts • Beneficial changes in body composition were observed at the end of the 6-month treatment period for the patients receiving GENOTROPIN as compared with the placebo patients. Lean body mass, total body water, and lean/fat ratio increased while total body fat mass and waist circumference decreased. These effects on body composition were maintained when treatment was continued beyond 6 months. Bone mineral density declined after 6 months of treatment but returned to baseline values after 12 months of treatment.
Nutropin/AQ (Genentech) 12.15.97*	• 12 month, PBO controlled, one study for adult onset GHD and once for childhood onset; 230 pts; • total body % fat mass (-3.5 relative to PBO), trunk % fat mass (-4.3 relative to PBO), total body % lean mass (+3.4 relative to PBO) by DEXA, LDL cholesterol, LDL/HDL ratio, BMD • VAT by CT scan at 32 weeks in another study (-14.2 relative to PBO)
Norditropin FlexPro (Novo Nordisk) 11.01.04*	• two 6 month, PBO controlled, 31 pts AOGHD, 49 pts COGHD • AOGHD: lean body mass (+1.74 kg relative to PBO) and percent total body fat (-4.74% relative to PBO). • COGHD: lean body mass (+1.4 kg relative to PBO), percent total body fat (-4.24% relative to PBO), total abdominal fat volume (intraabdominal and extraperitoneal), waist/hip ratio, LDL, osteocalcin.
Saizen (Emd Serono) 11.01.04*	• 6 month, PBO controlled, 115 pts • lean body mass by DEXA as primary (+2.1 kg) • total fat mass (statistically significant but no number given)
Valtropin (BioPartners GmbH) 4.19.07*	• 6 month, PBO-controlled, trial in 92 adults • primary endpoint: change in fat mass (-1.35 kg relative to PBO) • main secondary endpoint: change in lean body mass (0.88 kg relative to PBO)
Omnitrope (Sandoz)	• per Genotropin label

*Date of FDA approval

Source: Approved labels at: <https://www.accessdata.fda.gov/scripts/cder/daf/>

Although treatment with GH appears to be safe overall, GH replacement may unmask underlying hypothyroidism, or hypoadrenalism, with other common side effects including fluid retention (with associated clinical features such as peripheral edema, arthralgia, myalgia, nerve compression syndromes, paresthesia), headache, and hyperglycemia. Treatment with GH is

contraindicated in patients with active malignancy, due to a theoretical concern regarding potential effect of GH therapy on neoplasia development, given GH primary mechanism of action of growth promotion via direct effect and indirectly via IGF-1 synthesis. However, to date, there is no clear indication from long-term epidemiological studies that rhGH therapy is associated with an increased risk for cancer development/regrowth, or pituitary tumor recurrence/regrowth.^{22, 23, 24, 25, 26, 27}

Lack of adherence to GH therapy, which often necessitates many years or life-long treatment, has long been recognized as a major problem with daily rhGH injections. The reasons for non-adherence are extensive and include, but are not limited to, frequency and route of administration, perceived ineffectiveness, side effects, issues with device/supply/insurance, or cognitive/emotional issues.^{28, 29, 30, 31} Although convenient pen devices have simplified the administration process, the daily injections remain a burden for the patients and may affect treatment adherence and thereby treatment effectiveness.³²

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Somapacitan is not approved for the treatment of AGHD in US to date.

²² Bell J, et al. Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab. 2010; 95: 167–177

²³ Swerdlow AJ, et al. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. Lancet. 2002; 360: 273–277

²⁴ Ergun-Longmire B, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab. 2006; 91: 3494–3498

²⁵ Darendeliler F, et al. Recurrence of brain tumors in patients treated with growth hormone: analysis of KIGS (Pfizer International Growth Database). Acta Paediatr. 2006; 95: 1284–1290

²⁶ Arnold JR, et al. GH replacement in patients with non-functioning pituitary adenoma (NFA) treated solely by surgery is not associated with increased risk of tumor recurrence. Clin Endocrinol (Oxf). 2009; 70: 435–438

²⁷ Karavitaki N, et al. GH replacement does not increase the risk of recurrence in patients with craniopharyngioma. Clin Endocrinol (Oxf). 2006; 64: 556–560

²⁸ Holdaway IM, et al. Three-year experience with access to nationally funded growth hormone (GH) replacement for GH-deficient adults. Clin Endocrinol (Oxf) 2015; 83:85–90

²⁹ Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. Endocr Pract. 2008; 14:143-154

³⁰ Auer MK, et al. Is insulin-like growth factor-I a good marker for treatment adherence in growth hormone deficiency in adulthood? Clin Endocrinol (Oxf). 2016; 84(6): 862-869

³¹ Saenger PH, et al. Long-acting growth hormone: an update. Endocr Dev. 2016; 30: 79-97

³² Kremidas D, et al. Administration burden associated with recombinant human growth hormone treatment: perspectives of patients and caregivers. J Pediatr Nurs. 2013; 28:55-63

3.2. Summary of Presubmission/Submission Regulatory Activity

On April 10, 2014, the Applicant submitted a briefing document for a pre-IND End of Phase 2 (EOP2) type B meeting to discuss the CDP for somapacitan to support a license application for treatment of AGHD. The Applicant proposed initiation of a phase 3 pivotal trial (trial 4054) in AGHD as a multicenter, multinational, randomized, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of somapacitan with once weekly dosing of placebo and once daily dosing of Norditropin in AGHD.

The major discussion points during the meeting on May 19, 2014 are summarized below (refer to Meeting minutes in DARRTS, dated 6/12/14, for additional details)

- The Agency agreed with the proposed primary endpoint of change from baseline to end of main trial period in TFP.
- The Agency agreed with the proposed duration of 34 weeks for the placebo-controlled phase of the trial, and the 52 week duration of the extension phase of the trial.
- The Agency objected with the exclusion of all patients with diabetes mellitus (DM), as enrollment of such patients was considered desirable in order to understand the effect of the drug in this subgroup of patients. The Applicant agreed to include diabetic patients with metabolically stable disease, defined as glycosylated hemoglobin (HbA1c) < 7.0%, on oral diabetic therapies only. The Agency further commented that the proposed HbA1c inclusion criterion of 7% is too restrictive and proposed a higher threshold of HbA1c of 9.0-9.5%, which was not endorsed by the Applicant. The Applicant noted that patients with higher HbA1c levels are likely to require injectable anti-diabetic drugs, which will pose difficulty with assessing accurately the injection site safety of the drug. The Division agreed with this proposed exclusion criterion, but continued to advise the Applicant to use higher HbA1c threshold (9-9.5%) in order to better understand the effect of the drug on glucose metabolism. However, the Applicant decided not to include diabetic patients in the study with HbA1c >7% acknowledged that the exclusion of diabetic patients with HbA1c >7% may influence the product labeling.
- The Agency disagreed with the proposed population for the primary analysis, which was a completer population, and recommended the primary analysis for efficacy to be based on the intention to treat (ITT) population. The Applicant stated that since the only planned post-randomization assessment of the primary endpoint is at week 34, the mixed model repeated measures analysis [which is the preferred analysis under Missing at Random (MAR) assumption] of the primary end point will exclude patients without week 34 data. The Agency reiterated that the primary analyses should be performed on a population that is in line with the ITT principle, and MAR assumption should not be used.
- The Agency recommended considerable efforts to be made to avoid missing data, and inclusion in the protocol of the procedures to prevent missing data, documentation of reasons for missing data.

- The Agency recommended the Applicant to make a clear distinction in the protocol and informed consent between treatment discontinuation and study withdrawal, and to educate patients about the continued scientific importance of their data and follow up, even if they discontinued study treatment.
- The Agency asked the Applicant to clarify if the secondary comparison of somapacitan to Norditropin was intended for labeling claims, with the Applicant stating it was not intended for that reason, but planned to include the clinical trial results in the labeling.
- The Agency agreed that the proposed patient exposure for the Phase 3 clinical program was acceptable, pending review of preclinical safety data
- The Agency recommended for ECG data to be collected when Cmax of somapacitan is expected; the Applicant stated that ECG measurements will be collected the day after drug administration and close to expected Cmax, in addition to pre-dose (baseline) ECG measurements.
- There was agreement with regards to immunogenicity samples collection schedule to occur at baseline, week 2, 4, 8 and 16+3 days, and at appropriate intervals over the course of the rest of the treatment period. Also, there was agreement that PK sampling to be performed at the same time as antibody sampling.

On July 23rd, 2014, the Applicant submitted the initial IND 116327 including the phase 3 trial protocol for study NN8640-4054 in AGHD. The study was deemed safe to proceed from a clinical standpoint.

(b) (4)

On April 25, 2019 a pre-BLA meeting took place to discuss the adequacy of the clinical development program to support an indication for AGHD, as follows:

- The Applicant presented evidence that (b) (4) the proposed original BLA submission was solely to seek approval of the 10 mg/1.5 ml strength, (b) (4) (b) (4)
- The Agency requested that additional safety information from ongoing (b) (4) clinical development program available at the time of the BLA submission, regarding deaths, serious adverse events (SAEs) and adverse events leading to drug discontinuation to be included in the BLA submission.
- The Agency did not agree with the Applicant's proposed pooled strategy of the safety data to include all studies (4043, 4244 and 4054), given differences in studies design, randomization ratio, patient population, etc., and requested safety data for each study to be submitted separately as well.

3.3. Foreign Regulatory Actions and Marketing History

Somapacitan is not currently marketed in any foreign jurisdiction.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on 4/3/2020. Four clinical sites were investigated for pivotal trial 4054. Site 455 was chosen because of the large sample size, had high number of AEs reported, and had never been inspected. Site 204 was inspected because had a higher than average death rate and had never been inspected. Site 126 was inspected of the large sample size, high discontinuation rate, a higher than average site specific efficacy effect size and had never been inspected. Dr. Kleppinger concluded that the inspectional findings support validity of the data as reported by the Applicant under this BLA. The inspections at all four sites revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted at any site and no Form FDA-483, Inspectional Observations, was issued. (Table 2)

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Table 2: Clinical Inspection Sites and Classifications

Name of CI/ State/Country Site#	# Subjects Randomized	Inspection Date	Classification
Corin Virgil Badiu, MD, PhD Romania Site 455	16 subjects	01/27-01/31, 2020	No Action Indicated (NAI)
Hiroshi Nishioka, MD, PhD Japan Site 204	8 subjects	01/27-01/31/2020	No Action Indicated (NAI)
Larry D. Stonesifer, MD Washington Site 111	4 subjects	01/08-01/14/2020	No Action Indicated (NAI)
Michelle D. Welch, MD Texas Site 126	13 subjects	02/10-02/14/2020	No Action Indicated (NAI)

4.2. Product Quality

Drug substance

Generic name: somapacitan

Chemical name: Somatotropin [101-cysteine] (human), (101→4')-thioether with *N*-[14,14-dioxido-1,10,16-trioxo-31-(1*H*-tetrazol-5-yl)-3,6-dioxa-14-thia-9,15-diazahentriacont-1-yl]-L-γ-glutamyl-L-γ-glutamyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-*N*⁶-(2-mercaptoacetyl)-L-lysine

The drug substance is produced by recombinant DNA technology in cultures of *Escherichia coli* cells followed by chemical conjugation to the small molecule side-chain.

Drug product

Sogroya is supplied at 6.7 mg/mL strength. The prefilled pen contains 10 mg in 1.5 mL volume. Potency is defined as specific bioactivity relative to protein content. The specific bioactivity is (b) (4) U/mg for release and stability. Sogroya is supplied as a sterile solution for subcutaneous injection, which is provided in 1.5 mL glass cartridges assembled into prefilled pen-injectors. Each 10 mg prefilled pen of Sogroya is formulated in (b) (4) Histidine, (b) (4) Poloxamer 188, (b) (4) Phenol, (b) (4) and Mannitol at pH 6.8. The product is designed to allow

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for administration of multiple once-weekly doses from the prefilled pen. Once opened, Sogroya is stored for up to 6 weeks at 2-8°C, which is referred to as the in-use period.

The Office of Pharmaceutical Quality (OPQ), recommends approval of BLA 761156 for Sogroya manufactured by Novo Nordisk. The OPQ division concluded that the data submitted in this application are adequate to support the conclusion that the manufacture of Sogroya is well-controlled and leads to a product that is pure and potent. The overall control strategy for drug substance and drug product is comprehensive for control of raw materials, process performance, and product quality attributes. According to OPQ review, Sogroya is sensitive to temperature (b) (4).

(b) (4). Agreement was reached with Novo Nordisk to further mitigate this risk by tightening temperature control limits during transportation and adjusting recommended storage and handling instructions on the label for the drug product. OPQ recommends the label include clear instructions to not freeze the product, and to discard the product if exposed to temperatures above 30°C. The immunogenicity assays used to evaluate anti-drug antibodies in clinical studies provided in support of this BLA are adequately validated and suitable for their intended purpose.

Please refer to the primary reviews in Panorama for full details regarding drug substance, drug product and immunogenicity assays assessments (Dr. Arulvathani Arudchandran), and small molecule side-chain intermediate assessment (Dr. Sharon Kelly).

4.3. Clinical Microbiology

Drug product and drug substance microbiology reviewers recommended approval of Sogroya from sterility assurance and microbial control perspectives (see Drs. Wayne Seifert's drug product and Ziyang Su's drug substance reviews in Panorama, dated 04/22/2020, and 06/05/2020, respectively, for full details).

4.4. Nonclinical Pharmacology/Toxicology

For a detailed review of non-clinical Pharmacology/Toxicology data, please refer to Dr. Huiqing Hao review in DARRTS, dated 04/17/2020.

Pharmacology

In vitro studies showed that somapacitan binds to hGH receptor with approximately 3-fold lower potency than native hGH. IGF-1 levels were increased, but in a more fluctuating pattern than with daily hGH administration. Once a week administration of somapacitan to hypophysectomised rats (an animal model of GHD) resulted in sustained increases in body

weight gain. In a standard battery of safety pharmacology studies, somapacitan did not cause any effects on the central nervous, respiratory, or cardiovascular systems in monkeys at exposures more than 1000-fold maximum recommended human dose (MRHD).

General Toxicology

Toxicology studies with treatment durations of 2 weeks, 13 weeks and 26 weeks were conducted in both monkeys and rats. The majority of findings in both species were related or secondary to the pharmacological effects of growth hormone and were observed more prominently in rats despite the presence of anti-drug antibodies resulting in reduced somapacitan exposure following repeated dosing. In contrast, monkeys showed minimal antidrug antibody development and no reduction in exposure after repeat dosing. IGF-1 levels were increased throughout dosing in both species.

Reproductive and Developmental Toxicology

In animal reproduction studies, somapacitan was not teratogenic in rats and rabbits when administered subcutaneously during organogenesis at doses approximately 12-times the clinical exposure at the MRHD of 8 mg/week. No adverse developmental outcomes were observed in offspring of rats administered somapacitan during organogenesis through lactation at approximately 275 times the clinical exposure at the MRHD.

Carcinogenicity

Somapacitan was not tested in 2-year carcinogenicity studies in rodents. According to Pharm/Tox reviewer, the carcinogenic risk for somapacitan is expected to be similar to that of currently marketed hGH products, based on the effects related to GH and the genotoxicity evaluation of the albumin linker moiety.

Genotoxicity

Somapacitan was not mutagenic or clastogenic in a standard battery of genotoxicity tests.

4.5. Clinical Pharmacology

Somapacitan was evaluated in 5 clinical pharmacology trials (3915, 4237, 3947, 4297 and 4298). For detailed analyses of the Clinical Pharmacology (Clin/Pharm) data please refer to the Clin/Pharm review by Dr. Mohammad Absar in DARRTS, dated 05/04/2020.

4.5.1. Mechanism of action

Somapacitan acts either directly via binding to GH receptor and/or indirectly via IGF-1, the peripheral target hormone for GH, produced primarily in the liver. The GH receptor is expressed on multiple tissues, but especially liver, cartilage, muscle, adipose, cardiac and kidney tissues.

GH stimulates linear growth in children both directly and indirectly, via IGF-1, by acting on epiphyseal plates of long bones while regulating chondrocytes growth, proliferation and differentiation.

In adults, several metabolic functions are maintained by GH. These include: 1) anabolic effects via increased muscle protein synthesis, via both direct GH action and indirectly via IGF-1 effect; 2) catabolic effects via increased lipolysis primarily through direct GH action, with loss of adipose tissue, release of free fatty acids, as well as lowering of cholesterol and apolipoprotein B, and increased high-density lipoprotein levels, while IGF-1 may have a potential opposite effect of enhancing adipogenesis; 3) increased hepatic gluconeogenesis and glycogenolysis through direct GH action, while IGF-1 exerts insulin-like effects of increased tissue glucose uptake, and inhibition of gluconeogenesis, with the resulting net effect on glucose homeostasis being difficult to predict.³³

4.5.2. Pharmacokinetics

Absorption

The PK of somapacitan following subcutaneous administration was evaluated in healthy subjects (study 3915) at dose levels of 0.01, 0.04, 0.08, 0.16 and 0.32 mg/kg. The median time to peak serum concentration (T_{max}) ranged from 6 to 36 hours post-dose, while AUC_{0-168h} and C_{max} increased with a higher than dose-proportional manner within the investigated dose-range.

The steady state PK of somapacitan were evaluated in AGHD patients (study 3947), in healthy subjects (study 3915) and in specific population including otherwise healthy subjects with renal impairment (study 4297) and hepatic impairment (study 4298). In patients with AGHD, the median T_{max} at steady state ranged from 4 to 11.9 hour, while steady state occurred after 1 to 2 doses. Somapacitan displayed apparent linear pharmacokinetics in the clinically relevant dose range (0.02 to 0.12 mg/kg). In patients with AGHD, a 6-fold increase in somapacitan dose (from 0.02 mg/kg/week to 0.12 mg/kg/week) resulted in approximately 8-fold increase in both AUC_{0-168h} and C_{max} of somapacitan in study 3947. The total variability (CV) for AUC_{0-168h} ranged from 61.7% to 102.2% and for C_{max} from 113.3% to 201.2% across doses (0.02 to 0.12 mg/kg) at steady state in patients with AGHD. Based on population PK analyses on data from the Phase 3 trials, the intra-subject variability in somapacitan exposure (C_{avg}) was estimated to be 37% (CV). In renally impaired healthy subjects, the exposure to somapacitan was overall higher than subjects with normal renal function, and exposure tended to increase with decreasing GFR. In subjects with moderate hepatic impairment, the somapacitan exposure (AUC_{0-168h}) was 4.7-fold higher compared to subjects with normal, hepatic function, and subjects with mild hepatic impairment.

³³ Kaplan SA and Cohen P. The Somatomedin Hypothesis. J Clin Endocrinol Metab. 2007; 92: 4529-4535

Distribution

Somapacitan is extensively bound (>99%) to plasma proteins. Based on population PK models, the estimated volume of distribution (V/F) of somapacitan in AGHD patients is approximately 14.6 L.

Metabolism and elimination

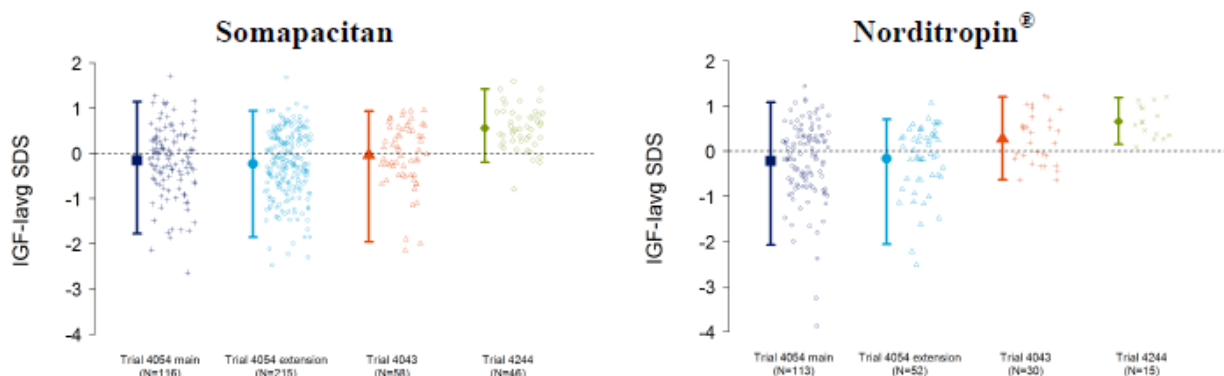
The plasma elimination half-life of somapacitan is approximately 2-3 days. Somapacitan is metabolized via proteolytic cleavage of the linker sequence between the peptide backbone and albumin binder sidechain. The primary routes of somapacitan excretion are urine (80.9%) and feces (12.9%), according to study 4237. No intact somapacitan was excreted, which indicates full breakdown of somapacitan prior to excretion.

4.5.3. Pharmacodynamics

The starting dose of somapacitan 1.5 mg/week was selected based on the outcome of dose finding study 3947 in adults with GHD, which showed that at steady state, the IGF-1 profiles of somapacitan doses of 0.02 and 0.04 mg/kg/week matched the IGF-1 level of the average Norditropin® dose of 0.004 mg/kg/day, indicating that the once-weekly somapacitan dose should be approximately 5 to 10-fold higher than the daily Norditropin® dose. Since the Norditropin® starting dose ranged from 0.15 to 0.3 mg/day, a 10-fold of the lower range of daily Norditropin® dose was selected for weekly somapacitan dose, i.e., 1.5 mg/week for the phase 3 trials. The maximum dose of somapacitan was 8 mg/week and was selected based on study 3947 that showed doses up to 0.12 mg/kg/week were well tolerated.

The dose titration scheme and the effects of somapacitan on IGF-1 levels in the phase 3 trials were discussed in details in Section 5 below. Overall, once-weekly somapacitan and daily Norditropin® resulted in similar average IGF-1 SDS levels at steady state (Figure 1), while the average weekly dose of somapacitan in all three Phase 3 studies (2.4 mg/week) corresponded approximately to the sum of daily doses of Norditropin® over one week (7 times 0.3 mg/day).

Figure 1: Average IGF-1 SDS at steady-state following once-weekly somapacitan and daily Norditropin (Trials 4054, 4043 and 4244)

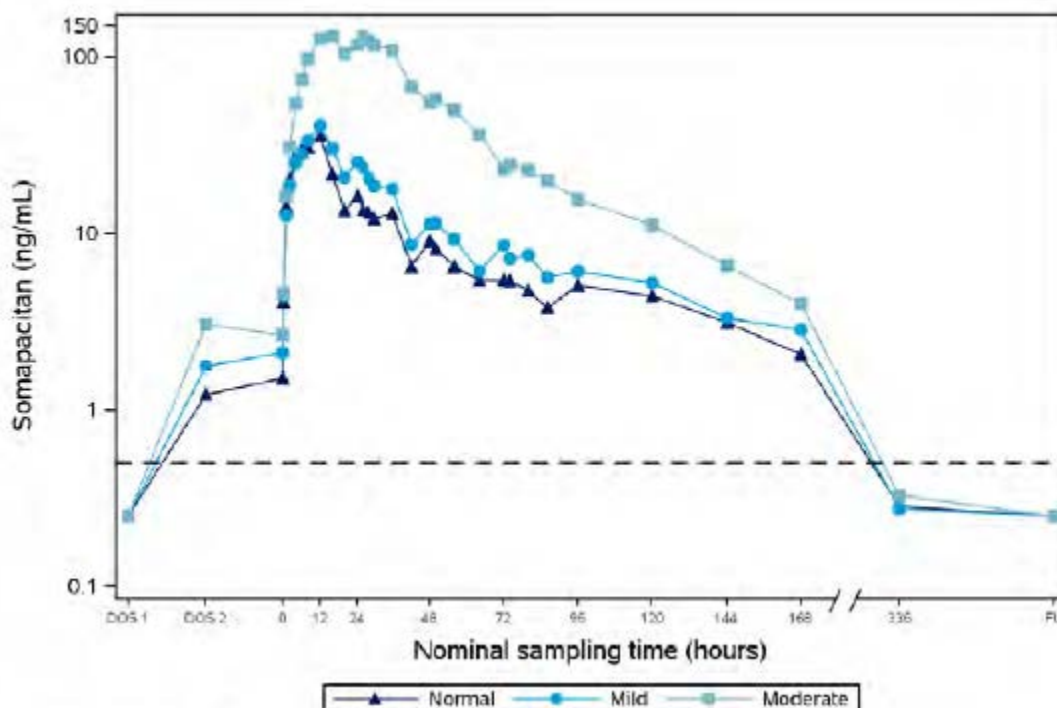


Source: Figure 3-3, Clinical overview

Hepatic impairment

The effect of hepatic impairment on the PK and PD properties of somapacitan was evaluated in trial 4298 after 3 doses of 0.08 mg/kg administered once weekly for 3 weeks to subjects with either normal hepatic function, or mild or moderately impaired hepatic function (defined according to Child-Pugh classification). The mean somapacitan concentration-time profile in the moderate hepatic impairment group was higher than in the mild impairment and normal hepatic function groups, with Steady-state somapacitan AUC_{0-168h} and C_{max} in the moderate hepatic impairment group being 4.7 and 3.5 times higher, respectively than in the normal hepatic function group, while the AUC_{0-168h} and C_{max} in the mild hepatic impairment group was similar to the normal hepatic function group (Figure 2).

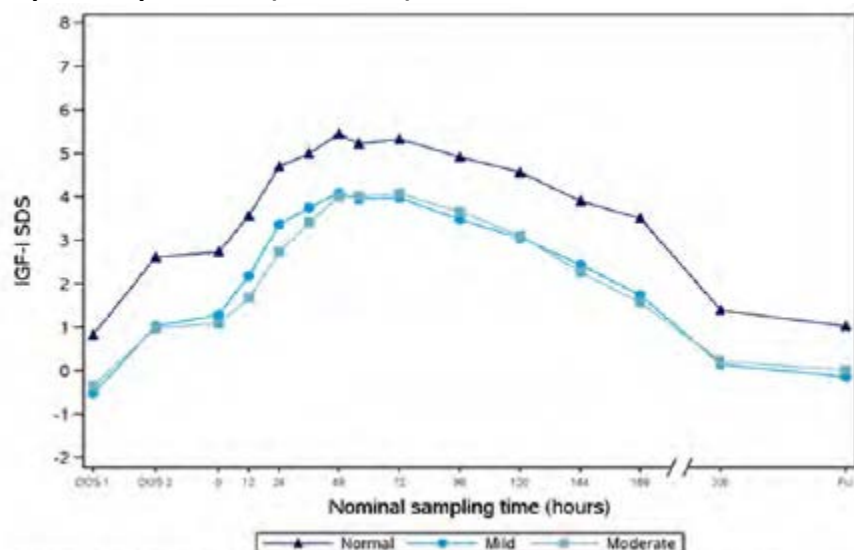
Figure 2: Mean somapacitan concentration-time profile (log scale) in subjects with normal hepatic function or mild or moderate hepatic impairment (trial 4298)



Source: Figure 3-22, SCP, p.63

Mean IGF-1 SDS levels were lower both at baseline and at steady state in the mild and moderate hepatic impairment groups, compared to the normal hepatic function group (Figure 3). For the moderate hepatic impairment group, IGF-1 AUC_{0-168h} was lower than in the normal hepatic function group with an estimated ratio of 0.75 [0.60, 0.95] 90%CI. Mean IGFBP-3 SDS levels were also lower both at baseline and at steady state in the mild and moderate hepatic impairment groups compared to normal hepatic function group.

Figure 3: Mean IGF-I SDS curves with normal hepatic function or with mild or moderate hepatic impairment (trial 4298)



Source: Figure 3-23, SCP, p.65

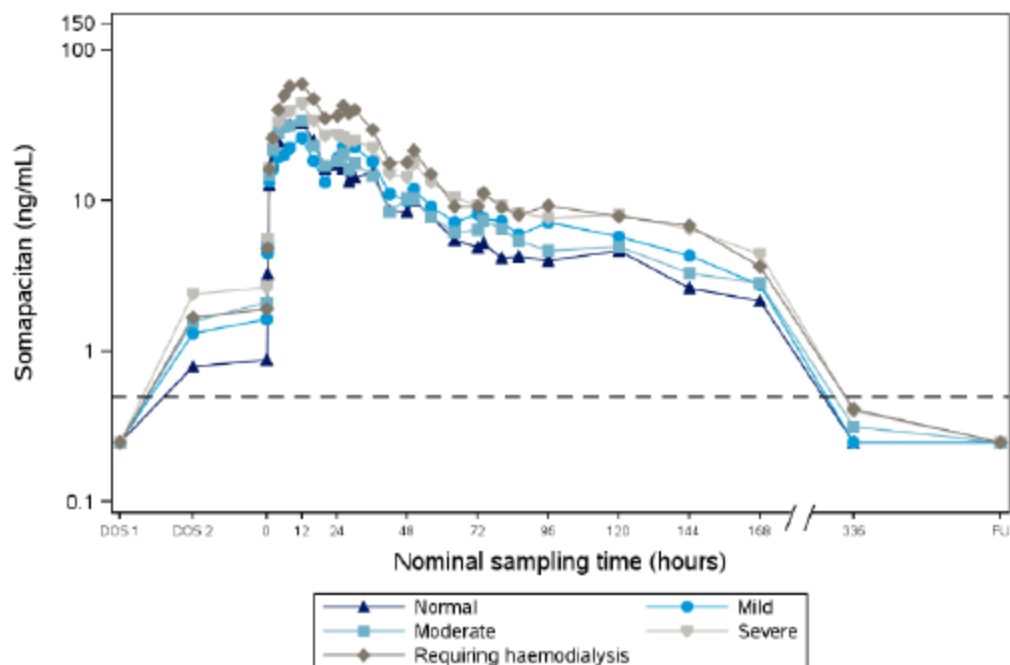
Medical officer's comments: Hepatic impairment was associated with increased somapacitan exposure, but decreased IGF-1 and IGFBP-3 levels compared to subjects with normal hepatic function. The lower IGF-1 and IGFBP-3 levels in moderately hepatic impairment group are likely explained by the decreased hepatic ability to produce adequate levels of IGF-1 and IGFBP-3, despite increased somapacitan exposure. Higher somapacitan doses are thus likely needed to obtain an adequate treatment response as compared to subjects with normal hepatic function, however the higher doses will likely result in significantly higher somapacitan exposure than currently studied in the CDP. Therefore, according to the available data from study 4298, Clin/Pharm recommends that patients with moderate hepatic impairment start with a lower dose (1.0 mg/week) with smaller dose increment and the maximum dose to be limited to 4.0 mg/week, information which should be labeled accordingly.

Renal impairment

The effect of renal impairment on the PK and PD properties of somapacitan was evaluated in trial 4297 after 3 doses of 0.08 mg/kg administered once-weekly for 3 weeks to subjects with either normal renal function, mild, moderate or severe renal impairment (categorized based on measured glomerular filtration rate [GFR] using exogenous sinistrin [Inutest®] as a filtration marker) or to subjects requiring hemodialysis. In addition, estimated GFR (eGFR) and creatinine clearance (CLcr) were calculated based on serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and Cockcroft-Gault equations, respectively. The mean concentration-time profiles for somapacitan at steady-state (after 3rd dose)

displayed higher somapacitan levels including higher trough levels in the renal impairment groups compared to the normal renal function group, with steady-state AUC_{0-168h} and C_{max} for somapacitan increasing with decreasing GFR, eGFR and CLcr (Figure 4).

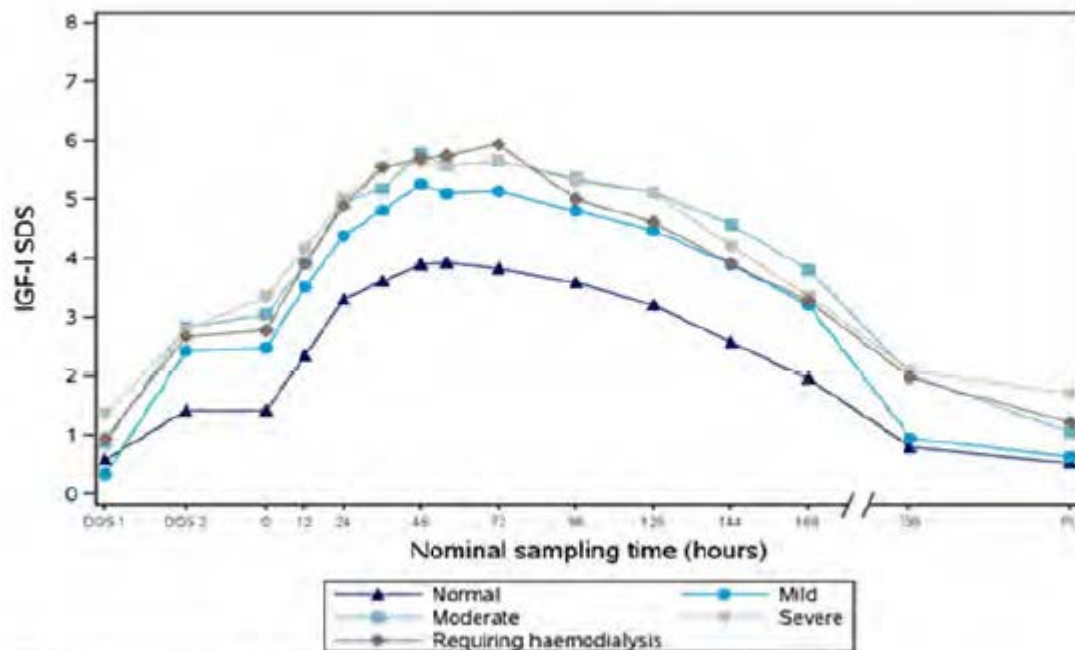
Figure 4: Mean somapacitan concentration-time profile (log scale) in subjects with normal renal function or various degrees of renal impairment (trial 4297)



Source: Figure 3-20, SCP, p.60

In line with the higher somapacitan exposure in all renal impairment groups, mean IGF-1 SDS and IGFBP-3 SDS levels were also elevated relative to the normal renal function group (Figure 5). The estimated ratios relative to the normal renal function group for IGF-1 AUC_{0-168h} at steady state were: 1.14 [0.90, 1.43] 90% CI (mild), 1.35 [1.09, 1.66] 90% CI (moderate), 1.40 [1.10, 1.78] 90% CI (severe) and 1.24 [1.01, 1.52] 90% CI (requiring hemodialysis).

Figure 5: Mean IGF-1 SDS curves for subjects with normal renal function or various degrees of renal impairment (trial 4297)



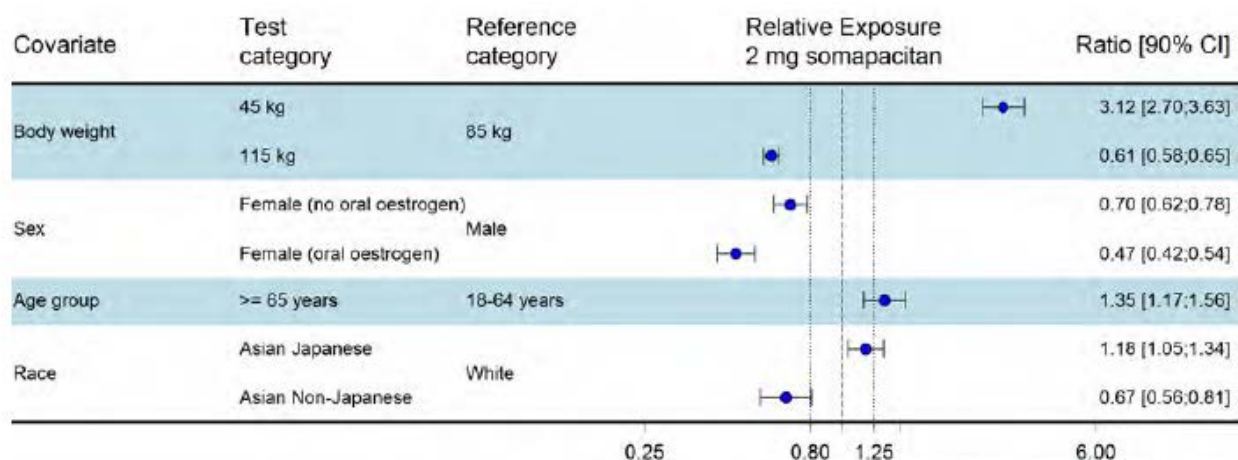
Source: Figure 3-21, SCP, p.62

Medical officer's comments: Renal impairment was associated with increased somapacitan exposure, as well as increased IGF-1 and IGFBP-3 levels compared to subjects with normal renal function, consistent with data from literature which indicates that subjects with renal impairment have reduced clearance of GH correlating with the degree of GFR loss. Since the dose of somapacitan is individually titrated based on IGF-1 levels, safety and efficacy, specific recommendations for dosing are not necessary.

The effects of various pre-specified covariates (i.e. weight, sex, oral estrogen use in females, age, and race) on somapacitan exposure and IGF-1 response was assessed using population PK and population PK/PD analyses based on data from the three Phase 3 studies in AGHD patients (studies 4054, 4244 and 4043). Of all investigated covariates, body weight, sex and concomitant oral estrogen intake, as well as age were the major covariates whereas race was less important (Table 3). Although the somapacitan exposure was approximately 3-fold higher in patients with lower body weight (BW; 45 kg) as compared to patients with 85 kg BW, the dose-response was expected to be similar across BW due to difference in baseline IGF-1 level. In addition, evaluation of the safety profile in the sub-group with lower BW in pivotal trial 4054 was acceptable. Therefore, since the dose will be titrated based on clinical response, no dose adjustment is recommended based on BW.

Medical officer's comments: Overall, the dose/exposure-response evaluation in clinically relevant sub-groups support the Applicant's dosing recommendations and the titration algorithms.

Table 3: Population pharmacokinetic covariate analysis of somapacitan exposure in patients with AGHD (Studies 4054, 4244 and 4043)



Source: Figure 3-15, SCP

4.6. Devices and Companion Diagnostic Issues

The CDRH division concluded that the device constituent parts of the pen-injector combination product are approvable (refer to Matthew Ondeck's review in Panorama, dated 05/14/2020, for full details).

4.7. Consumer Study Reviews

not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4: Listing of Clinical Trials Relevant to this BLA

Trial ID (countries)	Trial design and duration of treatment	Subjects exposed (M/F) Age	Dose regimen (and PYE for AGHD)
Phase 1 (Healthy subjects and special populations)			
3915 ^a (DE)	<i>Safety, tolerability, First human dose, PK/PD of somapacitan</i> Randomised, single-dose and multiple-dose, dose-escalating, double-blinded, placebo-controlled. Trial duration: 4 weeks.	105 healthy subjects Single-dose: 40 healthy subjects. (40/0) 22–43 years Multiple-dose: 32 Japanese healthy subjects ^b (32/0); 23–38 years 33 Non-Asian healthy subjects ^b (33/0) 22–45 years	Somapacitan s.c. 5 single-dose cohorts: 0.01, 0.04, 0.08, 0.16 and 0.32 mg/kg or placebo. Somapacitan s.c. 4 multiple-dose cohorts: 0.02, 0.08, 0.16 and 0.24 mg/kg or placebo once-weekly.
4237 (NL)	<i>Absorption, metabolism and excretion (AME) of somapacitan.</i> Single-dose, open-labelled. Trial duration: 5 weeks.	7 healthy subjects (7/0) 45–62 years	6 mg somapacitan containing [3H]-somapacitan up to 20 MBq, s.c.
4297 (DE)	<i>PK/PD and safety of somapacitan in subjects with renal impairment</i> Multiple-dose, open-labelled. Trial duration: approx. 6 weeks	44 subjects (25/19): • 15 healthy • 29 renal impaired (mild: 8; moderate: 8; severe: 5; haemodialysis: 8) 28–74 years	Somapacitan s.c. once-weekly for 3 weeks: 0.08 mg/kg
4298 (SK)	<i>PK/PD and safety of somapacitan in subjects with hepatic impairment</i> Multiple-dose, open-labelled. Trial duration: approx. 6 weeks	34 subjects (15/19): • 16 healthy • 18 hepatic impaired (mild: 9; moderate: 9). 37–69 years	Somapacitan s.c. once-weekly for 3 weeks: 0.08 mg/kg

Table 4: Listing of Clinical Trials Relevant to this BLA (cont.)

Trial ID (countries)	Trial design and duration of treatment	Subjects exposed (M/F) Age	Dose regimen (and PYE for AGHD)
Phase 1 (AGHD patients)			
3947 (DK, SE)	<i>Safety, tolerability, PK/PD</i> Randomised, multiple-dose, dose-escalating, sequential dose group, open-labelled, active-controlled (Norditropin®). Trial duration: 4 weeks	34 AGHD patients (25/9) 21–69 years	- Somapacitan s.c. once-weekly for 4 weeks: 0.02, 0.04, 0.08 and 0.12 mg/kg (6–7 patients per group corresponding to 0.4–0.5 PYE) In total, 26 patients, 1.8 PYE - Norditropin® s.c. daily: as pre-trial. 8 patients, 0.6 PYE
Phase 3a (AGHD patients)			
4054 ^a (AU, DE, IN, JP, LV, LT, MY, PL, RO, RU, ZA, SE, TR, UA, UK, US)	<i>Efficacy and safety</i> Randomised, parallel-group, placebo- (double-blinded) and active-controlled (open; Norditropin®) trial to compare the efficacy and safety of once-weekly somapacitan with once-weekly placebo and daily Norditropin® for 34 weeks (main), followed by a 52 weeks open-labelled extension period. ^e Trial duration: 86 weeks exposure and 88 weeks in trial.	300 treatment-naïve AGHD patients (including 46 Japanese patients) (145/155) 23–77 years	<i>Main period:</i> - Somapacitan s.c. once-weekly (individual dose titration based on IGF-I SDS; starting dose depends on age^c) or placebo once-weekly. - Norditropin® s.c. daily (individual dose titration based on IGF-I SDS; starting dose depends on age^d). 8 weeks dose titration and 26 weeks fixed-dose treatment. <i>Extension period:</i> - Somapacitan s.c. once-weekly or Norditropin® s.c. daily. 8 weeks dose titration and 44 weeks fixed-dose treatment. <i>Full trial:</i> - Somapacitan, actual mean dose: 0.040 mg/kg. 288.8 PYE. - Norditropin®, actual mean dose: 0.005 mg/kg. 123.2 PYE.
4043 ^a (DE, DK, FR, JP, SE, UK)	<i>Safety</i> Randomised, open-labelled, parallel-group, active-controlled (Norditropin®) to compare safety of once-weekly somapacitan with daily Norditropin®. Trial duration: 26 weeks exposure and 27 weeks in trial.	92 previously GH-treated AGHD patients (including 17 Japanese patients) (50/42) 19–77 years	- Somapacitan s.c. once-weekly (individual dose titration based on IGF-I SDS; starting dose depends on age^c). Actual mean dose: 0.027 mg/kg. 29.6 PYE. - Norditropin® s.c. daily (individual dose titration based on IGF-I SDS; starting dose depends on age^d). Actual mean dose: 0.003 mg/kg. 14.6 PYE. 8 weeks dose titration and 18 weeks fixed-dose treatment.

Table 4: Listing of Clinical Trials Relevant to this BLA (cont.)

Trial ID (countries)	Trial design and duration of treatment	Subjects exposed (M/F) Age	Dose regimen (and PYE for AGHD)
4244 ^a (JP)	<i>Safety and efficacy</i> Randomised, open-labelled, parallel-group, active- controlled (Norditropin®) to evaluate safety of once- weekly somapacitan and daily Norditropin®. Trial duration: 52 weeks exposure and 53 weeks in trial.	62 previously GH-treated Japanese AGHD patients (33/29) 20-75 years	• Somapacitan s.c. once-weekly (individual dose titration; starting dose depends on age^c). Actual mean dose: 0.029 mg/kg. 45.4 PYE. • Norditropin® s.c. daily (starting dose depends on age^d). Actual mean dose: 0.003 mg/kg. 14.8 PYE.

Abbreviations: AGHD = adult growth hormone deficiency; AME = absorption, metabolism and excretion; F = female; GH = human growth hormone; M = male; PYE = patient years of exposure; AU = Australia; DE = Germany; DK = Denmark; FR = France; IN = India; JP = Japan; LV = Latvia; LT = Lithuania; MY = Malaysia; NL = Netherlands; PL = Poland; RO = Romania; RU = Russia; ZA = South Africa; SE = Sweden; SK = Slovakia; TR = Turkey; UA = Ukraine; UK = United Kingdom; US = United States.

^a Trial includes Japanese subjects/patients.

^b In trial 3915, Japanese passport and Japanese born parents was required for Japanese subjects; non-Asian born parents was required for Non-Asian subjects.

^c Somapacitan starting dose: patients between 23-60 years (trial 4054) or 18-60 years (trials 4043 and 4244) of age start at 1.5 mg/week; females on oral oestrogen irrespective of age start at 2.0 mg/week, and patients older than 60 years of age start at 1.0 mg/week.

^d Norditropin® starting dose: patients between 23-60 years (trial 4054) or 18-60 years (trials 4043 and 4244) of age start at 0.2 mg/day; females on oral oestrogen irrespective of age start at 0.3 mg/day; patients older than 60 years of age start at 0.1 mg/day.

^e In the extension period, patients treated with somapacitan continued their once-weekly somapacitan treatment, patients treated with placebo were switched to somapacitan treatment and patients treated with Norditropin® were re-randomised to continue Norditropin® treatment or switch to somapacitan treatment.

Source: Applicant's Table 1-1, CSS, p.13

5.2. Review Strategy

Pivotal trial 4054 was the focus of this efficacy review. This review includes the Applicant's analyses for efficacy with this medical reviewer's commentary. A separate analysis and review was performed by the FDA statistician, Dr. Alexander Cambon and confirmed the Applicant's findings of efficacy. The safety data analyzed included all 3 phase 3 trials, 4054, 4244, and 4043. This review includes Applicant's analyses, as well as analyses generated by this medical reviewer using JMP and MAED software.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. NN8640-4054, A multicenter, multinational, randomized, parallel-group, placebo controlled(double blind) and active-controlled (open) trial to compare the efficacy and safety of once-weekly dosing of somapacitan (NNC0195-0092) with once-weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, followed by a 53-week open label extension period.

6.1.1. Study Design

Overview and Objective

Trial 4054 was designed to evaluate the safety and efficacy of once weekly dosing of somapacitan in AGHD.

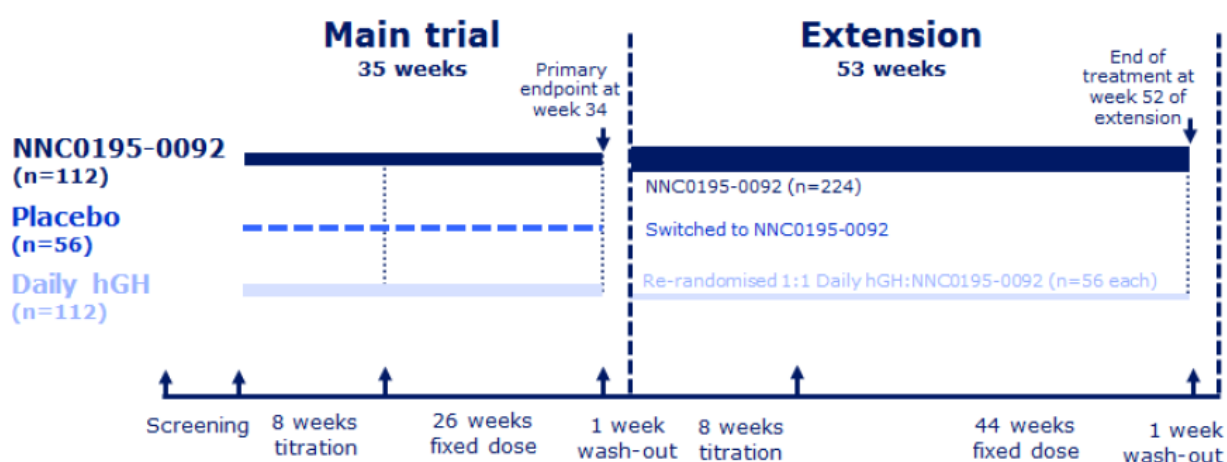
The primary objective of the trial was to demonstrate the efficacy of once-weekly dosing of somapacitan compared to placebo after 34 weeks of treatment in AGHD patients. The secondary objectives were evaluation of the clinical safety of once-weekly dosing of somapacitan during 34 weeks of treatment in AGHD patients, and evaluation of the efficacy and safety of somapacitan for up to 86 weeks of treatment in AGHD.

Trial Design

Trial 4054 was a multicenter, multinational, randomized, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial in AGHD patients to compare the efficacy and safety of once-weekly dosing of somapacitan with once-weekly dosing of placebo and daily dosing of Norditropin. A total of 280 AGHD patients were planned for enrollment, and 301 AGHD patients were randomized. The subjects were hGH treatment-naïve or with no exposure to hGH or GH secretagogues for at least 180 days prior to randomization. The trial consisted of a 35-week main trial period (double-blind), followed by a 53-week open-label extension period.

The main trial was blinded with respect to somapacitan and placebo, only. The total duration of the study for each patient was up to 86 weeks. Both the main trial period and the extension consisted of 8 weeks dose titration followed by 26 weeks (main) and 44 weeks (extension) fixed dose treatment, followed by 1 week washout. Therefore, subjects were treated for 34 weeks in the main trial (followed by 1 week washout) and for 52 weeks in the extension trial (followed by 1 week washout). See Figure 6 below.

Figure 6: Schematic trial 4054 overview



NNC0195-0092=somapacitan; hGH=human growth hormone.

Source: Figure 9-1, CSR Trial 4054

The study flow sheet details the specific procedures to be carried out at each visit Appendix 1. All study drugs were self-injected by the subjects.

All subjects were randomized in a 2:2:1 ratio to receive somapacitan, Norditropin or placebo, respectively, during a 35-week period. The randomization was stratified according to region (Japan and all other countries), sex and diabetic status. In extension period, subjects who received placebo in main period were switched to somapacitan treatment, and subjects who received Norditropin in main period were randomized to somapacitan or Norditropin in 1:1 ratio.

The starting doses of somapacitan and Norditropin are shown in Table 5.

Table 5: Starting doses for study drugs

Group	somapacitan or placebo	Norditropin
Subjects <60 years old age	1.5 mg/week	0.2 mg/day
Females on oral estrogen	2.0 mg/week	0.3 mg/day
Subjects > 60 years old	1.0 mg/week	0.1 mg/day

Source: Table 9-4, CSR 4054, p.55; modified

During the first 8 weeks the dose was individually titrated every second week (at week 2, 4, 6, and 8) in order to achieve IGF-1 between -0.5 SDS and + 1.75 SDS. Dose titration was based on IGF-1 SDS values (Table 6). For somapacitan, the minimum and maximum weekly dose was set to 0.1 mg and 8 mg, respectively. For Norditropin, the minimum and the maximum daily dose was set to 0.05 mg and 1.1 mg. Titration of placebo subjects mirrored the titration of somapacitan subjects to avoid un-blinding. The starting doses and dose titration algorithm during extension phase of the trial were similar to the main phase.

If for any reason a subject could not be dose titrated on a scheduled day (i.e. IGF-1SDS was not available), the visit was rescheduled to 2 weeks later. All subsequent visits during the titration periods were also rescheduled to 2 weeks later. Visits could be rescheduled up to 2 times during each titration period. The fixed dose IGF-1 sample visits [i.e. Visit (V)11 and V24, respectively] were rescheduled to 2 weeks later as well. Dose reduction by 25% was allowed for safety reasons during the entire trial. According to the Applicant, if a subject would undergo < 3 dose adjustments, it would most likely not be sufficient to achieve optimal serum IGF-1 concentration, and would be considered a protocol violation.

The treatment was to be discontinued if subject reported symptoms which were considered unacceptable by the subject or the investigator, if subject developed conditions cited in the exclusion criteria, if subject developed neutralizing antibodies to somapacitan, or if subject became pregnant, or manifested intention of becoming pregnant during the trial. In addition, any subject could discontinue the treatment at will at any time, and the investigator could discontinue the drug due to safety concerns or due to non-compliance with trial procedures. All the procedures in the trial after treatment discontinuation (except trial drug administration) were to be continued by the investigator.

The subjects were to be withdrawn from the study if they were included in the trial in violation of the inclusion/exclusion criteria, or if they used weight loss medications during the trial. Subjects who discontinued treatment or were withdrawn were not replaced.

Table 6: Dose titration algorithm for study drugs

IGF-I SDS Interval (1 week and 3 days after last dose adjustment)	somapacitan* or placebo Increment/reduction of weekly dose		Norditropin® FlexPro® Increment/reduction of daily dose	
	Δ IGF-I SDS >1	Δ IGF-I SDS $\leq$ 1	Δ IGF-I SDS >1	Δ IGF-I SDS $\leq$ 1
IGF-I SDS > 3	-1 mg		-0.1 mg/day	
$1.75 < \text{IGF-I SDS} \leq 3$	-0.5 mg		-0.05 mg/day	
$-0.5 < \text{IGF-I SDS} \leq 1.75$	-	+0.5 mg	-	+0.05 mg/day
$-2 < \text{IGF-I SDS} \leq -0.5$	+0.5 mg	+0.5 mg	+0.05 mg/day	+0.05 mg/day
IGF-I SDS ≤ -2	+1 mg	+1.5 mg	+0.1 mg/day	+0.2 mg/day

Δ : Change in IGF-I SDS from screening.

Source: Table 9-5, CSR 4054, p.56

A trial-specific, interactive voice/web-response system (IV/WRS) was used for screening, randomization and stratification, drug supply and drug accountability, dose adjustments, treatment discontinuation, completion, code break, and data change. An internal somapacitan safety committee performed ongoing safety surveillance during the trial. An independent, internal titration surveillance group performed ongoing surveillance of the trial product titration until all patients had completed the dose titration period in the main trial. The titration group was blinded towards treatment allocation.

Compliance with treatment was evaluated based on time stamps from the electronic pen caps (ecaps) in the extension period and based on diary data in the main trial and the extension period. The endpoint is defined as percentage of doses taken as prescribed. Treatment compliance was assessed by recording of doses (date and time of each dose as well as any missed doses), comparing of prescribed and actual doses, adherence and drug accountability. Serum concentrations of somapacitan and hGH after dose administration retrospectively supported surveillance of the patient.

Key Inclusion Criteria:

1. Male or female 23 - 79 years old
2. GHD fulfilling either one of the following criteria:
 - a. Adult onset: subjects diagnosed with GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or traumatic brain injury (TBI)
 - b. Childhood Onset: Subjects who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes
2. hGH treatment naïve or no exposure to hGH or GH secretagogues for at least 180 days prior to randomization

3. Patients using hormonal replacement therapy(s) for any other hormone deficiencies should be on adequate and stable treatment regimen for at least 90 days prior to randomization

4. Confirmed diagnosis of adult growth hormone deficiency:

For all countries except Japan:

-all subjects need to satisfy at least one of the following criteria:

a. Insulin tolerance test (ITT) or glucagon test: a peak GH response of < 3 ng/mL ($\mu\text{g/L}$)

b. Growth hormone releasing hormone (GHRH) + arginine test:

i. Body Mass Index (BMI) < 25 kg/m², a peak GH < 11 ng/mL ($\mu\text{g/L}$)

ii. BMI 25–30 kg/m², a peak GH < 8 ng/mL ($8 \mu\text{g/L}$)

iii. BMI > 30 kg/m², a peak GH < 4 ng/mL ($4 \mu\text{g/L}$)

c. Three or more pituitary hormone deficiencies at screening and IGF-1 SDS < -2.0

For Japan only:

Subjects with adult onset GHD need to satisfy at least one of the following criteria, subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria:

a. ITT test or glucagon test: a peak GH of ≤ 1.8 ng/mL

b. Growth Hormone Releasing Peptide (GHRP)-2 tolerance test: a peak GH of ≤ 9 ng/mL

5. IGF-1 SDS < -0.5 at screening relative to the mean of the age and sex normal ranges according to the central laboratory measurements

6. Subjects must have serum levels of total testosterone (males only) and free T4 within normal limits

9. Adequate adrenal function [confirmed with adrenocorticotrophic hormone (ACTH) stimulation test within the last 90 days prior to randomization; if no result is available, ACTH stimulation test will be performed as part of the screening procedure] or adequate and stable replacement therapy for at least 90 days prior to randomization

10. Subjects with diabetes mellitus need to meet all the following criteria:

–DM diagnosed ≥ 6 months prior to screening

–stable oral anti-diabetic treatment for ≥ 90 days prior to screening

–no history of use of injectable anti-diabetic agents

–HbA1c $< 7.0\%$ at screening

–no diabetes related co-morbidities at screening

–fundus photography performed ≤ 90 days prior to randomization without proliferative retinopathy or severe non-proliferative diabetic retinopathy

Key exclusion criteria:

1. Known or suspected hypersensitivity to trial product(s) or related products

2. Previous participation in this trial.

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive methods (as required by local regulation or practice)

4. Active malignant disease or history of malignancy.

Exceptions to this exclusion criterion:

- Resected in situ carcinoma of the cervix and squamous cell or basal cell carcinoma of the skin with complete local excision
- Subjects with GHD attributed to treatment of intracranial malignant tumors or leukemia, provided that a recurrence-free survival period of at least 5 years is documented in the subject's file

5. Male of reproductive age who or whose partner(s) is not using adequate contraceptive methods (as required by local regulation or practice)

6. Any disorder which, in the opinion of the investigator might jeopardize subject's safety or compliance with the protocol

7. For subjects with a history of pituitary adenoma or other benign intracranial tumor:

- a. Surgical removal of pituitary adenoma or other benign intracranial tumor ≤ 12 months before randomization.

- b. Evidence of growth of pituitary adenoma or other benign intracranial tumor within the last 3 years before randomization.

Absence of growth must be documented by 2 post-surgery magnetic resonance imaging (MRI) or computed tomography (CT) scans. The most recent MRI or CT scan must be performed ≤ 9 months prior to randomization.

8. Clinically significant hepatic disease defined as alanine amino transferase (ALT) $> 3 \times$ upper normal limit (UNL)

9. Clinically significant chronic renal impairment defined as creatinine level $> 1.5 \times$ UNL

10. Acute severe illness associated with weight loss $> 5\%$ in the last 180 days prior to randomization

11. Active Cushing's syndrome within the last 24 months prior to randomization

12. For Japan only: Diabetes mellitus

13. Heart insufficiency, New York Heart Association (NYHA) functional class > 2

14. Use of weight loss medications within the last 12 months.

15. History of acromegaly

16. Systemic corticosteroids other than in replacement doses within 90 days before randomization

17. Inability to undergo dual energy x-ray absorptiometry (DXA) whole body scanning due to a body weight or size which exceeds the limit of the DXA scanner.

18. Female subject who plans to change estrogen therapy during the trial

Clinical and laboratory measurements for safety are detailed for each study visits in Appendix 1.

Medical officer's comments: A 34 week (> 6 months), randomized, multinational, placebo-controlled (double-blind), and active-controlled (open) trial is an adequate trial design to address the objectives of the trial and is in accordance with the regulatory requirements

for adequate and well-controlled trials (FDA 21 CFR 314.120). The randomization of treatment allocation and the blinding of the main trial period with respect to somapacitan and placebo groups were intended to reduce the selection bias. According to the Applicant, the inclusion of the active controlled arm was done to compare efficacy and safety, including local tolerability of somapacitan, to an existing daily hGH replacement therapy, which is standard therapy for AGHD. A multinational approach was appropriate, in order to address applicability of the results to subjects with different demographic characteristics. The Applicant justified the parallel design over a cross-over design, as with the later design the carry-over effects (i.e. on body composition) would affect interpretability of the efficacy results, which is appropriate.

The Applicant included a titration period (8 weeks) which allowed for 4 dose adjustments of somapacitan to achieve an optimal serum IGF-1 concentration. Based on PK/PD characteristics it is expected that the majority of patients will achieve pre-defined IGF-1 levels after 4 titrations at doses below maximum doses. However, some patients who require higher maintenance doses (i.e. females on oral estrogen, patients with higher BMI) may need more than 4 titration periods to achieve pre-defined IGF-1 levels and ultimately, improvement in body composition. For example, a patient who was started on somapacitan dose of 1.5 mg with baseline IGF-1 levels > -2 SDS could have been up titrated to 3.5 mg/week at the end of the 8-week titration period using 0.5 mg/week increments and 4 titrations [1.5 mg + (0.5 mg/weekX4)] and continue with this dose in fixed dose treatment period even if IGF-1 levels were still below target range. The titration does not allow to achieve higher than 3.5 mg or maximum doses in this patient, and theoretically, better response on higher doses with longer titration. According to Endocrine Society guidelines ⁵, individualized dose titration regimens with IGF-1 level as the titration target are preferred over a fixed body weight based regimen, as AEs are less frequent in subjects receiving dose-titration compared to weight-based dosing. The 26 week fixed dose period is consistent with the expected minimal time needed for changes in body composition parameters (particularly body fat composition) to occur in AGHD patients as a results of therapy with GH ⁵. The wash-out periods were included to evaluate the antibody response to this product. Although the Applicant's rationale for the extension period trial was to provide long-term evaluation of efficacy and safety, due to the complex re-randomization design interpretability of the efficacy results would be challenging. While comparison of efficacy data between active treatment arms (somapacitan/somapacitan vs Norditropin/Norditropin) could be carried out, it is unclear if the results could be interpretable from a statistical standpoint, as most likely the study subgroups would be underpowered. The long-term safety data will be evaluated as supportive evidence of safety.

The once weekly dosing regimen for somapacitan is expected to provide improved convenience/compliance over the existing hGH therapy which must be dosed daily. The

weekly dosing was supported by 3 previous clinical trials (NN8640-3915, healthy subjects; NN8640-3947, AGHD and NN8640-4042, children with GHD), which showed that increased IGF-I levels from baseline were maintained for at least 1 week after dosing.

The starting doses for somapacitan were tested to be safe in the completed phase 1 clinical trial NN8640-3947 in AGHD patients, and were expected to be below the ideal maintenance dose for IGF-1 SDS target for most AGHD patients, for both somapacitan and Norditropin. According to the Applicant, the size of the dose adjustments during the titration period was derived from the PK/PD analysis of the data from previous clinical trials with somapacitan. The Applicant selected the dose titration algorithm to reach a mean IGF-1 SDS value during steady state of -0.5SDS to +1.75 SDS was a conservative approach, in order to avoid potential AEs related to drug overdosing.

Overall, the inclusion/exclusion criteria were acceptable for the stated objectives. The Applicant elected to include only patients with DM whose HbA1c was < 7% and who were on stable oral antidiabetic medications only, despite the Agency's recommendation during the EOP2 meeting to include subjects with higher Hba1c levels (i.e. Hba1c < 9.0 – 9.5%), in order to assess effect of the study drug on glucose metabolism. See details in Section 3.2.

The safety provisions outlined in the protocol were found to be appropriate.

Study Endpoints

1. Primary endpoint:

- Change from baseline to the end of main trial period (Week 34) in TFP.

TFP was defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass (kg) and truncal lean body mass (kg).

2. Secondary endpoints:

- Efficacy endpoints
 - Changes from baseline to the end of main trial period (Week 34) in truncal fat mass (kg), truncal lean body mass (kg);
 - Change from baseline to end of main trial period (Week 34) in total fat mass, appendicular skeletal muscle mass (ASMM), and lean body mass
 - Change from baseline to the end of main trial period (Week 34) in visceral adipose tissue (VAT), android fat mass, gynoid fat mass (only if the DXA scanner permits)
 - Changes from baseline to the end of main trial period in IGF-1 SDS, IGFBP-3 SDS

- Changes from baseline to the end of main trial period in scores of the patient reported outcome (PRO) questionnaires [Treatment Related Impact Measure (TRIM)-AGHD, Short Form (SF)-36v2, Treatment Satisfaction Questionnaire for Medication (TSQM)-9]
 - Changes from baseline to the end of main trial period in lipid parameters [total cholesterol, high density lipoprotein (HDL)- cholesterol, low density lipoprotein (LDL)- cholesterol and triglycerides], cardiovascular parameters [high-sensitivity C-Reactive Protein (hsCRP) and interleukine (IL)-6], body weight and waist circumference
 - Changes from baseline to end of extension period (Week 87) in all of the above mentioned variables as well as bone mineral content (BMC) and bone mineral density (BMD) will be used to support the secondary objective regarding evaluation of efficacy during the extension period.
- Safety endpoints
 - Incidence of adverse events, including injection site reactions
 - Occurrence of anti-NNC0195-0092 antibodies
 - Incidence of technical complaints
 - Changes from baseline in physical examination, ECG results and vital signs
 - Changes from baseline in clinical laboratory test results including hematology, biochemistry, fasting glucose, fasting insulin, and insulin resistance (IR) [homeostatic model assessment (HOMA) estimates], and HbA1c levels

Medical officer's comments: Body composition measurements to assess effect of GH replacement therapy in adults are surrogate endpoints accepted by FDA and previously used for approval of other GH products in patients with AGHD.

The benefit of GH replacement therapy on body composition in AGHD patients is recognized by the Endocrine Society clinical practice guidelines for treatment of AGHD, which further state that decreased total body fat content via increased lipolysis and increased lean body mass are one of the most consistent metabolic responses to GH therapy⁵. Indeed, the primary efficacy endpoint - change in TFP- does incorporate both parameters (fat mass and lean mass). In clinical studies, the changes in body fat content and lean body mass were noted to occur within 6 months after initiation of GH therapy, with persistence of effect, if treatment is continued. However, to date, there is no established cut-off level for improvement in any body composition parameters in response to GH therapy, that would define clinical meaningfulness. In fact, the long-term benefit of GH replacement therapy on cardiovascular morbidity, and/or mortality has not been demonstrated, nor has it been rigorously studied to date. In the absence of well-established criteria for a treatment effect size that defines clinical benefit, most clinicians would regard a composite of decrease in fat mass, and improvement in lean body mass parameters, accompanied by a normalization in IGF-1 levels, as meaningful clinical benefit. Indeed, improvement in body composition parameters as surrogate efficacy endpoints has

been used for all FDA-approved GH products, with primary and secondary endpoints varying amongst products, without a specific parameter being used on a consistent basis. Examples of surrogate efficacy endpoints previously used include changes in total body fat, total lean mass, truncal or total body fat %, and total lean mass %. The magnitude of change from baseline compared to placebo in these parameters varied amongst studies, with commonly reported parameters being total lean mass (changes at 6 month from placebo range: +0.88 kg to +2.81 kg), total body fat (changes at 6 month from placebo range: -1.35 kg to -3.83 kg), and total body fat % (changes at 6 month from placebo range: -4.24% to -4.74%). However, it is important to keep in mind that a meaningful comparison with, or between other GH products from an efficacy standpoint is challenging and difficult to make, given differences in study designs, baseline patient population characteristics, dose titration regimens, statistical analysis plans, methods of assessments for the efficacy endpoints, etc. .

Absent new scientific data informing the benefit-risk profile of improvement in body composition parameters as a result of GH replacement therapy in AGHD patients, the Division continues to accept improvement in various body composition parameters as surrogate markers to determine efficacy of rhGH for the AGHD indication.

The body composition endpoints were discussed during EOP2 meeting and were found to be acceptable. No hierarchical testing for the secondary endpoints was proposed by the Applicant, with regards to the body composition endpoints. The secondary surrogate endpoints IGF-1 SDS and IGFBP-3 SDS represent the biomarkers of GH replacement therapy and are based on the drug mechanism of action, in which GH activates GH receptors, with subsequent increase in hepatic production of IGF-1 and IGFBP-3.

The use of PROs as secondary endpoints and potential labeling claims were discussed with the Applicant during EOP2 meeting (see Section 3.2 for details).

Statistical Analysis Plan (SAP)

Power calculation: 280 patients were planned to be included in the trial, expecting at most 7% drop-out from the trial (leaving 260 patients to complete the main trial: somapacitan: 104 patients; placebo: 52 patients; Norditropin: 104 patients). The power calculation was based on: a true mean difference of 2.5% between somapacitan and placebo; a standard deviation (SD) of 4.5% for the primary endpoint; a 2-sided, 2-sample t-test with a significance level of 5%; and 2:1 randomization ratio between somapacitan and placebo. According to the Applicant, 104 patients in the somapacitan treated group and 52 patients in the placebo treated group completing the main trial should ensure a 90% power for detecting a difference between somapacitan and placebo. Simulations under the assumption of a drop-out rate of 7% and that 50% of the patients not completing the main trial contribute to the primary analysis with post randomization DXA data, gave 89% power for detecting a difference between somapacitan and placebo, with 112 patients in the somapacitan group and 56 patients in the placebo group.

Full analysis set (FAS) (for efficacy endpoints): all randomized patients that received at least one dose of randomized treatment; Patients were analyzed 'as randomized'.

Safety analysis set (SAS) (for safety evaluation): as above but patients were analyzed 'as treated'.

In the extension period the data for the efficacy analysis was analyzed using the randomized treatment from the start of the main trial period in combination with the allocated/ randomized treatment in the extension period.

Analysis primary endpoint: Truncal fat percentage as a function of time since baseline was expected to be monotone if the patient stayed on the randomized treatment in the main trial period. Based on this assumption, the primary analysis of the primary endpoint was conducted using a multiple imputation technique where the track after a withdrawn patient's last observation is imputed based on data from the placebo arm.

An analysis of covariance (ANCOVA) model with GHD onset type (adult or child), sex, region, diabetes status and sex by region by diabetes status interaction as factors and baseline TFP as a covariate was fitted to the change in truncal fat percentage from baseline to 34 weeks data for the placebo group only. The estimated parameters and their variances from this model were used to impute missing values at 34 weeks for patients in all treatment groups, based on their sex, region, diabetes status, GHD onset type and baseline truncal fat values.

The change in TFP from baseline to 34 weeks was analyzed using an ANCOVA model with treatment, GHD onset type, region, sex, diabetes status and sex by region by diabetes status interaction as factors and the baseline truncal fat value as a covariate. From this model, the treatment difference at week 34 between somapacitan and placebo was estimated and the corresponding 95% CI and p-value was calculated. As a secondary comparison, the treatment difference at week 34 between somapacitan and Norditropin was estimated and the corresponding 95% CI was calculated. Furthermore, a secondary analysis of the primary endpoint based on an assumption of 'missing at random' (MAR) was done including only patients with week 34 data (for the endpoint) in the analysis. A sensitivity analysis assessed the robustness of the results.

Analyses secondary efficacy endpoints: DXA body composition variables, waist circumference and lipids: changes from baseline to week 34 were analyzed using an ANCOVA model based on the same multiple imputation technique as was used in the primary analysis of the primary endpoint. Data on lipids were log transformed before analysis, both baseline and week 34 values.

Analyses other secondary endpoints: IGF-1 SDS and IGFBP-3 SDS: changes from baseline to week 34 were analyzed using a mixed model for repeated measurements (MMRM), with treatment, GHD onset type, sex, region, diabetes status and sex by region by diabetes status interaction as factors and baseline value as a covariate, all nested within week as a factor.

PRO questionnaires (TSQM-9, TRIM-AGHD and SF-36v2): change in PRO scores from baseline to week 34 were analyzed by the MMRM (see above).

Cardiovascular parameters (hsCRP and IL-6): changes from baseline to week 34 were analyzed by the MMRM.

Analyses extension period: changes from baseline to week 87 (end of extension period) in all of the above mentioned variables (except TSQM- 9) and bone mineral content and bone mineral density (extension part only) to support the secondary objective of efficacy during the extension period. For TSQM-9, the scores assessed at week 87 were analyzed. The data was analyzed using descriptive statistics.

Somapacitan and hGH serum concentration data was analyzed using descriptive statistics.

Safety analyses: all safety endpoints were evaluated by descriptive statistics. Safety is reported for the main period (up to week 35) in the current report and for the extension (up to week 88) in the final clinical trial report.

For additional details regarding SAP, see Statistical Review by Dr. Alexander Cambon.

Protocol Amendments

Amendment # 1 (07/02/2014):

- The primary analysis of the primary endpoint was changed to an analysis based on the ITT principle rather than on an assumption of missing at random, according to the Agency's advice
- Implemented measures having a general focus on the avoidance of missing data
- Additional antibody and PK sampling were added to align with the time points for immunogenicity assessments as recommended in the Agency's Immunogenicity guideline of February 2013
- Inclusion of subjects with DM in order to understand the effect of the drug in this subgroup of subjects, as recommended by the Agency. As a result of including subjects with DM, fundus photography of these subjects was introduced as a safety precaution. An additional stratum for subjects with DM was added to randomization.

Amendment #2 (09/09/2014):

- for Japan only: This amendment is based on the request from Japanese regulatory agency after clinical trial protocol submission in Japan, with most notable changes including modifications to the criteria for confirmed diagnosis of AGHD according to local guidelines, exclusion of subjects with diabetes if diagnosed during the trial, as well as other small changes to satisfy local procedural regulatory guidelines.

Amendment #. 3 (11/28/2014):

- Alternative test for ACTH stimulation test (i.e. ITT) for evaluation of adrenal (in)sufficiency due to limited availability in some countries. This amendment had an impact on inclusion criterion 9 and the patient informed consent form.

- Process for local tolerability assessments includes external review of photos by a dermatologist.
- Clarification of follow-up process after last patient last visit (LPLV) if 2 consecutive positive antibody results.
- Two additional exclusion criteria added, applicable to Germany only, based on feedback from Ethics committee. These criteria cover exclusion of patients committed to an institution and persons employed with the Applicant /CRO/trial center.
- Clarifications when and how deviation from the titration schedule should be handled.
- Modification for the option of re-screening adrenal insufficient patients on stable replacement therapy for 3 months

Amendment# 4 (01/06/2015):

- for India only: Indian Health Authority requested central lab analysis of the following tests performed at screening to confirm patient eligibility, if relevant: ITT/glucagon diagnostic tests and for female patients: luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol tests.

Amendment #. 5 (01/13/2015):

- for Japan only: error in Table 2 footnote 5 in the final protocol version 4.0 corrected, to reflect previous protocol amendments: 'At all visits planned to perform a pregnancy test, urine pregnancy test in women of childbearing potential will be performed.'

Amendment # 6 (05/26/2015):

- Allowed visits 1a and 1b to be combined into one visit.
- Inclusion criteria :
 - subjects can be included based on historical medical record data for IGF-1 SDS or new IGF-1 value obtained at screening (either at local or central lab)
 - subjects who are already on testosterone replacement therapy for 90 days are allowed to participate
 - Subjects who have a stable adenoma can be included in the trial
- ECG monitoring on visit 13 and visit 26 was updated according to FDA request (around the mean C_{max}).

Medical Officer's comments: All protocol changes did not have an impact on the integrity of the trial or interpretation of the study results.

Data Quality and Integrity: Applicant's Assurance

The Applicant and/or its designee were responsible for monitoring the study in accordance with the requirements of the ICH/GCP, and in accordance with written SAPs and the Clinical

Monitoring Plan. Monitoring visits were to be performed to evaluate study conduct, data integrity, protocol, and GCP compliance. The study was to be monitored by the Applicant or designee at all stages of study conduct from inception to completion in accordance with current ICH/GCP. This monitoring was to be in the form of on-site visits, telephone calls, and regular inspection of the eCRFs with sufficient frequency (12 weeks intervals) to verify the following: patient enrolment; compliance with the protocol; the completeness and accuracy of data entered in the eCRFs by verification against original source documents; compliance in the use of trial product; drug accountability and recording of AEs. The investigator was to ensure that the monitor or other compliance or quality assurance reviewers were given access to all the above noted study-related documents and study-related facilities (i.e., pharmacy, diagnostic laboratory, etc.), and had adequate space to conduct the monitoring visit. Each investigator was to be responsible for the accuracy, completeness, legibility, and timeliness of the data reported. All source documents were to be completed in a neat, legible manner to ensure accurate interpretation of data. Completed eCRFs were required for each subject randomly assigned to study drug. Study data management, monitoring, statistical analysis, and reporting were performed by the Applicant using the Applicant's SAPs. Source documents, laboratory results and imaging laboratory reports were to be reviewed to ensure that they were accurate and complete.

Body composition were to be measured using DXA whole body scans. The overall process of image acquisition, transfer, central analysis, reporting of results and archiving was described in an Imaging Charter prepared by the imaging laboratory. Processes for image acquisition were outlined in an image acquisition guideline (IAG). Each trial site DXA scanner needed to be qualified by the imaging laboratory prior to scanning subjects. DXA instruments had to undergo quality control procedures through cross-calibration procedures, detailed in the Imaging Charter. Also, each subject had to be scanned using the same DXA scanner for the duration of the trial. The imaging laboratory was to be informed of any scanner software or hardware upgrades. If scanning on the same scanner was not possible or software or hardware upgrades occurred, procedures as outlined in the IAG had to be followed. Each trial site further received an imaging manual prepared and distributed by the imaging laboratory which included machine specific instructions for acquiring DXA scans. The manual served as a reference tool for use during the trial and in training technologists. DXA technologist training occurred at the start of the trial and at any time deemed necessary to assure proper scan acquisition.

Following DXA scan acquisition each trial site was responsible for transferring each DXA scan to the imaging laboratory for quality review and analysis, while the central reader was blinded to the treatment allocation. DXA analysis data was transferred from the imaging laboratory to Novo Nordisk immediately prior to the database locks of the main and extension periods. To avoid un-blinding, the investigators received the results from the analysis after last subject last visit of the extension period. Central laboratories with inter-laboratory standardization methods were to be used. All laboratories used for this study were to have had appropriate accreditation.

Clinical Review
Geanina Roman-Popoveniuc, MD
BLA 761156
SOGROYA/somapacitan-beco

On 09/03/2019, Office of Computational Science (OCS) Core Data Fitness Service evaluated the current application for data quality and found no significant issues with regards to data quality and integrity. Also, Dr. Alexander Cambon, the statistical reviewer, evaluated the application for data quality and found it to be satisfactory.

6.1.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in compliance with the protocol and standard operating procedures that meet the current US regulatory requirements per Title 21 US Code of Federal Regulations Parts 50 & 312 and the International Conference on Harmonization guidelines on Good Clinical Practice (GCP), including where applicable, principles of the Declaration of Helsinki, and any applicable local regulations.

Financial Disclosure

A completed FDA 3454 form was submitted confirming that the applicant did not enter into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), and each listed clinical investigator required to disclose to the applicant whether the investigator had a proprietary interest in this product or a significant equity in the applicant as defined in 21 CFR 54.2(b) did not disclose any such interests. The applicant also certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Medical officer's comments: The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. There is no reason to suspect that the integrity of the study results was affected due to financial arrangements.

Patient Disposition

Out of 510 screened subjects, 301 AGHD patients were randomized, 300 patients were exposed to the treatment drug, and 277 patients completed the trial. Of these, 120 patients were randomized to somapacitan, 61 patients were randomized to placebo, and 119 patients to Norditropin (Table 7).

Table 7: Patients disposition

	Placebo N (%)	Norditropin N (%)	Somapacitan N (%)	Total N (%)
Screened*				510
Randomised	61 (100.0)	119 (100.0)	121 (100.0)	301 (100.0)
Exposed	61 (100.0)	119 (100.0)	120 (99.2)	300 (99.7)
Completed treatment	55 (90.2)	107 (89.9)	115 (95.0)	277 (92.0)
Discontinued trial product	1 (1.6)	4 (3.4)	0 (0.0)	5 (1.7)
- Adverse event	1 (1.6)	4 (3.4)	0 (0.0)	5 (1.7)
Withdrawn	6 (9.8)	15 (12.6)	7 (5.8)	28 (9.3)
- Lost to follow-up	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
- Other	2 (3.3)	2 (1.7)	0 (0.0)	4 (1.3)
- Protocol violation	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.7)
- Withdrawal by subject	4 (6.6)	12 (10.1)	5 (4.1)	21 (7.0)
Full analysis set	61 (100.0)	119 (100.0)	120 (99.2)	300 (99.7)
Safety analysis set	61 (100.0)	119 (100.0)	120 (99.2)	300 (99.7)

N: Number of subjects, %: Percentage of randomised subjects

* Re-screened subjects are counted only once.

Source: Table 10-1, CSR, p 98

Five (5) patients discontinued the trial product due to adverse events (AEs) during main phase of trial 4054, 1 subject in the placebo group and 4 subjects in Norditropin group. Importantly, no subjects in somapacitan group discontinued the study drug due to AEs. The completion treatment rate was higher in somapacitan group (95%) than placebo (90%) and Norditropin (90%).

Protocol Violations/Deviations

Important protocol deviations (PDs) by category at patient level in main trial 4054 are summarized in Table 8 and detailed further below.

Table 8: Important protocol deviations by category at patient level

Protocol deviation category	Placebo	Norditropin	Somapacitan	Blank ^a	Total
Informed consent	23	34	36	43	136
Inclusion/exclusion/randomisation criteria	1	2	5	1	9
Withdrawal criteria	.	.	.	.	0
Discontinuation criteria (if used)	.	.	.	.	0
Trial product handling	10	29	31	1	71
Treatment compliance	36	45	62	0	143
Assessment deviations	42	55	69	3	169
Other	10	28	39	2	79
Total	122	193	242	50	607

Source: Table 10-8; CSR 4054 main, p.112

Informed consent (IC)

All patients provided IC, with most PDs related to IC occurring due to subjects not signing the most recent version of IC, or PDs related to sites where visit 1a and 1b were combined, prior to receiving IRB approval for protocol amendment 6.0 (which allowed visits 1a and 1b to be combined into one visit).

Inclusion/exclusion/randomization criteria

Subjects (b) (6) and (b) (6) in somapacitan group violated exclusion criteria 9/9b because investigator omitted the date of last MRI/CT scan performed and adenoma was resected < 12 months prior to randomization, respectively. Both subjects were withdrawn from trial. Subjects (b) (6) took 1 dose of somapacitan before withdrawal, where regarding subj (b) (6) exposure to somapacitan was not provided.

Subject (b) (6) in Norditropin group and subj. (b) (6) in somapacitan group did not comply with inclusion criteria no 11 [stable oral antidiabetic drugs (OAD) prior to screening], as their diabetes was managed via diet and exercise. No safety issues were identified by Investigator and the subjects were allowed to continue in the trial.

Subject (b) (6) in placebo group violated withdrawal criterion #3: Use of weight loss medications known to affect body weight substantially. The subject was prescribed liraglutide, a GLP-1 analogue known to reduce body weight and change body composition, with subsequent decrease in body weight and TFP observed after initiation of liraglutide treatment. Of note, use

of liraglutide in violation of withdrawal criteria # 3 was not reported as a PD by the Applicant with the initial submission, but in a response to an IR to the Agency on 04/23/2020. See section 7.1.2 for details.

Subject (b) (6) in somapacitan group was pre-diabetic but was incorrectly stratified at randomization as diabetic. Patient's status was corrected to pre-diabetic.

Subject (b) (6) in placebo group was considered eligible for the trial based on adequate adrenal function with a previous glucagon test within 90 days prior to randomization rather than an ACTH test (as stated in inclusion criteria 10).

Treatment compliance

The majority of deviations in treatment compliance covered 1-2 missed doses or missed washout periods. Four (4) patients had taken an additional dose of trial medication after visit 14 by mistake. At 1 site in India (impacting 8 patients), the timing of treatment was misunderstood and was done in the evening rather than in the morning. Some patients (across countries and treatment arms) used at least 1 pen-injector beyond the in-use time specified, as the subjects looked at the expiry date which was different from the in-use time. However, the in-use time for somapacitan/placebo was extended from 4 weeks to 6 weeks as new stability data for 6 weeks became available during the conduct of the trial, which resulted in approximately 4-6% of all doses in the trial being taken beyond the in-use time.

Assessment deviations

Assessment deviations included missing or delayed assessments, with most deviations in: ECG not done on time of C_{max} ; missing ACTH or ITT tests, signing of lab reports, acceptance of DXA scans and blood sampling for antibody assessment.

Fifteen (15) subjects (12.5%) in somapacitan group had ECG assessments not done on time of C_{max} .

None of the patients in whom an ACTH and ITT test was not done had AEs related to the adrenal gland.

At a few sites the secondary efficacy endpoint VAT was not measured as the DXA scanners at the sites did not have the VAT capability, with Applicant being aware of the issue at trial initiation. At baseline VAT data were available for 274 of 300 (91%) patients.

Medical Officer's comments: The most of PDs categories occurred in small number of patients, the majority of violations were minor and did not affect the integrity of the efficacy or safety results.

Demographic Characteristics

Of the 300 subjects (51.7% females and 48.3% males) with AGHD enrolled in the trial, majority of patients belonged to age group 23-64 years (86.3%) [mean (SD) age 45 (15.0) years], the mean BMI (SD) was 27.4 (6.3), reflecting an overall overweight population, and most of the subjects had AO GHD (70%). Most of the patients (67%) were white, followed by Asians (29%). The patients were enrolled at 92 sites in 16 countries, with most of the patients enrolled in US (26.3%), Japan (15.3%), Australia (10.0%), India and Romania (each 9.3%). (Table 9)

Table 9: Demographic characteristics trial 4054 (FAS)

	Placebo	Norditropin	Somapacitan	Total
Number of Subjects	61	119	120	300
Age (years), N	61	119	120	300
Mean (SD)	45.0 (15.7)	45.7 (15.3)	44.6 (14.3)	45.1 (15.0)
Median	46	46	44	44.5
Min ; Max	23 ; 76	23 ; 77	23 ; 75	23 ; 77
Agegroup, N (%)	61 (100.0)	119 (100.0)	120 (100.0)	300 (100.0)
23-64 years	51 (83.6)	101 (84.9)	107 (89.2)	259 (86.3)
>= 65 years	10 (16.4)	18 (15.1)	13 (10.8)	41 (13.7)
Sex, N (%)	61 (100.0)	119 (100.0)	120 (100.0)	300 (100.0)
Female	32 (52.5)	61 (51.3)	62 (51.7)	155 (51.7)
Male	29 (47.5)	58 (48.7)	58 (48.3)	145 (48.3)
Ethnicity, N (%)	61 (100.0)	119 (100.0)	120 (100.0)	300 (100.0)
Hispanic or Latino	4 (6.6)	8 (6.7)	6 (5.0)	18 (6.0)
Not Hispanic or Latino	57 (93.4)	109 (91.6)	114 (95.0)	280 (93.3)
NA	0	2 (1.7)	0	2 (0.7)
Race, N (%)	61 (100.0)	119 (100.0)	120 (100.0)	300 (100.0)
Asian	16 (26.2)	36 (30.3)	34 (28.3)	86 (28.7)
Black or African American	2 (3.3)	3 (2.5)	2 (1.7)	7 (2.3)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.8)	1 (0.3)
White	42 (68.9)	76 (63.9)	82 (68.3)	200 (66.7)
Other: Hispanic	1 (1.6)	0	1 (0.8)	2 (0.7)
Other: Hispanic or Latino	0	1 (0.8)	0	1 (0.3)
Other: Caucasian	0	1 (0.8)	0	1 (0.3)
NA	0	2 (1.7)	0	2 (0.7)
Country, N (%)	61 (100.0)	119 (100.0)	120 (100.0)	300 (100.0)
Australia	7 (11.5)	10 (8.4)	13 (10.8)	30 (10.0)
Germany	2 (3.3)	3 (2.5)	3 (2.5)	8 (2.7)
India	6 (9.8)	11 (9.2)	11 (9.2)	28 (9.3)
Japan	10 (16.4)	18 (15.1)	18 (15.0)	46 (15.3)
Latvia	2 (3.3)	1 (0.8)	0	3 (1.0)
Lithuania	4 (6.6)	3 (2.5)	1 (0.8)	8 (2.7)
Malaysia	0	3 (2.5)	4 (3.3)	7 (2.3)
Poland	1 (1.6)	2 (1.7)	8 (6.7)	11 (3.7)
Romania	2 (3.3)	14 (11.8)	12 (10.0)	28 (9.3)
Russian Federation	5 (8.2)	6 (5.0)	7 (5.8)	18 (6.0)
South Africa	1 (1.6)	4 (3.4)	4 (3.3)	9 (3.0)
Sweden	0	2 (1.7)	0	2 (0.7)
Turkey	3 (4.9)	1 (0.8)	4 (3.3)	8 (2.7)
Ukraine	4 (6.6)	1 (0.8)	3 (2.5)	8 (2.7)
United Kingdom	0	6 (5.0)	1 (0.8)	7 (2.3)
United States	14 (23.0)	34 (28.6)	31 (25.8)	79 (26.3)

N: Number of subjects, SD: Standard deviation, %: Percentage of subjects, BMI: Body mass index, NA: Not applicable

Source: Table 10-3, CSR 4054, main, p.101

Table 9: Demographic characteristics trial 4054 (FAS) cont.

	Placebo	Norditropin	Somapacitan	Total
Height (m), N	61	119	120	300
Mean (SD)	1.63 (0.10)	1.64 (0.14)	1.65 (0.10)	1.64 (0.12)
Median	1.64	1.64	1.65	1.64
Min ; Max	1.39 ; 1.83	1.07 ; 1.93	1.38 ; 1.87	1.07 ; 1.93
Body Weight (kg), N	61	119	120	300
Mean (SD)	69.8 (19.7)	76.0 (22.7)	76.2 (21.0)	74.8 (21.5)
Median	69.0	74.1	72.9	72.4
Min ; Max	39.0 ; 114.9	22.5 ; 140.9	44.5 ; 134.1	22.5 ; 140.9
BMI (kg/m ²), N	61	119	120	300
Mean (SD)	26.1 (6.4)	27.7 (6.2)	27.9 (6.3)	27.4 (6.3)
Median	25.4	26.8	26.9	26.7
Min ; Max	13.3 ; 44.3	17.0 ; 45.0	17.6 ; 47.2	13.3 ; 47.2
Waist circumference (cm), N	61	119	120	300
Mean (SD)	88.5 (14.2)	94.0 (16.1)	93.9 (14.7)	92.8 (15.3)
Median	87.1	94.6	93.1	92.8
Min ; Max	61.0 ; 119.0	45.8 ; 151.1	66.9 ; 135.5	45.8 ; 151.1
GHD Onset, N (%)	61 (100.0)	119 (100.0)	120 (100.0)	300 (100.0)
Adulthood	41 (67.2)	86 (72.3)	82 (68.3)	209 (69.7)
Childhood - Idiopathic	13 (21.3)	21 (17.6)	21 (17.5)	55 (18.3)
Childhood - Organic	7 (11.5)	12 (10.1)	17 (14.2)	36 (12.0)
Diabetes Mellitus, N (%)	61 (100.0)	119 (100.0)	120 (100.0)	300 (100.0)
Diabetic	3 (4.9)	6 (5.0)	7 (5.8)	16 (5.3)
Non-Diabetic	58 (95.1)	113 (95.0)	113 (94.2)	284 (94.7)

N: Number of subjects, SD: Standard deviation, %: Percentage of subjects, BMI: Body mass index, NA: Not applicable

Source: Table 10-3, CSR 4054, main, p. 101

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline characteristics were relatively similarly distributed amongst treatment groups, except for a lower BMI and waist circumference observed in the placebo group, compared to active treatment groups, as follows: mean BMI(SD) (kg/m²): placebo 26.1 (6.4), somapacitan 27.9 (6.3), Norditropin 27.7 (6.2); mean(SD) (cm) waist circumference: placebo 88.5 (14.2), somapacitan 93.9 (14.7), Norditropin 94.0 (16.1).

The mean (SD) IGF-1 SDS levels at screening were similar amongst treatment groups, as follows: -2.54 (1.26) (somapacitan), -2.64 (1.28) (placebo), -2.53 (1.27) (Norditropin), whereas mean (SD) TFP value was slightly lower in placebo group, compared to active treatment groups: 39.11 (8.81) (somapacitan), 36.9 (8.98) (placebo), 38.1 (9.65) (Norditropin).

Sixteen (16) patients had diabetes at baseline, of these, 7 (5.8%) were in somapacitan group, 6 (5%) were in Norditropin group, and 3 (4.9%) were in placebo group. Mean fasting glucose, HbA1c and fasting insulin levels were within normal ranges at baseline amongst treatment groups.

The concomitant illness of the subjects in the trial are summarized in Table 10 and they reflect the expected associated pituitary hormonal deficiencies seen in patients with AGHD, as well as the comorbidities associated with AGHD, such as hyperlipidemia, hypertension. Amongst pituitary hormonal deficiencies, adrenal insufficiency (AI) and secondary hypothyroidism were more common (21% and 18%, respectively) in placebo group than somapacitan (13% and 14%, respectively) and Norditropin (14% and 11%, respectively) groups. Of note, the diagnosis of GHD was included as a concomitant illness in some patients, however, all the patients in the trial had AGHD at baseline, as part of inclusion criteria.

Headache and depression were more frequently reported as concomitant illnesses/symptoms in somapacitan and Norditropin groups, compared to placebo group.

The use of oral estrogen per treatment group was as follows: somapacitan group: 61.3% of females (31.6% of all subjects), Norditropin group: 37.7% of females (19.3% of all subjects), placebo group: 31.7% of females (16.4% of all subjects). (Table 11)

Table 10: Most frequent concomitant illnesses ≥10% of the patients

	Placebo N (%)	Norditropin N (%)	Somapacitan N (%)	Total N (%)
Adrenal insufficiency	13 (21.3)	17 (14.3)	16 (13.3)	46 (15.3)
Diabetes insipidus	11 (18.0)	12 (10.1)	27 (22.5)	50 (16.7)
Growth hormone deficiency	6 (9.8)	23 (19.3)	22 (18.3)	51 (17.0)
Hypogonadism	9 (14.8)	16 (13.4)	17 (14.2)	42 (14.0)
Hypopituitarism	26 (42.6)	55 (46.2)	63 (52.5)	144 (48.0)
Hypothyroidism	18 (29.5)	37 (31.1)	31 (25.8)	86 (28.7)
Secondary hypogonadism	14 (23.0)	13 (10.9)	17 (14.2)	44 (14.7)
Secondary hypothyroidism	11 (18.0)	13 (10.9)	11 (9.2)	35 (11.7)
Dyslipidaemia	9 (14.8)	16 (13.4)	20 (16.7)	45 (15.0)
Hyperlipidaemia	5 (8.2)	16 (13.4)	15 (12.5)	36 (12.0)
Vitamin D deficiency	9 (14.8)	19 (16.0)	23 (19.2)	51 (17.0)
Headache	4 (6.6)	14 (11.8)	13 (10.8)	31 (10.3)
Depression	3 (4.9)	13 (10.9)	15 (12.5)	31 (10.3)
Hypertension	8 (13.1)	20 (16.8)	16 (13.3)	44 (14.7)

Source: Table 10-4, CSR 4054, main, p.105

Table 11 Proportion of females on oral estrogen in trial 4054

Oral estrogen use	somapacitan	Norditropin	placebo
Number of patients on oral estrogen, n	38	23	10
Proportion of patients on oral estrogen in female subgroup, % (n/N)	61.3 (38/62)	37.7 (23/61)	31.3 (10/32)

Source: adapted from Applicant Response to IR from 04/16/2020 and modified

The most frequent (> 10%) reported concomitant medications included: levothyroxine, hydrocortisone, prednisolone/prednisone, testosterone, desmopressin, paracetamol, ibuprofen and Vitamin D. (Table 10) The concomitant medications were judged not to have any impact on the bioavailability of the trial product.

Medical Officer's comments: Patients' baseline and disease characteristics are generally consistent with those of patients with GHD seen routinely in clinical practice. The concomitant medical illnesses adequately represent the underlying comorbidities in patients with AGHD and were relatively equally distributed amongst the treatment groups.

Of note, the higher prevalence of headache as a concomitant symptom in somapacitan and Norditropin groups, compared to placebo, could impact interpretability of trial drug safety results since headache is a known class effect of hGH therapy as well. In addition, the higher percentage of females on oral estrogen therapy in somapacitan group, may influence the efficacy results, since oral estrogen therapy has a known antagonizing effect on the GH metabolic actions.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance

There were no major non-compliance issues reported. Important PDs related to treatment compliance are described in this section above, subsection Protocol Deviations.

Exposure and adherence in trial 4054 from an efficacy standpoint is provided below. Additional information regarding exposure to study drug in the CDP of somapacitan from a safety perspective is presented in Section 8.2.1.

The majority of subjects received the planned treatment, with an adherence of 95.5% to somapacitan group, 93.9% to placebo and 90.6% to Norditropin (Table 12).

Table 12: Summary of treatment adherence(%)

	Placebo	Norditropin	Somapacitan
Number of Exposed Subjects	61	119	120
Number of reported dosing	1954	25780	3926
Adherence according to diary*			
Mean (SD)	93.9 (16.58)	90.6 (23.83)	95.5 (16.94)
Median	100.0	99.2	100.0
Min; Max	11.8; 100.0	0.4; 100.0	2.9; 100.0

* Number of reported dosing from diary is observed dosing visits divided by number of planned dosing multiplied by 100.

Source: Table 14.2.5, CSR 4054, p.260

Efficacy Results – Primary Endpoint

Somapacitan vs. placebo

The primary efficacy endpoint was change in TFP from baseline to week 34 in FAS population.

The study met its primary end point: the estimated mean change in TFP from baseline to end of main treatment period (week 34) in somapacitan group was superior when compared to placebo [upper boundary of the 2-sided 95% CI of the treatment difference (somapacitan – placebo) was below 0] (Table 13). According to the Applicant’s analysis, the estimated mean treatment difference in TFP between somapacitan and placebo was -1.53% [95% CI -2.68; -0.38, p = 0.009], which was statistically significant. The absolute mean change from baseline to week 34 in TFP was -1.06% in somapacitan group, compared to 0.47% in placebo group, which suggests worsening of the condition over time, if left untreated.

Table 13: Estimated change in TFP (%) from baseline to week 34 (ITT)

Endpoint	FAS	N	Estimate	[95% CI]	p-value
Truncal fat percentage (%)					
Change from baseline at week 34					
Placebo	61	61	0.47		
Norditropin	119	119	-2.23		
Somapacitan	120	120	-1.06		
Treatment difference at week 34					
Somapacitan - Placebo			-1.53	[-2.68 ; -0.38]	0.0090
Secondary comparison					
Treatment difference at week 34					
Somapacitan - Norditropin			1.17	[0.23 ; 2.11]	

FAS: Full analysis set, N: Number of subjects in analysis, CI: Confidence interval.
DM: diabetes mellitus. Changes in truncal fat percentage from baseline to the 34 week’s measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate.
nn8640/nn8640-4054/freeze_20171115_ctr_er

Source: Table 11-1, CSR 4054, p. 117

The primary analysis results were also independently verified and confirmed by the FDA’s statistician, Dr. Alexander Cambon, using the Applicant’s analysis for primary endpoint (for details, see Statistical Review by Dr. Alex Cambon in DARRTS, dated 04/27/2020).

In addition, Dr. Cambon performed a separate analysis of the primary efficacy endpoint. Dr. Cambon’s treatment policy estimand included all data available at week 34, regardless of intercurrent events such as treatment discontinuation or initiation of alternative therapy. The analysis population was all randomized subjects who have been exposed to treatment and had a baseline measure (as opposed to FAS population which included 2 patients with imputed baseline data). The preferred analysis method was an ANCOVA with the same covariates and factors as proposed by the Applicant. Because the missing data and discontinuation rates were very low (i.e. missing efficacy data: 1.7% for somapacitan, 3.6% for Norditropin and 3.5% for

placebo), and the reasons for discontinuations were not related to AE in most of the patients (i.e. consistent with missing at random approach), Dr. Cambon did not use a method to address missing data. According to Dr. Cambon, the results using this separate ANCOVA method were very similar to the Applicant's analysis results, with treatment difference in TFP between somapacitan and placebo of -1.41% [95% CI -2.61; -0.22, p = 0.02], which was statistically significant (Table 14).

Table 14: Change in TFP (%) from baseline to week 34 (FDA's stats analysis set)

Endpoint	Estimate	[95% CI]	p-value
Truncal fat percentage (%)			
Change from baseline at week 34			
Placebo	0.31		
Norditropin	-2.38		
Somapacitan	-1.10		
Treatment difference at week 34			
Somapacitan - Placebo	-1.41*	[-2.61 ; -0.22]	0.02
Secondary comparison			
Treatment difference at week 34			
Somapacitan – Norditropin	1.28	[0.29 ; 2.26]	0.011

*If the three-way interaction is taken out, the treatment difference is -1.50, and p-value is 0.01.

Source: adapted from Dr. Alexander Cambon's statistical review

In addition, in an Information Request submitted to the Applicant on 4/16/2020, Dr. Cambon requested a separate analysis (hereon referred to as FDA-requested analyses) for the primary endpoint for somapacitan vs. placebo, somapacitan vs. Norditropin, as well as Norditropin vs. placebo, using the final assessment window of 34 weeks +/- 4 weeks, as opposed to week 34 only, which was used for the primary analysis. Dr. Cambon requested that patients that do not have a final assessment within this window should be treated as having a missing final assessment, or as discontinuing treatment early (if treatment discontinuation is < 210 days). For patients with a missing final assessment who discontinued treatment early, the missing final assessment should be multiply imputed using a washout multiple imputation (a multiple imputation approach based on results from patients on placebo arm). For patients with missing final assessments who did not discontinued treatment early, a MAR multiple imputation approach should be used (if reason for discontinuation was a not due to AEs). The Applicant was asked to include all randomized treated patients with a baseline measure in the analyses, but to exclude patients with an imputed baseline measure.

Differences in treatment effects between somapacitan vs. placebo and somapacitan vs. Norditropin from the analysis approach specified by the FDA, were consistent with those obtained from the prespecified analysis of the primary endpoint (Table 15).

Table 15: Change from baseline to week 34 in TFP(%) (trial 4054)- predefined and FDA-requested analyses

	Estimated change from baseline to week 34			Estimated treatment difference [95% CI] at week 34	
	Soma (N = 120/ 115) ^a	PBO (N = 61/ 59) ^a	Nordi (N = 119/ 117) ^a	Soma – PBO	Soma – Nordi
Truncal fat percentage, %					
Predefined analysis ^b	-1.06	0.47	-2.23	-1.53 [-2.68; -0.38] ^s	1.17 [0.23; 2.11]
FDA-requested analysis ^c	-1.07	0.51	-2.31	-1.58 [-2.76; -0.40]	1.24 [0.28; 2.20]

Notes: ^aNumber of patients in prespecified analysis/FDA requested analysis. Estimates are from the analysis of covariance model with treatment, GHD onset type, sex, region, diabetic status and sex by region by diabetic status interaction as factors and baseline as covariate incorporating a multiple imputation technique where missing week 34 values were imputed based on data from the ^bplacebo group and ^caccording to FDA specifications (Section 1.1).

^s superiority confirmed.

Abbreviations: CI = confidence interval; N = number of patients; Nordi = Norditropin®; PBO = placebo; Soma = somapacitan.

Source: The Applicant's response to Agency's IR on 4/22/2020

Somapacitan vs. Norditropin

According to the Applicant, a secondary comparison of the primary endpoint between somapacitan and Norditropin (active treatment arm) was performed in order to provide context for standard-of-care, which is daily GH replacement therapy, and to support the evaluation of the clinical meaningfulness of the changes in the primary endpoint observed in somapacitan and placebo groups. This secondary comparison showed greater effect on the TFP reduction for Norditropin compared to somapacitan, with an estimated treatment difference of 1.17% [95% CI 0.23; 2.11] (Table 13). The change from baseline to end of week 34 in TFP was less than half in somapacitan group compared to Norditropin (-1.06% vs. -2.23%) (Table 13). The results of this secondary comparison analysis were also confirmed by the Dr. Cambon's separate statistical analysis, with results demonstrating statistical inferiority of somapacitan vs. Norditropin, with treatment difference of 1.28% [95% CI 0.29; 2.26, p = 0.011] (Table 14). Of note, statistical non-inferiority margin was not pre-specified or required. The FDA-requested analysis (Table 15) for the comparison of the primary endpoint between somapacitan and Norditropin also confirmed the pre-defined analysis, showing a treatment difference of 1.24% [95% CI 0.28; 2.20].

Additionally the FDA-requested analysis on the treatment difference for the primary endpoint between Norditropin and placebo, revealed an estimated treatment difference of – 2.82% [95% CI -4.0; -1.63] (Table 16).

Table 16: Change from baseline in TFP (%) for Norditropin vs placebo after 34 weeks of treatment (trial 4054) – FDA-requested analysis

	Norditropin® (N = 117)	Placebo (N = 59)	ETD [95% CI]
Truncal fat percentage, %	-2.31	0.51	-2.82 [-4.0; -1.63]

Notes: Changes in truncal fat percentage from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate.

Abbreviations: CI = confidence interval; ETD = estimated treatment difference; N = number of patients.

Source: The Applicant's response to Agency's IR on 4/22/2020

Medical officer's comments: The study met the primary efficacy endpoint, with results showing statistically significant reduction in TFP from baseline in somapacitan treated patients compared to placebo using different analysis population sets and demonstrated the superiority of somapacitan over placebo in reduction of TFP. The secondary comparison (somapacitan vs. Norditropin) of the primary endpoint, although only intended to help assess the clinical meaningfulness of the primary comparison of the primary endpoint, and not to claim superiority of the study drug, demonstrated statistical inferiority of somapacitan vs. Norditropin. Because of the low missing data rates overall, the primary efficacy results do not differ significantly between different analysis populations (FAS vs FDA stat reviewer analysis population vs FDA-requested analysis).

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy endpoints analyses were not hierarchy tested and no adjustment for multiplicity was performed.

Changes in DXA body composition assessments from baseline to week 34

Somapacitan vs. placebo

All body fat assessments [VAT, android fat mass, truncal body fat mass, body fat mass], but gynoid body fat mass, decreased from baseline to week 34 in somapacitan group, whereas all body lean mass assessments [truncal lean body mass, ASMM and total body lean mass] increased from baseline to week 34 in somapacitan group. According to the Applicant's analyses, statistically significant improvement in body composition parameters in somapacitan group compared to placebo was seen in VAT, android fat mass, truncal lean body mass, ASMM and lean body mass (Table 17).

Table 17: Changes from baseline to week 34 in body composition parameters for somapacitan vs placebo (trial 4054)

Change from baseline	Somapacitan (N = 120)	Placebo (N = 61)	ETD	[95% CI]	P-value
Visceral adipose tissue (cm ²)	-10	3	-14	[-21; -7]	0.0001
Truncal fat mass (g)	-123	373	-496	[-1049; 57]	0.0786
Android fat mass (g)	-68	48	-116	[-223; -10]	0.0326
Gynoid fat mass (g)	26	11	15	[-144; 175]	0.8511
Total fat mass (g)	-31	236	-266	[-1197; 664]	0.5746
Truncal lean body mass (g)	804	352	452	[25; 880]	0.0380
ASMM (g)	558	-121	679	[340; 1019]	0.0001
Total lean body mass (g)	1394	250	1144	[459; 1829]	0.0011

Abbreviations: ASMM = appendicular skeletal muscle mass; CI = confidence interval; ETD = estimated treatment differences; GHD = growth hormone deficiency; N = number of patients in full analysis set.

Source: Applicant's Table 3-10, SCE, p. 47

Somapacitan vs. Norditropin

Overall, the observed changes from baseline to week 34 were larger in Norditropin group compared to somapacitan for the majority of the body fat assessments (except for VAT, for which DXA is likely not a reliable measurement instrument), whereas the changes from baseline to week 34 in the lean body mass assessments were similar between Norditropin and somapacitan groups (Table 18).

However, there were no statistically significant differences between somapacitan and Norditropin in the secondary supportive body composition endpoints. Of note, VAT, android fat mass and gynoid fat mass were assessed only if the DXA scanner permitted.

Table 18: Changes from baseline to week 34 in body composition parameters for somapacitan vs Norditropin (trial 4054)

	Somapacitan (N = 120)	Norditropin® (N = 119)	ETD	[95% CI]
Secondary endpoints				
Visceral adipose tissue (cm ²)	-10	-9	-1	[-7; 4]
Truncal fat mass (g)	-123	-534	411	[-41; 864]
Android fat mass (g)	-68	-143	74	[-12; 161]
Gynoid fat mass (g)	26	-120	146	[16; 276]
Total fat mass (g)	-31	-755	724	[-39; 1487]
Truncal lean body mass (g)	804	843	-38	[-388; 311]
ASMM (g)	558	462	96	[-182; 374]
Total lean body mass (g)	1394	1345	49	[-513; 610]

Abbreviations: ASMM = appendicular skeletal muscle mass; CI = confidence interval; ETD = estimated treatment difference; GHD = growth hormone deficiency; N = number of patients in full analysis set.

Source: Applicant's Table 3-12, SCE, p. 50

Medical officer's comment: According to the Applicant's analyses, statistically significant improvement in body composition parameters in somapacitan group compared to placebo was seen in VAT, android fat mass, truncal lean body mass, ASMM and total lean body mass. The supportive secondary endpoints of efficacy, truncal fat mass and truncal lean body mass, are both components of the primary efficacy endpoint equation (see TFP definition above) and as expected the observed changes are correlated with the primary endpoint results. Since the Applicant's secondary endpoints analyses did not include adjustment for multiplicity, the statistically significant difference observed in some body composition parameters could be due to chance, consistent with the principle and limitations of multiple endpoints testing, therefore the interpretation of the results should be made with caution. In addition, the changes in VAT should be interpreted with caution, since DXA is not a reliable and commonly used instrument to assess the VAT changes. However, it is important to note that changes in lean body mass parameters were all congruent and the comparison to placebo reached statistical significance for all parameters, suggesting a primary effect of somapacitan on lean body mass compartments improvement. In addition, the changes from baseline to week 34 in the lean body mass assessments were similar between Norditropin and somapacitan groups, whereas the changes in body fat assessments were larger in Norditropin group compared to somapacitan. The overall effects on body composition parameters are in line with observed changes with other approved rhGH products, although direct comparison with other GH products is difficult to make due to differences in study designs, baseline patient

population characteristics, dose titration targets, statistical analysis plans, methods of assessments for the efficacy endpoints, etc.

The less pronounced effect of somapacitan compared to Norditropin observed for some of the adipose tissue parameters after 34 weeks of treatment is unclear and could not be explained by different tissue-level responses to GH between the treatment groups, as the mean IGF-1 SDS (marker of GH action) levels at the end of titration period and end of main period were similar between somapacitan vs. Norditropin, while the distribution of IGF-1 SDS levels after 34 weeks of treatment was similar between somapacitan and Norditropin, as well.

In summary, the current trial demonstrated that somapacitan has a beneficial effect on lean body mass parameters, and a modest effect on the body fat mass parameters, whereas Norditropin has a beneficial effect on both. Although the treatment difference in several body composition endpoints reached statistical significance, I agree with Dr. Cambon recommendation (see Dr. Cambon's statistical review for details) that the results of the secondary supportive body composition parameters assessments should only be presented in the label descriptively, due to the lack of adjustment for multiple testing procedures.

IGF-1 SDS and IGFBP-3 SDS

The mean IGF-1 SDS normalized from baseline to end of titration period (week 9) and end of main trial period (week 34) in both somapacitan and Norditropin groups, from a baseline value below -2 to a value within the mean of the reference range at both time points, as seen in Table 19. The estimated mean increases in IGF-1 SDS were 2.40 and 2.37 in the somapacitan and Norditropin groups and -0.01 in the placebo group from baseline to week 34 (Table 20). Statistically significant differences in change from baseline to week 34 in IGF-1 SDS were observed between somapacitan and placebo, while no statistically significant differences in changes from baseline to week 34 in IGF-1 SDS were observed between somapacitan and Norditropin (Table 20).

Table 19: Summary of IGF-1 SDS by visit (FAS)

Mean IGF-1 SDS (SD)	Somapacitan	Norditropin	Placebo
Baseline (week 0)	-2.54 (1.26)	-2.53 (1.27)	-2.64 (1.28)
End of titration (week 9)	0.10 (0.98)	-0.14 (1.29)	-2.56 (1.30)
End of main period (week 34)	-0.17 (1.25)	-0.23 (1.11)	-2.62 (1.33)
End of extension period (week 86)			

Source: adapted from Table 14.2.59, CSR 4054 main, p. 318

Table 20: Change from baseline to week 34 in IGF-1 SDS in trial 4054 main

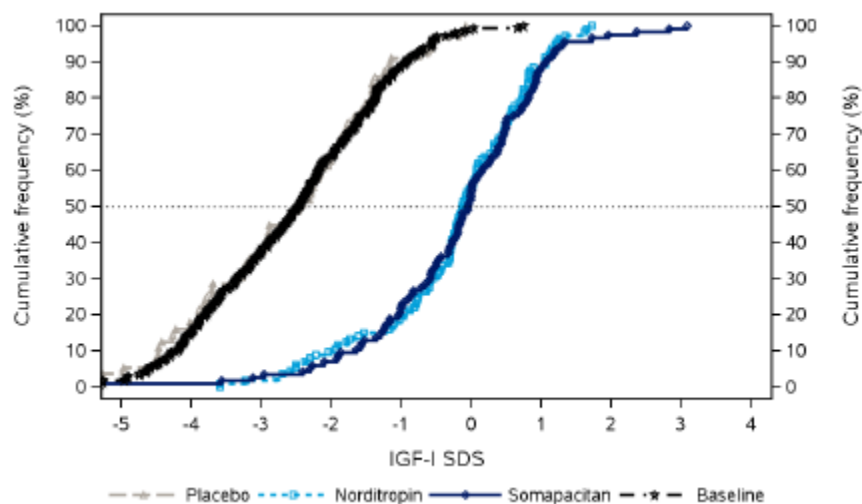
IGF-1 SDS	Estimate	[95% CI]	p-value
Change from baseline at week 34			
Somapacitan	2.40		
Norditropin	2.37		
Placebo	-0.01		
Treatment difference at week 34			
Somapacitan - Placebo	2.40	[2.09; 2.72]	0.000
Somapacitan - Norditropin	0.02	[-0.23; 0.28]	0.8531

Source: adapted from Table 11-5, CSR 4054 main, p.125

A similar pattern of changes during trial period was observed in mean IGFBP-3 SDS, though increase was smaller than observed for IGF-1 SDS (see Applicant's CSR 4054, Table 11-5, page 125 for details).

According to the Applicant, 16 patients had IGF-I SDS values above +2 at one or more time points during the trial (titration period and/or fixed dose period) in the active treatment groups (somapacitan: 10 patients; Norditropin: 6 patients), and quite a few patients with IGF-1 SDS values below -2, after the titration. After 34 weeks, both somapacitan and Norditropin normalized the mean IGF-1 level to a value within reference range (-2 to +2) in majority of patients (Figure 7). However, approximately 20% of subjects (in both, somapacitan and Norditropin groups) did not reach the IGF-1 SDS titration target of -0.5 at week 34 (Figure 7).

Figure 7: IGF-1 SDS – Empirical distribution at week 34 compared to baseline for placebo, Norditropin and somapacitan



Source: Figure 14.2.62, CSR 4054, p.323.

Medical Officer Comment:

Somapacitan is a rhGH and is proposed as a replacement therapy in adult patients with GHD. As such, it is mechanistically expected that GH replacement should lead to the improvement in the levels of the major tissue marker of GH action, i.e. IGF-1. Thus, observed improvement and normalization of IGF-1 levels in the majority of patients with GHD is supportive of primary endpoint. However, the relatively high percentage of subjects (approximately 20%) in both somapacitan and Norditropin groups not reaching the IGF-1 SDS titration target suggest that a longer titration period and/or better titration regimen would have likely resulted in more subjects achieving the IGF-1 titration target that could have translated into better overall clinical response in body composition.

Body weight and waist circumference

A larger change from baseline to end of main trial period, 1.40 kg, was noted in somapacitan group compared to very small changes in body weight in placebo and Norditropin groups. While there were no statistically significant differences in estimated change in weight between somapacitan and placebo at week 34, an estimated difference of 1.13 kg (95% CI: 0.13; 2.12; p = 0.02) between somapacitan and Norditropin was noted at week 34, which was statistically significant (Table 21).

Table 21: Body weight change from baseline to week 34 and week 87 trial 4054 (FAS)

Body weight	Estimate	[95% CI]	p-value
Change from baseline at week 34			
Placebo	0.39		
Norditropin	0.27		
Somapacitan	1.40		
Treatment difference at week 34			
Somapacitan - Placebo	1.00	[-0.21 ; 2.22]	0.1051
Somapacitan - Norditropin	1.13	[0.13 ; 2.12]	0.0265
Change from baseline at week 87			
somapacitan/somapacitan	1.53		
Norditropin/Norditropin	0.45		
Treatment difference at week 87			
Somapacitan/somapacitan – Norditropin/Norditropin	1.09	[-0.5 ; 2.7]	0.1767

Source: adapted from Table 11-6, CSR 4054(main), p. 130 and Table 11-3, CSR 4054 (ext.), p. 142

No significant changes in waist circumference from baseline to end of main trial period were noted in any treatment groups, although a trend towards decreasing waist circumference was noted in Norditropin arm at week 34. There were no statistically significant changes in waist circumference from baseline to end of main trial period between any treatment groups (i.e. somapacitan vs placebo, and somapacitan vs Norditropin) (Table 22).

Cardiometabolic parameters

Lipid profile parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) and cardiovascular markers (hsCRP and IL-6) were evaluated in trial 4054 and were noted to be unchanged from baseline to end of main treatment period (week 34) and end of the extension period (week 87) in any treatment groups.

Table 22: Waist circumference change from baseline to week 34 and week 87 trial 4054 (FAS)

Waist circumference	Estimate	[95% CI]	p-value
Change from baseline at week 34			
Placebo	0.40		
Norditropin	-0.49		
Somapacitan	0.14		
Treatment difference at week 34			
Somapacitan – Placebo	-0.26	[-1.73 ; 1.21]	0.7290
Somapacitan – Norditropin	0.63	[-0.56 ; 1.82]	0.2973
Change from baseline at week 87			
somapacitan/somapacitan	0.65		
Norditropin/Norditropin	-1.88		
Treatment difference at week 87			
Somapacitan/somapacitan – Norditropin/Norditropin	2.53	[0.6 ; 4.5]	0.0106

Source: adapted from Table 11-6, CSR 4054(main), p. 130 and Table 11-3, CSR 4054 (ext.), p. 142

Medical officer's comment: The observed difference in body weight change in somapacitan group compared to placebo and Norditropin ranged between 1.0 – 1.13 kg at the end of main trial period, and reached statistical significance when compared to Norditropin. The observed change in body weight in somapacitan group was of small magnitude overall, and it could be a result of fluid retention, known adverse effect of GH therapy. Whereas the effect of somapacitan on waist circumference appears to be neutral, there appears to be a trend towards decreasing waist circumference in Norditropin arm at week 34.

PRO questionnaires

Scores of the following PRO questionnaires were assessed in trial 4054: SF-36v2 (summary and domain scores), TRIM-AGHD (disease specific, total and domain scores) and TSQM-9 (effectiveness, convenience and global satisfaction scores).

SF-36v2:

The generic questionnaire SF-36 was applied to subjects in study 4054 to assess the patients' functional status and well-being, with higher scores (range: 0–100) relating to better health status. According to the Applicant, improvements from baseline were observed with somapacitan and Norditropin across the eight SF-36 domains (role-physical, bodily pain, general health, physical functioning, social functioning, vitality, role-emotional, and mental health) after 34 and 86 weeks of treatment, respectively, and statistically significant differences in change from baseline were found between the somapacitan and placebo in several domains (i.e.

mental health and social functioning) in favor of somapacitan after 34 weeks. However, the observed changes were not large enough to be considered clinically relevant by the Applicant.

TRIM-AGHD

The disease specific TRIM-AGHD questionnaire was applied to subjects in study 4054 to assess the impact of GH treatment on the functioning and well-being of adults with GHD, with lower scores (range: 0-100) relating to better functioning and well-being.

According to the Applicant, although improvements from baseline in all 4 domains (cognitive, energy, physical, psychological) and the total score were observed with both somapacitan and Norditropin after 34 and 86 weeks of treatment, respectively, the changes were not large enough to be considered statistically significant, or clinically relevant by the Applicant.

TSQM-9

The TSQM-9 questionnaire was applied to subjects across all phase 3 trials (4054, 4043 and 4244), to evaluate aspects of treatment satisfaction: effectiveness, convenience, and global satisfaction, with higher scores (range: 0–100) indicating higher treatment satisfaction. Of note, in trial 4054, the TSQM-9 assessment was not feasible to be performed at baseline as ‘treatment satisfaction’ could not be assessed in a treatment-naïve patient population. Across the phase 3 trials, somapacitan was consistently considered more convenient than Norditropin, but no consistent trends across trials for the other TSQM-9 domains (effectiveness and global satisfaction) were observed. In trial 4054, the results indicated that treatment with somapacitan resulted in higher treatment convenience scores compared to Norditropin after 34 and 86 weeks of treatment. In trials 4244 and 4043, treatment with somapacitan and Norditropin both led to improved treatment convenience scores compared to baseline, and greater improvements were observed with somapacitan as compared to Norditropin (see Table 3-17 in SCE, page 60, for details).

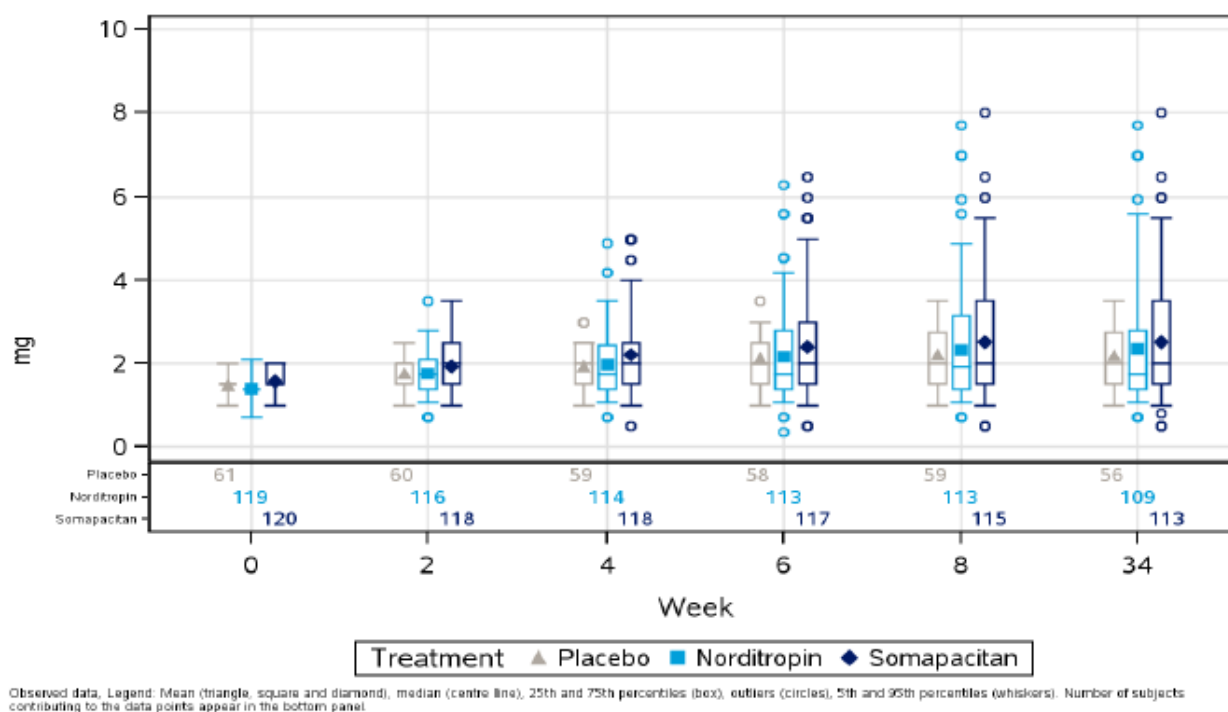
Medical officer’s comments: None of PROs used in the somapacitan CDP were validated by the Agency in the intended population to date and clinical meaningfulness of the observed small changes remains unknown. Therefore, none of the PRO assessments results observed in the somapacitan CDP are eligible for any labeling claims. In fact, the Applicant did not propose any PROs labeling claims either.

Dose/Dose Response

The dose exposure during the titration visits (8 weeks) and the fixed dose period (26 weeks) is summarized in Figure 8. The mean (SD) somapacitan dose was 2.52 mg/week (1.44) in the 26 weeks period with fixed dose treatment, and 2.56 mg/week in the 34 week period. The mean (SD) somapacitan dose in the 86 week (main + extension) 4054 trial was 2.59 mg/week, which was similar to main part of the trial. The dose range for somapacitan use during the entire trial

was of minimum 0.5 mg/week to maximum 8.00 mg/week. Of note, a somapacitan dose of 8.00 mg/week was the maximum dose allowed according to the protocol. The majority of the patients (59.6%) increased their somapacitan dose during the titration period, where 30.7% patients did not adjust the dose. A similar pattern was observed in the two supportive Phase 3 studies (4244 and 4043). Thus, the maintenance dose of somapacitan was generally higher than the starting dose.

Figure 8: Summary of weekly exposure at titration visits and fixed dose period



Source: Figure 12-1, CSR 4054, p.134

See Section 7.1.4. for detailed assessment of dose/dose response during the entire CDP of somapacitan.

Durability of Response

Durability of response was addressed in the extension part of the pivotal trial 4054. The changes in all efficacy endpoints (primary and secondary) from baseline to the end of extension period (total of 86 weeks of exposure) were assessed in three groups of patients separately: patients who were treated with somapacitan during the core period of the study and continued treatment with the drug in the extension period of the study (somapacitan/somapacitan), patients who were treated with Norditropin in core phase and

continued treatment with Norditropin in the extension phase (Norditropin/Norditropin) and patients who were treated with placebo in core phase and were switched to somapacitan treatment in the extension phase (placebo/somapacitan).

Body composition parameters

Change in body composition endpoints pertaining to the 86-week treatment period in trial 4054 compared to corresponding results for the 34-week main period are summarized in Table 23. Somapacitan-induced effect on TFP after 34 weeks of treatment was further maintained during extended exposure up to 86 weeks, with estimated mean change from baseline to week 86 of -1.52% vs. -1.06% after 34 weeks of treatment. The durability of the effect on the majority of body composition parameters was maintained after 86 weeks of treatment when compared to week 34 results, for both somapacitan and Norditropin, with no notable differences between somapacitan and Norditropin. The estimated treatment difference between somapacitan and Norditropin in TFP change from baseline to week 87 was similar to the treatment difference observed at week 34 (1.17 vs. 1.15).

Evaluation of somapacitan-induced effects on TFP was also performed on the patients who were re-allocated from placebo to somapacitan during the extension period for 52 weeks. At week 87, 52 weeks of somapacitan treatment resulted in reductions in TFP from baseline of -2.28%. Additionally favorable changes from baseline to week 87 were observed on other body composition parameters, such as VAT, truncal fat mass, android fat mass, total fat mass, truncal lean mass, total lean body mass and ASMM (Table 24). Of note, the reported estimated changes from baseline to week 87 in the body composition parameters did not account for any changes in body composition parameters in the placebo group from baseline to week 34, therefore any deterioration in body composition parameters occurring while on placebo was masked.

Table 23: Changes from baseline to weeks 34 and 87 in body composition parameters for subjects exposed to somapacitan and Norditropin only (trial 4054)

Endpoints	Week	Somapacitan (N = 120/120)	Norditropin® (N = 119/52)	ETD	[95% CI]
Truncal fat %	Week 34	-1.06	-2.23	1.17	[0.23; 2.11]
	Week 87 ^a	-1.52	-2.67	1.15	[-0.10; 2.40]
Visceral adipose tissue (cm ²)	Week 34	-10	-9	-1	[-7; 4]
	Week 87 ^a	-6.6	-6.9	0.2	[-10; 10]
Visceral adipose tissue % ^b	Week 34	N/A	N/A	N/A	N/A
	Week 87 ^a	-5.16	-7.32	2.16	[-9.68; 13.99]
Truncal fat mass (g)	Week 34	-123	-534	411	[-41; 864]
	Week 87 ^a	-175	-781	606	[-90; 1303]
Android fat mass (g)	Week 34	-68	-143	74	[-12; 161]
	Week 87 ^a	-37	-134	97	[-41; 235]
Gynoid fat mass (g)	Week 34	26	-120	146	[16; 276]
	Week 87 ^a	7	-134	142	[-68; 351]
Total fat mass (g)	Week 34	-31	-755	724	[-39; 1487]
	Week 87 ^a	-78	-1058	980	[-249; 2209]
Truncal lean body mass (g)	Week 34	804	843	-38	[-388; 311]
	Week 87 ^a	1160	891	269	[-183; 721]
ASMM (g)	Week 34	558	462	96	[-182; 374]
	Week 87 ^a	546	449	97	[-362; 556]
Total lean body mass (g)	Week 34	1394	1345	49	[-513; 610]
	Week 87 ^a	1739	1306	433	[-404; 1271]
Total bone mineral content (corrected) (g)	Week 87 ^a	4.67	-11.41	16.07	[-16.00; 48.15]
Total bone mineral density (corrected) (g/cm ³)	Week 87 ^a	-0.006	-0.015	0.009	[-0.01; 0.02]

Abbreviations: ASMM = appendicular skeletal muscle mass; CI = confidence interval; N = number of patients in full analysis set for main/extension period; 'Norditropin®/-' = patients treated with Norditropin® in the main period not participating in extension period were not re-randomised. **Notes:** Change from baseline to 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, diabetic status and sex by region by diabetic status interaction as factors and baseline as a covariate incorporating a multiple imputation technique where missing week 34 values were imputed based on data from the placebo group. Changes from baseline to end of extension period (week 87) was analysed based on MMRM analysis models. Patients from the Norditropin®/- group contribute to the analysis with measurements from main period. ^a Week 87: end of extension period (86 weeks of treatment + 1 week washout between main and extension). ^b Visceral adipose tissue in % is a *post hoc* defined endpoint.

Source: Table 5-1, SCE, p. 74

Table 24: Body composition parameters for placebo patients reallocated to somapacitan in extension period from baseline to week 34 and week 87 (trial 4054)

	Placebo/somapacitan			Estimated change from baseline to week 87 (N = 61)
	Baseline ^a	Week 34 ^b	Week 87 ^c	
Truncal fat %	37.00	37.86	35.59	-2.28
Visceral adipose tissue (cm ³)	107	111	93	-10
Visceral adipose tissue % ^d	-	107	84	-16
Truncal fat mass (g)	12717	13320	12680	-354
Android fat mass (g)	2095	2184	2024	-112
Gynoid fat mass (g)	4052	4185	4094	-74
Total fat mass (g)	24858	25559	24766	-573
Truncal lean body mass (g)	20683	21118	21587	1160
ASMM (g)	18958	18904	19256	411
Total lean body mass (g)	42492	42893	43758	1661

Abbreviations: ASMM = appendicular skeletal muscle mass; N = number of patients in full analysis set;

‘Placebo/somapacitan’ = patients in the placebo group reallocated to 52 weeks of somapacitan in extension period.

Notes: Baseline, week 34 and week 87 are observed mean. Exploratory analyses of changes from baseline to week 87 data were based on a MMRM analysis model. Small variation in the number of patients included in the analysis across the secondary endpoints due to limitations in DXA capabilities.

^a For one patient different baseline values for the DXA parameters were used for reporting in the extension period than were used for reporting of the main period. Therefore, minor variations in the observed mean baseline values between main and extension period can be observed. ^b Week 34: end of main period. ^c Week 87: end of extension period including 86 weeks of treatment + 1 week washout between main and extension period. ^d Visceral adipose tissue in % is a *post hoc* defined endpoint.

Source: Table 3-11, SCE, p. 49

Body weight and waist circumference

The mean weight change from baseline to week 87 in somapacitan/somapacitan arm was similar to the change observed at week 34, suggesting no progression of treatment effect, but rather stabilization. In addition, there was no statistically significant treatment difference in estimated changes in body weight from baseline to week 87 between somapacitan/somapacitan and Norditropin/Norditropin arms (Table 21).

No significant changes were observed in the mean waist circumference from baseline to week 87 in the somapacitan/somapacitan arm, whereas a decrease of -1.88 cm was observed in the

Norditropin/Norditropin arm. The treatment difference between the somapacitan/somapacitan and Norditropin/Norditropin arms at week 87 was statistically significant (Table 22).

IGF-1 SDS levels

The somapacitan-induced increase in mean IGF-1 SDS was maintained for up to 86 weeks of treatment, from a baseline value of -2.54 to -0.22 after 86 weeks of treatment, similar to the changes observed in mean IGF-1 SDS levels after 34 weeks of treatment. A similar pattern of IGF-1 SDS response after 86 weeks of treatment was observed for patients who continued on Norditropin therapy.

Medical officer's comments:

Data from the extension period provide some evidence of durability of the response after 86 weeks of treatment through evaluation of changes in body composition parameters and maintained IGF-1 SDS levels for patients who remained on the same treatment for the entire trial period. However, the quantitative efficacy data obtained from such open-label, uncontrolled trials should not be used for labeling purposes because by the very nature of its design, the trial selected a patient population likely to have benefited from the drug, and a control group is lacking.

Persistence of Effect

The persistence of the drug effect over time after treatment is stopped or withheld was not evaluated during the CDP.

Additional exploratory Analyses Conducted in the Trial

Bone mineral content (BMC) and bone mineral density (BMD) were evaluated as secondary endpoints of efficacy after 86 weeks of exposure in somapacitan/somapacitan, and Norditropin/Norditropin arms, as well as after 52 weeks of exposure in placebo/somapacitan arm, and no changes from baseline were observed in any treatment group (Table 25)

Table 25: Changes from baseline to week 87 in bone parameters (trial 4054)

Treatment arms	Total bone mineral content (corrected) (g)	Total bone mineral density (corrected) (g/cm ²)
Somapacitan/somapacitan* (N = 120/120)	4.67	- 0.006
Norditropin/Norditropin* (N = 119/52)	-11.41	- 0.015
Placebo/somapacitan# (N = 61/61)	-27	-0.006

*after 86 weeks of exposure to treatment; # after 52 weeks of exposure to treatment

Source: adapted from Tables 3-11 and 5-1 of SCE, p.49 & 74

6.2. A multicenter, randomized, open-labelled, parallel-group, active-controlled trial to evaluate the safety of once-weekly dosing of somapacitan (NNC0195-0092) and daily Norditropin® FlexPro® for 52 weeks in previously human growth hormone treated Japanese adults with growth hormone deficiency (AGHD) (Trial 4244)

6.2.1. Study Design

Overview and Objective

Trial 4244 was designed to evaluate the safety (primary objective) and efficacy (secondary objectives) of once weekly somapacitan injection compared to daily Norditropin therapy.

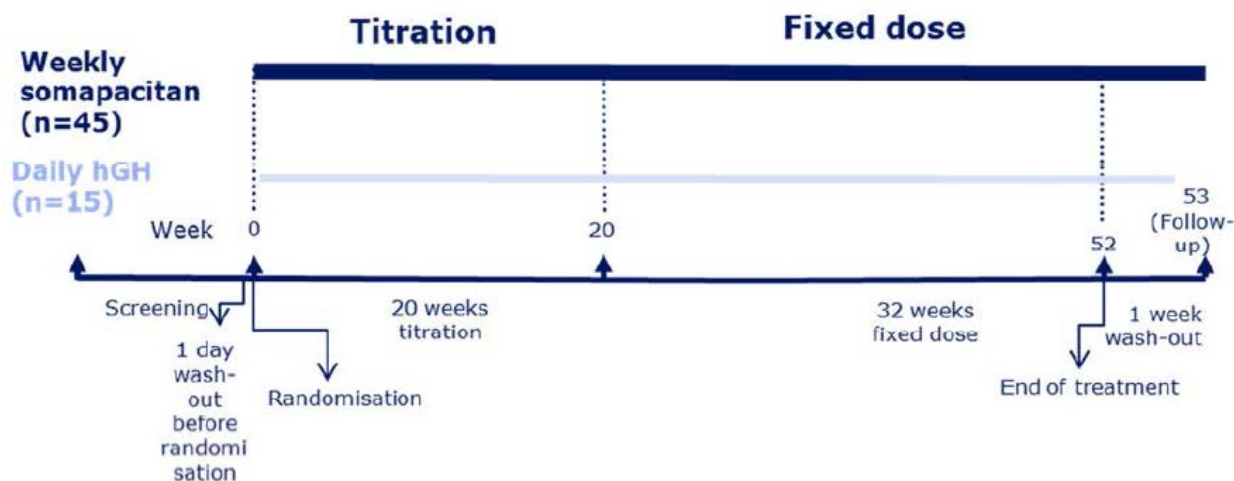
The efficacy was evaluated by measuring the effect on abdominal adipose tissue and the degree of treatment satisfaction of once weekly dosing of somapacitan compared to daily Norditropin.

Trial Design

This trial was a multicenter, randomized, open labelled, parallel-group, active controlled trial in previously hGH treated Japanese AGHD patients.

The trial consisted of 52 weeks treatment period (20 weeks dose titration, 32 weeks fixed dose treatment) followed by 1 week washout. AGHD patients were randomized in a 3:1 ratio (somapacitan: Norditropin) and the randomization was stratified according to sex. Discontinued patients were not replaced. (Figure 9)

Figure 9: Trial design (4244)



Source: Figure 5-1, CSR, 4244, p. 28

The somapacitan and Norditropin doses could be adjusted based on IGF-1 SDS. During the first 20 weeks, the somapacitan or Norditropin doses could be adjusted every 4th week, which allowed for 5 opportunities for dose adjustment. The starting doses in both treatment groups were similar to trial 4054 [somapacitan 1.5 mg/week (18-60 years) (except females on oral estrogen 2.0 mg/week; patients older than 60 years 1.0 mg/week) and Norditropin 0.2 mg/day (except females on oral estrogen: 0.3 mg/day; patients older than 60 years: 0.1 mg/day)]. The titration algorithms for somapacitan and Norditropin applied in trials 4244 and 4043 are shown in Table 26. The IGF-1 SDS target range was $0 < \text{IGF-1 SDS} \leq 2$, with dose reductions for IGF-1 SDS higher than 2 IGF-1 SDS and dose increases for IGF-1 SDS at or lower than 0 IGF-1 SDS.

Table 26: Dose titration algorithm for somapacitan and Norditropin® in trials 4244 and 4043

IGF-I SDS interval ^a	Somapacitan	Norditropin®
	Increment/reduction of weekly dose	Increment/reduction of daily dose
IGF-I SDS > 3	Decrease by 1 mg/week	Decrease by 0.1 mg/day
$2 < \text{IGF-I SDS} \leq 3$	Decrease by 0.5 mg/week	Decrease by 0.05 mg/day
$0 < \text{IGF-I SDS} \leq 2$	No adjustment	No adjustment
$-2 < \text{IGF-I SDS} \leq 0$	Increase by 0.7 mg/week	Increase by 0.1 mg/day
IGF-I SDS ≤ -2	Increase by 1.5 mg/week	Increase by 0.2 mg/day

Abbreviations: IGF-I SDS = insulin-like growth factor - I standard deviation score.

^a Trial 4244: 3 weeks and 3 days after last dose adjustment; Trial 4043: 1 week and 3 days after last dose adjustment.

Source: Table 1-6, SCE, p. 24

The key inclusion criteria included, patients with documented GHD previously treated with rhGH, age bracket between 18 years of age and not more than 79 years of age, previous treatment with hGH for at least 6 consecutive months at screening, IGF-1 level $-2 \text{ SDS} \leq \text{IGF-1 level} \leq +2 \text{ SDS}$.

The key exclusion criteria included active malignant disease or history of malignancy, subjects with GHD attributed to treatment of intracranial malignant tumors or leukemia, provided there was a recurrence-free survival period of at least 5 years, evidence of growth of pituitary adenoma or other benign intracranial tumor within the last 12 months before randomization. Patients with a diagnosis of diabetes at baseline were excluded as well.

Study Endpoints

Primary endpoint

Incidence of adverse events, including injection site reactions.

Secondary efficacy endpoints

Change from baseline to end of treatment period (52 weeks) in cross-sectional total adipose tissue compartments (TAT), subcutaneous adipose tissue compartments (SAT), and intra-abdominal or visceral adipose tissue compartments (VAT) determined by quantitative CT scans. Change from baseline to end of treatment period (52 weeks) in TSQM-9 scores for effectiveness, convenience and global satisfaction.

The primary and secondary safety endpoints were similar to the safety endpoints in trial 4054.

Statistical Analysis Plan

The sample size was not based on any formal statistical calculation. The FAS and SAS included all patients who were treated during the trial. The FAS used for evaluations of efficacy endpoints included all randomized patients that received at least one dose of randomized treatment. Patients were analyzed “as randomized”. The SAS used for evaluations of safety endpoints included all randomized patients that received at least one dose of randomized treatment. Patients were analyzed “as treated”.

Changes in abdominal adipose tissue compartments (TAT, SAT and VAT) from baseline to week 52 was analyzed using an analysis of covariance (ANCOVA) model with treatment, GHD onset type and sex as factors and baseline value as a covariate. From the model the treatment difference at week 52 between somapacitan and Norditropin was estimated and the corresponding 95% confidence interval and p-value was calculated for each endpoint. Patients without week 52 data for the analyzed endpoint were not included in the analysis. It was expected that less than 7% of the patients will not have week 52 data for the CT scan based endpoints. The change in TSQM-9 scores (effectiveness, convenience and global satisfaction

scores) at 32 weeks and 52 week's measurements were analyzed using a mixed model for repeated measurements (MMRM), with treatment, GHD onset type and sex as factors and baseline as a covariate, all nested within week as a factor. All secondary safety endpoints were analyzed using descriptive statistics. Thee somapacitan and hGH serum concentration data were analyzed using descriptive statistics.

Protocol Amendments

None

6.2.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013) and ICH Good Clinical Practice, including archiving of essential documents, (June 1996) and 21 CFR 312.120 (2010).

Patients disposition

A total of 62 patients were randomized and exposed to trial products (3:1): 46 patients in the weekly somapacitan arm and 16 patients in the Norditropin arm. In total, 60 patients completed the trial period and 59 patients completed the treatment period , with only 1 patient (in Norditropin arm) prematurely discontinuing the treatment due to AE of DM at visit 13; however, this patient completed the trial.

Demographic Characteristics

Of the total 62 ADHD patients, 33 (53.2%) were male and 29 (46.8%) were female; of which 48 patients were 18-64 years old and 14 patients were ≥ 65 ' years of age at baseline. At baseline, the mean (SD) body weight was 69.0 kg and mean (SD) BMI was 26.0 kg/m². The majority of patients (51 patients; 82.3%) had GHD onset in their adulthood, 11 patients had suffered from GHD since childhood (organic: 6 (9.7%) patients; idiopathic 5 (8.1%) patients). At baseline, the most common medical history and concomitant illness included hypopituitarism, diabetes insipidus, dyslipidemia, obesity, hyperlipidemia, osteoporosis, hypertension etc. The mean (SD) IGF-1 SDS at baseline was 0.64 (0.72) on somapacitan group and 0.88 (0.82) in Norditropin group. Overall, two treatment arms (somapacitan and Norditropin) were well balanced at baseline. For further details see CSR 4244, Table 10-2, page72.

Dosing:

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The mean (SD) prescribed doses during 52 weeks (20 weeks dose titration, 32 weeks fixed dose treatment) was 1.78 (1.058) mg/week for the somapacitan arm and 0.197 (0.083) mg/day for the Norditropin arm.

Adherence:

The mean adherence according to the patients' diary was 98.7% in somapacitan group and 92.2 % in Norditropin group.

Efficacy endpoints:

Primary endpoints: there were no primary efficacy endpoints; the primary endpoint was related to safety.

Secondary efficacy endpoints:

The cross-sectional adipose tissue compartments (TAT, SAT and VAT) were measured by CT scan. There was no statistically significant difference between treatment arms in estimated change from baseline to week 52 for any of the abdominal adipose tissue endpoints. The estimated treatment differences between somapacitan and Norditropin for change from baseline to week 52 in TAT, SAT and VAT (cm²) were -12.85, -11.53, and -1.74; respectively (Table 27).

Table 27: Changes from baseline to end of 52 week period in abdominal adipose tissue compartments (trial 4244)

	Estimate	95% CI	p-value
TAT (cm²)			
Change from baseline at week 52			
Norditropin	6.17		
Somapacitan	-6.67		
Treatment difference at week 52			
Somapacitan - Norditropin	-12.85	[-47.31 ; 21.62]	0.4578
SAT (cm²)			
Change from baseline at week 52			
Norditropin	6.57		
Somapacitan	-4.96		
Treatment difference at week 52			
Somapacitan - Norditropin	-11.53	[-35.54 ; 12.48]	0.339
VAT (cm²)			
Change from baseline at week 52			
Norditropin	-0.51		
Somapacitan	-2.25		
Treatment difference at week 52			
Somapacitan - Norditropin	-1.74	[-18.13 ; 14.66]	0.8324

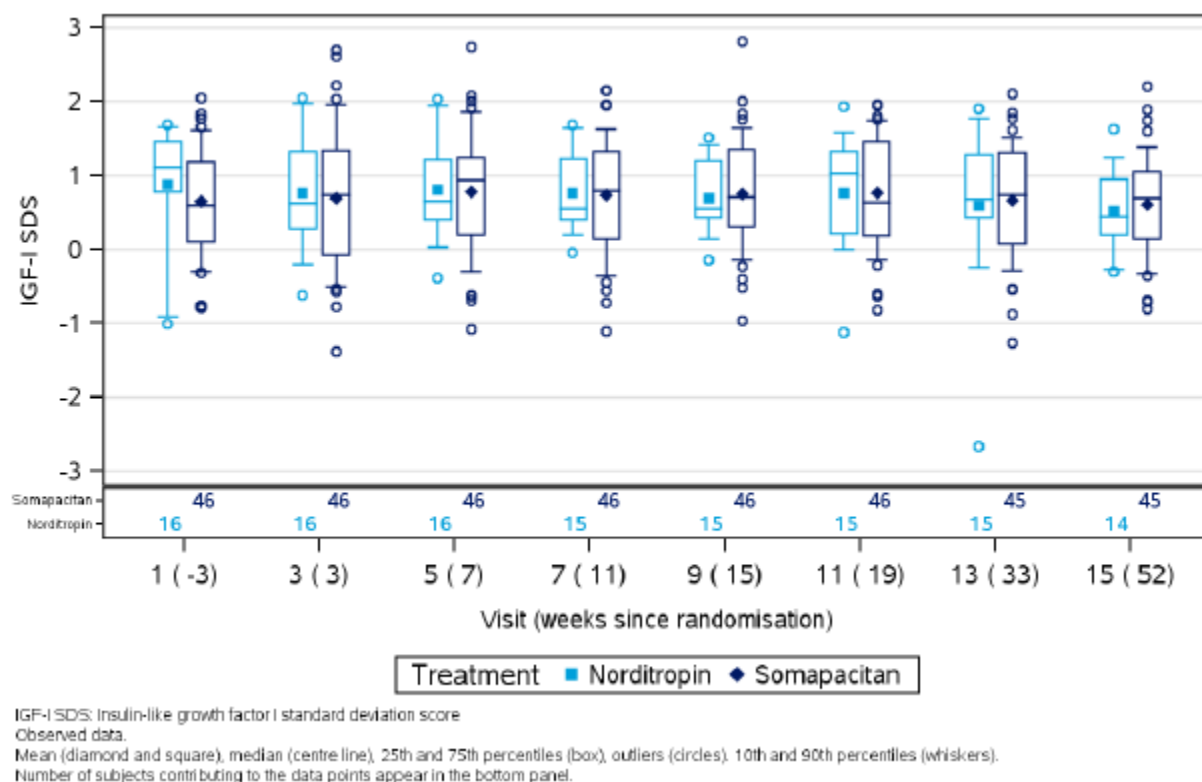
SAT: Subcutaneous adipose tissue compartments, TAT: Cross-sectional total adipose tissue compartments, VAT: Intra-abdominal or visceral adipose tissue compartments

Source: adapted from Table 11-1, CSR 4244, p. 80

Medical officer's comments: Based on the observed values, the pre-trial TAT, SAT and VAT compartments values were maintained in both the somapacitan and Norditropin arms from baseline to week 52 and there was no statistically significant difference between treatment arms for any of the abdominal adipose tissue endpoints, as expected.

The mean IGF-1 SDS at baseline was maintained in both the treatment arms in previously hGH treated patients (Figure 10).

Figure 10: IGF-1 SDS by visit (trial 4244)



Source: Figure 12-3, CSR 4244, p. 100

The treatment satisfaction questionnaire for medication (TSQM-9) score assessed the key dimensions of treatment satisfaction: effectiveness, convenience, and global satisfaction. TSQM-9 scores ranges from 0 to 100, with higher scores indicating higher satisfaction. The patients completed their TSQM-9 questionnaire at visit 2 (randomization), visit 13 (32 weeks) and at visit 15 (52 weeks, at end of treatment).

At week 52, the effectiveness, convenience, and global satisfaction scores indicated a favorable response for once-weekly treatment of somapacitan compared to daily Norditropin; however, there were no statistically significant differences in change from baseline to week 52 in any of the TSQM-9 instrument components scores between somapacitan and Norditropin arms (Table 28).

Table 28: Changes from baseline to end of 52 week period in TSQM-9 scores (trial 4244)

	Estimate	95% CI	p-value
Convenience			
Change from baseline at week 52			
Norditropin	7.22		
Somapacitan	14.01		
Treatment difference at week 52			
Somapacitan - Norditropin	6.79	[-1.04 ; 14.61]	0.0877
Effectiveness			
Change from baseline at week 52			
Norditropin	3.12		
Somapacitan	7.99		
Treatment difference at week 52			
Somapacitan - Norditropin	4.37	[-3.46 ; 13.20]	0.2462
Global satisfaction			
Change from baseline at week 52			
Norditropin	3.18		
Somapacitan	10.07		
Treatment difference at week 52			
Somapacitan - Norditropin	6.88	[-1.08 ; 14.85]	0.0890

Source: adapted from Table 11-2, CSR 4244, p. 85

Medical officer's comment: There was no statistically significant difference between somapacitan and Norditropin arms in change from baseline to week 52 in any of the TSQM-9 scores. However, these results should be interpreted with caution since TSQM-9 is not validated instrument to evaluate treatment satisfaction in the intended population.

6.3. A multicenter, multinational, randomized, open-labelled, parallel-group, active-controlled trial to compare the safety of once-weekly dosing of somapacitan (NNC0195-0092) with daily Norditropin® FlexPro® for 26 weeks in previously human growth hormone treated adults with growth hormone deficiency (trial 4043)

6.3.1. Study Design

Overview and Objective

Trial 4244 was designed to evaluate the safety (primary objective) and efficacy (secondary objective) of once weekly somapacitan compared to daily Norditropin therapy in previously hGH-treated AGHD subjects.

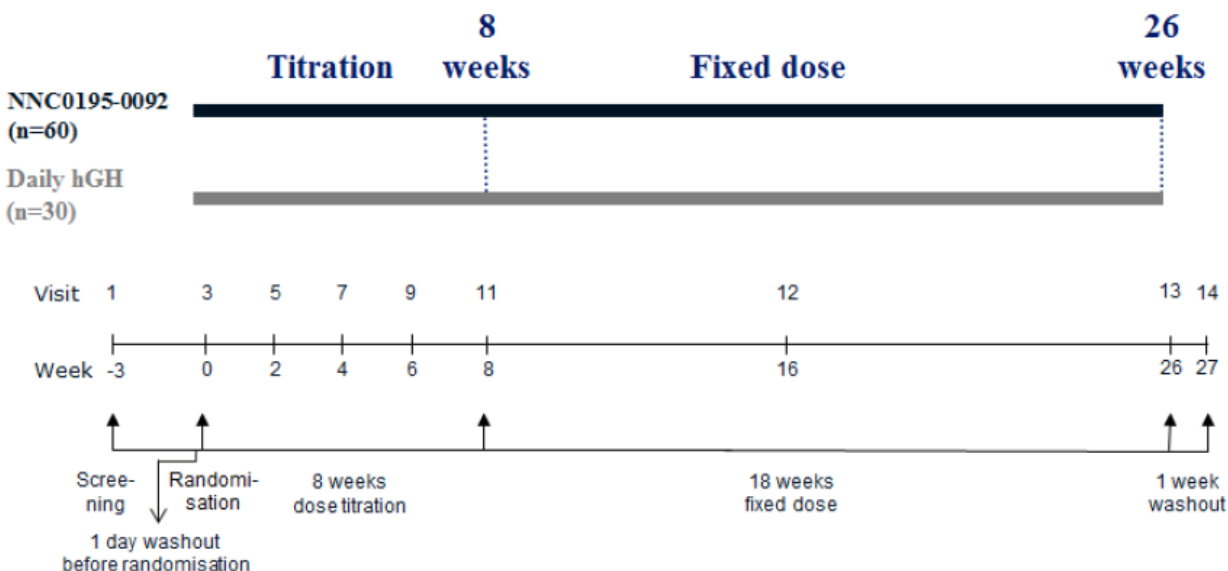
As per Applicant, the efficacy was evaluated by measuring the degree of treatment satisfaction of once weekly dosing of somapacitan compared to daily Norditropin.

Trial Design

This was a multicenter, multinational, randomized, open-labelled, parallel-group, active-controlled trial to compare the safety of once-weekly dosing of somapacitan with daily Norditropin in previously hGH-treated AGHD subjects for 26 weeks followed by 1 week washout. The trial was open-labelled in order to be able to compare treatment satisfaction related to daily vs weekly injections (Figure 11).

AGHD patients were randomized in a 2:1 (somapacitan: Norditropin) ratio to receive somapacitan or Norditropin for 26 weeks (8 weeks of dose-titration followed by 18 weeks of fixed-dose treatment). The randomization was stratified according to 2 region levels (Japan and all other countries), sex and diabetic status (diagnosed with DM vs. not diagnosed with DM). During the first 8 weeks, the dose was titrated every 2 weeks starting from week 2. The last dose adjustment was done at week 8. This allowed for 4 opportunities for dose adjustment (weeks 2, 4, 6, and 8). Dose titration was based on insulin-like growth factor-I standard deviation score (IGF-1 SDS). The starting dose and titration algorithms for somapacitan and Norditropin were similar to trial 4244 (see Table 26 in Section 6.2.1 above). After the last dose adjustment (if any) at week 8, the individual dose level was fixed. The investigator could reduce the dose (in consecutive steps of 25% of the current dose) of somapacitan or Norditropin if AEs occurred.

Figure 11: Trial 4043 design



Source: Figure 9-1, CSR 4043, p. 33

The key inclusion and exclusion criteria were similar to Trial 4244 (see Section 6.2.1, above). Patients with stable diabetes at baseline (defined as HbA1c < 7.0% and on stable oral antidiabetic treatment) were allowed to participate, except for subjects from Japan, for whom diabetes was part of the exclusion criteria (as in trial 4244).

Study Endpoints

The secondary efficacy endpoint was change from baseline (randomization) to end of treatment period (26 weeks) in TSQM scores (effectiveness, convenience, and global satisfaction scores). The primary and secondary supportive safety endpoints were similar to the safety endpoints in trials 4054 and 4244.

Statistical Analysis Plan

The change in TSQM scores at 17 and 26 week's measurements was analyzed using same model as in trial 4244. All secondary safety endpoints were analyzed using descriptive statistics.

6.3.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013) and ICH Good Clinical Practice (GCP) (May 1996), ISO 14155 and FDA 21 CFR 312.120.

Patient Disposition

A total of 92 AGHD patients were randomized and exposed, whereof 86 patients completed the trial (85 patients completed the treatment as 1 subject discontinued treatment due to travel abroad but completed the trial). Six patients were withdrawn, equally split on 3 withdrawn patients in each group. Two patients were withdrawn due to AEs (please see safety results section below) and 4 patients withdrew due to personal reasons.

Demographic Characteristics

A total of 92 AGHD patients were exposed (50 male/42 female). A total of 34 (37%) patients had suffered from GHD since childhood (organic: 25 (27.2%) patients; idiopathic: 9 (9.8%) patients), while 58 (63.0%) patients were first diagnosed as adults. Their pre-trial hGH dose was 0.5 mg/day. The patients were included from Denmark, Sweden, Germany, France, United Kingdom and Japan. A total of 54 AGHD patients were white and 18 patients were Asian (hereof 17 Japanese patients). Race and ethnicity were not reported for 20 patients in France due to local regulations. Mean age: 49.3 years (min: 19 years; max: 77 years); mean weight: 81.7 kg (min: 46.8; max: 151.2 kg); mean BMI 28.6 kg/m² (min: 19.3 kg/m²; max: 42.4 kg/m²).

Demographic and disease characteristics were well-balanced between treatment groups at baseline. Mean fasting glucose and insulin were within normal ranges. One patient (Norditropin group) was reported as diabetic at baseline. The medical history and concomitant illnesses reflected the trial population of AGHD patients.

Dosing

The mean (SD) prescribed doses during 26 weeks (8 weeks dose titration, 18 weeks fixed dose treatment) was 1.96 (1.45) mg/week for the somapacitan arm and 0.2 (0.14) mg/day for the Norditropin arm. The doses of somapacitan were similar to the ones used in the other two trials discussed above.

Adherence

The mean adherence according to the patients' diary was 93.1 % in somapacitan group and 90.4% in Norditropin group.

Efficacy Results

There were no primary efficacy endpoints; the primary endpoint was related to safety.

Secondary efficacy endpoints

The secondary efficacy endpoint was change from baseline to end of treatment period (26 weeks) in TSQM scores (effectiveness, convenience, and global satisfaction scores). After 26 weeks treatment, once-weekly somapacitan was considered more convenient than daily Norditropin in AGHD patients previously treated with daily hGH. The difference between treatments in TSQM convenience scores was statistically significant. Scores for TSQM effectiveness and treatment satisfaction were similar after 26 weeks treatment (Table 29).

Table 29: Change from baseline to end of 26 week treatment period in TSQM-9 scores (trial 4043)

	FAS	N	Estimate [95% CI]	p-value
Somapacitan vs Norditropin				
Change from baseline in effectiveness score	92	84	3.30 [-4.14 ; 10.75]	0.3793
Change from baseline in convenience score	92	86	8.22 [1.51 ; 14.93]	0.0171
Change from baseline in global satisfaction score	92	85	3.07 [-4.70 ; 10.83]	0.4342

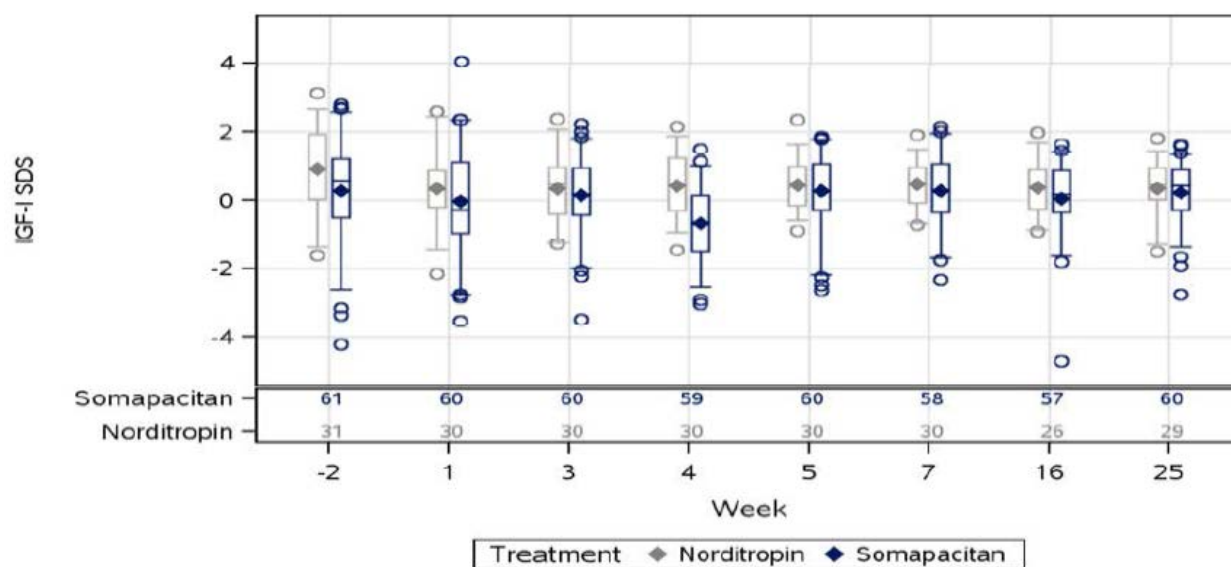
FAS: Full analysis set, N: Number of subjects, CI: Confidence interval.

Change in TSQM scores at 17 and 26 week's analysed using a MMRM 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.

Source: Table 11-2, CSR 4043, p. 98

The mean IGF-1 SDS profile was similar in both treatment groups, both at baseline and at end-of-treatment (somapacitan 0.28 and 0.22; Norditropin 0.91 and 0.35, respectively), and it was maintained throughout the trial period. At baseline and during the titration period, the number of patients with IGF-1 SDS below -2 was higher in the somapacitan group than in the Norditropin group, indicating that some patients may not have been IGF-1 dose titrated in the hGH treatment at trial initiation. Three patients in somapacitan group had IGF-1 SDS < -2.0 (IGF-1 SDS from -3.2 to -4.2). The initially rather wide range in IGF-1 values/scores tended to decrease, and may reflect the effect of the titration (Figure 12).

Figure 12: Mean IGF-1 SDS by visit, trial 4043



IGF-1: insulin-like growth factor -1. Observed data. Legend: Mean (diamond), median (centre line), 25th and 75th percentiles (box), outliers (circles), 5th and 95th percentiles (whiskers). Number of subjects contributing to the data points appear in the bottom panel.

Note: week 4 is trough value/measured before trial drug administration

Source: Figure 11-4, CSR 4043, p. 95

Medical officer's comments: Once-weekly dosing of somapacitan was more convenient than daily dosing of Norditropin in AGHD patients previously treated with daily hGH, but similar with respect to effectiveness (as assessed by IGF-1 SDS) and global satisfaction scores. However, these results should be interpreted with caution since TSQM-9 is not validated instrument to evaluate treatment satisfaction in the intended population.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Pivotal trial 4054 was the only trial which was designed to evaluate efficacy as a primary endpoint, namely reduction in TFP after 34 weeks of treatment with somapacitan, compared to placebo and Norditropin therapy in treatment-naïve adult patients with GHD. The estimated mean treatment difference in TFP reduction between somapacitan and placebo was -1.53% [95% CI: -2.68; -0.38, $p = 0.009$], demonstrating superiority of somapacitan vs. placebo, whereas the estimated treatment difference in TFP between somapacitan and Norditropin was 1.17% [95% CI: 0.23; 2.11]. Please refer to Section 6.1.2 for details.

7.1.2. Secondary and Other Endpoints

Trial 4054 was the pivotal trial assessing secondary and other efficacy endpoints, such as changes in various body composition parameters, changes in body weight and waist circumference, changes in lipid profile, and cardiovascular endpoints (i.e. IL-6 and hsCRP) in treatment-naïve adult patients with GHD (refer to Section 6.1.2 for details).

The overall changes in other body composition parameters observed in trial 4054 were supportive of primary endpoints and were consistent with changes in these parameters observed during the treatment with other rhGH formulations (i.e. truncal lean body mass, total lean body mass). Trial 4244 in Japanese adult patients with GHD previously exposed to hGH therapy demonstrated that pre-trial total adipose tissue compartments (TAT), subcutaneous adipose tissue compartments (SAT), and intra-abdominal or visceral adipose tissue compartments (VAT) values were maintained after 52 week therapy with somapacitan, and the effects were similar between the 2 treatment groups (somapacitan and Norditropin) (refer to Section 6.2.2 for details).

Lastly, although patients' well-being, and treatment satisfaction were evaluated by using multiple PRO tools in all trials, none of these PROs were validated by the Agency to date. Thus, no conclusion on the improvement in patients well-being and overall satisfaction with long-acting rhGH formulation can be made at this time.

Subgroups

The Applicant evaluated the efficacy of somapacitan on the primary endpoint (change in TFP) in the following subgroups: age, sex, and GHD onset. These analyses were prespecified analyses.

Additional request for post-hoc subgroup analysis by region was requested to be performed by the statistical reviewer (Information Request from 04/16/2020) due to the observed differences in primary efficacy endpoint results for the North American subgroup, compared to rest of the regions. In addition, the Applicant performed a post hoc analysis to assess whether the differential effect observed for some of the adipose tissue parameters (refer to the discussion of primary endpoint in section 6.1.2) could be driven by differences in the efficacy of somapacitan and Norditropin in female patients on oral estrogen, given the known antagonistic effect of oral estrogen on GH action.

Age

Subgroup analyses were performed for age groups ≤ 64 years of age, and ≥ 65 years of age. A similar reduction in TFP was observed with somapacitan compared to placebo in both age groups [ETD: ≤ 64 years of age: -1.71% (95% CI -2.99; -0.43); ≥ 65 years of age: -1.52% (95% CI -4.31; 1.28)].

Sex

A greater reduction in the estimated change from baseline in truncal fat % was observed for male patients than for female patients after 34 weeks of treatment with somapacitan, although a treatment difference versus placebo was observed in both sexes [ETD: males: -2.49 (95%CI -4.19; -0.79); females: -0.92 (95%CI -2.5; 0.66)]. The lower treatment effect of somapacitan in females vs males is most likely due to increased estrogen levels in female (please see further post-hoc analysis discussion in the subgroup of females on oral estrogen below).

GHD onset

The estimated change from baseline in TFP did was not affected by GHD onset (CO AGHD or AO AGHD) after 34 weeks of treatment with somapacitan. A reduction in TFP was observed with somapacitan compared to placebo for both CO AGHD [ETD: -1.97 (95% CI -4.3; 0.36)] and AO AGHD [ETD: -1.41 (95% CI -2.72; -0.1)].

Regions

The statistical reviewer noted different changes in TFP in active treatment groups and placebo groups when the data was analyzed by regions (North America vs. Asia vs Europe). To evaluate the difference further, Dr. Cambon submitted an Information Request on 04/16/2020 asking the Applicant to evaluate treatment effects by the following regions: Asia (including Australia), Europe (including Russia and Turkey) and North America (N-A). The analysis was performed using FDA pre-specified analysis method for the primary endpoint (see Section 6.1.2, subsection Efficacy Results – Primary Endpoint, for details).

Treatment effects were consistent across Asia and Europe (Table 30) and in line with the overall results of the entire trial population of trial 4054. For both Asia and Europe, reductions in TFP from baseline to week 34 was observed with somapacitan and Norditropin, compared to an

increase with placebo. In addition, the estimated treatment difference for somapacitan vs placebo (at week 34) was statistically significant for both regions.

For N-A, a smaller reduction in TFP from baseline to week 34 was observed with somapacitan and Norditropin, compared to the other regions, and an unexpected reduction in TFP was seen with placebo. The estimated treatment difference for somapacitan vs placebo from baseline to week 34 was numerically in favor of placebo [ETD: 0.59% 995% CI -1.47; 2.66]. The estimated treatment difference for Norditropin vs. placebo (at week 34) was less pronounced for the US population compared to Asia and Europe [ETD: -0.31% 995% CI -2.39; 1.76].

Different changes in TFP with placebo were seen across regions; in Europe and Asian placebo treatment was associated with an increase in TFP during the 34 weeks of treatment, as expected in patients with AGHD not receiving replacement therapy, whereas a reduction in TFP was observed in the placebo group comprising N-A patients only.

Potential explanations for the differences observed include small subset of patients in the N-A subgroup (14 placebo-treated N-A patients), and, according to Applicant report, there were 3 patients with a reduction in TFP of > 5%, who largely influenced the overall reduction in TFP in N-A placebo subgroup. These patients were all from the same investigational site:

- Patient (b) (6) a 38-year old, non-diabetic, obese (BMI 44.3) female, had a decrease in TFP of 5.4%. Due to an initial increase in body weight the patient was prescribed liraglutide, a GLP-1 analogue known to reduce body weight and change body composition (in violation of withdrawal criterion #3: *Use of weight loss medications known to affect body weight substantially. Withdrawal based on this criterion is at the investigator's discretion*). Decreases in body weight and TFP was observed after initiation of liraglutide treatment. Of note, use of liraglutide in violation of withdrawal criteria # 3 was not reported as a PD by the Applicant.
- Patient (b) (6) a 66-year-old male, had a decrease in TFP of 7.7%. The patient experienced a large decrease in body weight (from 88 to 78 kg) during a 16-week period in the last part of the main phase, with subsequent decrease in TFP. Furthermore, an increase in liver function tests was observed, with an up to threefold increase in liver enzymes, at the end of the main period. The patient was withdrawn before the end of the main phase according to protocol excl. criterion #10 (*clinically significant hepatic disease defined as ALT levels greater than 3 times the ULN*) and was subsequently diagnosed with an amiodarone induced lung fibrosis. Note that in the FDA-requested analysis, imputed values were included for this patient based on data from placebo-treated patients.
- Patient (b) (6) a 63-year old, non-diabetic obese (BMI 31.4) female, had a decrease in TFP of 5.5%. Due to loss of energy during the main phase of the trial, this

patient was prescribed multivitamins and other combinations of nutritional supplements. It is not known whether these “other combinations” could impact energy expenditure and subsequently body composition.

Post-hoc exploratory summary of mean changes excluding these 3 placebo-treated patients from the analysis set provided changes in truncal fat percentage during 34 weeks of treatment in the N-A placebo-treated patients (Table 31) comparable to mean changes in the non-North American (regions Asia, Europe and Africa) placebo-treated patients and the estimated mean changes obtained in placebo-treated patients from regions Asia and Europe (Table 30).

The Applicant stated that no other differences in the baseline characteristics, or in standard-of-care across regions were noted, to explain the regional differences observed for the primary endpoint analysis.

Table 30: Changes from baseline to week 34 in TFP by region (trial 4054) – FDA requested analysis

	FAS	N	Estimate	95% CI	p-value
Truncal fat percentage (%)					
Asia					
Change from baseline at week 34					
Placebo	23	23	0.29		.
Norditropin	42	41	-2.44		.
Somapacitan	46	46	-1.70		.
Treatment difference at week 34					
Somapacitan - Placebo	.	.	-1.99	[-3.65 ; -0.13]	0.0361
Somapacitan - Norditropin	.	.	0.74	[-0.82 ; 2.29]	.
Norditropin - Placebo	.	.	-2.73	[-4.63 ; -0.83]	.
Europe					
Change from baseline at week 34					
Placebo	23	21	1.62		.
Norditropin	39	39	-3.53		.
Somapacitan	39	35	-1.07		.
Treatment difference at week 34					
Somapacitan - Placebo	.	.	-2.69	[-5.01 ; -0.38]	0.0226
Somapacitan - Norditropin	.	.	2.46	[0.42 ; 4.49]	.
Norditropin - Placebo	.	.	-5.15	[-7.41 ; -2.90]	.
North America					
Change from baseline at week 34					
Placebo	14	14	-0.75		.
Norditropin	34	33	-1.06		.
Somapacitan	31	30	-0.15		.
Treatment difference at week 34					
Somapacitan - Placebo	.	.	0.59	[-1.47 ; 2.66]	0.5749
Somapacitan - Norditropin	.	.	0.90	[-0.71 ; 2.52]	.
Norditropin - Placebo	.	.	-0.31	[-2.39 ; 1.76]	.

Notes: Analysis performed according to FDA specifications, see Section 1.1 for details. Europe includes the following countries: Germany, Great Britain, Latvia, Lithuania, Poland, Romania, Russia, Sweden, Turkey, and Ukraine.

Asia includes the following countries: India, Japan, Malaysia, and Australia. Changes in truncal fat percentage from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate. Note that the region factor only will attain one level in the subgroup analyses of Europe and North America, respectively.

Abbreviations: CI = confidence interval; FAS = full analysis set; N = number of patients.

Source: The Applicant's response to Agency's IR on 4/22/2020

Table 31: Summary of change from baseline in truncal fat percentage (%) at week 34 excluding patients Nos. (b) (6) (trial 4054) - region North America

	Placebo	Norditropin	Somapacitan
Number of Exposed Subjects	11	34	31
Visit 14 (Week 34)			
Number of subjects	11	30	30
Mean (SD)	0.28 (2.80)	-0.91 (2.30)	-0.58 (3.33)
Median	0.79	-0.75	-0.93
Min; Max	-4.89; 5.42	-5.68; 3.60	-8.63; 4.77

Source: The Applicant's response to Agency's IR on 4/22/2020

Females on oral estrogen vs rest of the population

It is well known that oral estrogen formulations decrease the effect of GH and patients on oral formulations of estrogen require treatment with higher GH doses. An uneven random distribution of females on oral estrogen was observed in trial 4054, with a higher percentage in the somapacitan group (31.7%, 38 of 120 patients) as compared to the Norditropin (19.3%, 23 of 119 patients) and placebo (16.4%, 10 of 61) groups. Thus, to evaluate one of the possible factors that may account for the less pronounced effect on body fat parameters observed for somapacitan compared to Norditropin, i.e. use of estrogen by enrolled population, the additional post-hoc subgroup analysis was conducted by the Applicant, which evaluated the effect of somapacitan, placebo and Norditropin on the change from baseline to week 34 in TFP separately for female patients on oral estrogen and for the entire trial population excluding female patients on oral estrogen (i.e., female patients not on oral estrogen and male patients) (Table 32). Though the somapacitan-induced reduction in TFP appeared less pronounced in female patients on oral estrogen (estimated change from baseline: -0.15%) compared with the trial population excluding this subgroup (estimated change from baseline: -1.41%), the treatment difference of somapacitan vs. placebo for female patients on oral estrogen [ETD: -1.44% (95%CI:-3.97; 1.09)] (Table 32) was consistent with the result of the primary analysis [ETD: -1.53% (95%CI:-2.68; -0.38)]. This was due to a significant increase from baseline in TFP for the female patients on oral estrogens in the placebo group, and supports the hypothesis that somapacitan has an overall beneficial effect in this subgroup of female patients as well. For female patients on oral estrogen, the reduction in TFP was more pronounced with Norditropin compared to somapacitan [ETD: 2.21% (95%CI: 0.29; 4.141)], indicating that Norditropin may be more efficacious than somapacitan in this subgroup. This is further supported by the results of the post hoc analysis excluding female patients on oral estrogen, which showed a less pronounced treatment difference between somapacitan and Norditropin for the change from baseline in TFP [ETD: 0.84% (95% CI: -0.28; 1.96)] (Table 32) compared to the treatment difference observed for the entire trial population [ETD: 1.17% (95% CI: 0.23; 2.11)].

According to the Applicant, these results suggest that the less pronounced effect observed for some of the adipose tissue parameters for somapacitan vs Norditropin in the entire trial population to some extent may be driven by a more pronounced effect of Norditropin relative to somapacitan in the subgroup of female patients on oral estrogen.

Table 32: Change from baseline in TFP in females on oral estrogens vs. rest of population after 34 weeks of treatment (FAS)

Endpoint	FAS	N	Estimate	[95% CI]	p-value
Truncal fat percentage (%)					
Women having oral oestrogen replacement					
Change from baseline at week 34					
Placebo	10	10	1.29		
Norditropin	23	23	-2.37		
Somapacitan	38	38	-0.15		
Treatment difference at week 34					
Somapacitan - Placebo			-1.44	[-3.97 ; 1.09]	0.2645
Somapacitan - Norditropin			2.21	[0.29 ; 4.14]	
Population with no oral oestrogen replacement					
Change from baseline at week 34					
Placebo	51	51	0.27		
Norditropin	96	96	-2.25		
Somapacitan	82	82	-1.41		
Treatment difference at week 34					
Somapacitan - Placebo			-1.67	[-3.02 ; -0.33]	0.0149
Somapacitan - Norditropin			0.84	[-0.28 ; 1.96]	

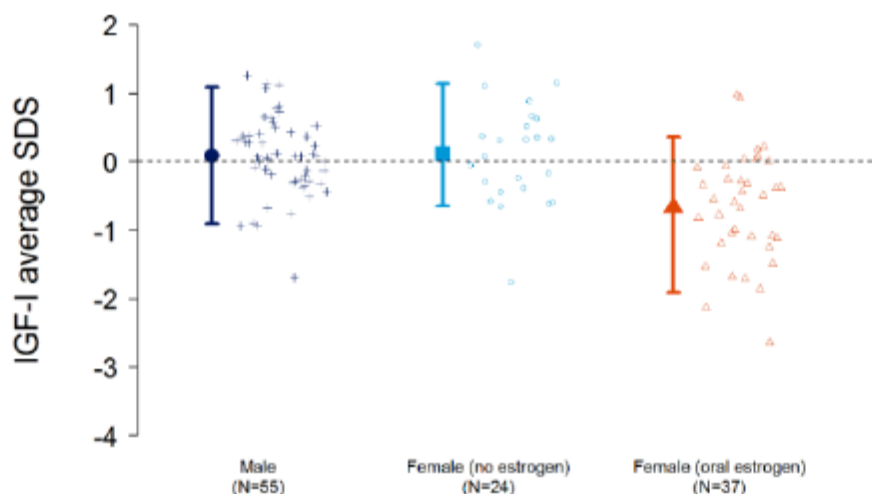
N: Number of subjects, CI: Confidence interval, FAS: Full analysis set
Changes in truncal fat percentage from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate.
DM: Diabetes mellitus.

Source: Applicant's Appendix 6.1 Table 4, SCE

The Applicant submitted further analysis to explain the observed differences in a response to Agency's IR from 4/16/2020, which revealed that weekly IGF-1 SDS levels post-titration period in females on oral estrogen were in general lower than in the other gender subgroups, and the difference appeared to be most pronounced for somapacitan-treated females on oral estrogen (Figure 13). According to the Applicant, 42% (16 out of 38) of females on oral estrogen in somapacitan group did not reach the pre-defined IGF-1 SDS target post-titration of -0.5 IGF-1 SDS, compared to 17% (4 out of 24) of females not on oral estrogen. In addition, a lower mean IGF-1 SDS at baseline was observed in females on oral estrogen [-2.93 (somapacitan), -3.23 (Norditropin), -3.12 (placebo)] compared to females not on oral estrogen [-1.85 (somapacitan), -1.96 (Norditropin), -2.20 (placebo)], which likely further contributed to the higher percentage of failure to reach the IGF1-SDS titration target in the former group of females.

Thus, the relatively high number of somapacitan-treated females on oral estrogen not reaching IGF-1 SDS target in the main phase of the pivotal 4054 trial, paired with the significantly higher percentage of female patients on oral estrogen in somapacitan group compared to Norditropin and placebo may explain the less pronounced effect on body fat parameters observed for somapacitan compared to Norditropin.

Figure 13: Model derived weekly IGF-1 (IGF-1avg) SDS with somapacitan by gender and females on oral estrogen (trial 4054 main)



Notes: Data are individual IGF-I average SDS estimates at the fixed dose levels after titration for patients completing titration. Small symbols are individual values, large symbols with error bars are means with 5th to 95th percentiles.

Source: The Applicant's response to Agency's IR on 4/22/2020

Also, the Applicant submitted an analysis of the somapacitan doses used during the main phase of trial 4054 by all females on oral estrogen, and further stratified by reaching vs. not reaching lower IGF-1 SDS target status, in response to Agency's IR from 04/30/2020 (Table 33).

Table 33: Summary of somapacitan dose (mg) by IGF-1 SDS for females on oral estrogens (trial 4054 main)

	IGF-I SDS≤-0.5	IGF-I SDS>-0.5	Missing IGF-I SDS	total
Overall dose of main phase* (mg)				
Mean (SD)	4.36 (1.06)	2.82 (1.16)	2.00 (.)	3.45 (1.35)
Median	4.12	2.76	2.00	3.31
Min ; Max	2.88 ; 6.85	1.30 ; 5.56	2.00 ; 2.00	1.30 ; 6.85
Fixed dose after titration** (mg)				
Mean (SD)	4.84 (1.31)	2.99 (1.34)	. (.)	3.79 (1.61)
Median	4.50	3.00	.	3.90
Min ; Max	3.00 ; 8.00	1.30 ; 6.00	. ; .	1.30 ; 8.00
End of main phase dose*** (mg)				
Mean (SD)	4.85 (1.31)	2.99 (1.34)	. (.)	3.79 (1.61)
Median	4.50	3.00	.	3.90
Min ; Max	3.00 ; 8.00	1.30 ; 6.00	. ; .	1.30 ; 8.00

Abbreviations: SD: standard deviation

Notes: Stratification of subjects is based on first measurement of IGF-I in main trial maintenance period taken at visit 11

*Overall average calculated for each subject based on diary reported doses

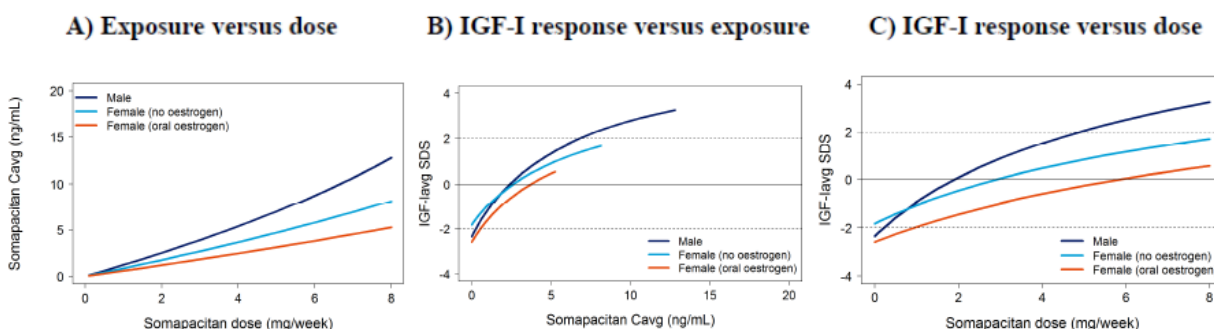
**Prescribed dose at visit 10

***Last diary reported dose after visit 10

Source: The Applicant's response to Agency's IR on 05/06/2020

The analysis showed that the mean (SD) and median doses of somapacitan after titration, and at the end of the main phase were the same in females on oral estrogen, namely 3.79 (1.61) mg, and 3.90 mg, ranging from 1.30 to 8.00 mg. The mean and median doses of somapacitan after titration and at the end of the main phase were higher among females on oral estrogen not reaching the titration target (4.84 mg and 4.5 mg) than in females on oral estrogen reaching the titration target (2.99 mg and 3.00 mg), respectively. These findings are in line with the dose-titration to IGF-1 response approach, in which patients titrated to the higher doses are expected to have the lowest IGF-1 SDS levels after titration. These findings are also in line with the known GH dose-exposure relationship in females on oral estrogen, who generally require higher doses of GH to achieve similar exposure compared to females not on oral estrogen. Population-based modelling analysis performed by the Applicant evaluated the impact of sex and oral estrogen on the dose-exposure, exposure-response, and dose-response (Figure 14), and demonstrated a lower somapacitan exposure in females, and particularly, females on oral estrogen, than in males across the entire dose range, the baseline IGF-I SDS and IGF-I response versus somapacitan exposure were marginally different for males and females including females on oral estrogen, and the IGF-I response was lower in females compared to males and lowest in females on oral estrogen for similar doses of somapacitan (see Clin Pharm review for details). Most importantly, the modelling analysis showed that target IGF-1 SDS levels can be achieved in the female patients on oral estrogen using within proposed dose ranges of somapacitan (Figure 14 C).

Figure 14. Exposure versus dose (A), IGF-1 response versus exposure (B) and IGF-1 response versus dose (C) for males and females with and without oral estrogen (phase 3 trials)



Notes: Lines are estimated typical patient relationships using modelling data (population PK and PK/PD models). All profiles are for a reference patient (male, white, 85 kg, age 40 years) except for the investigated covariate.
Source: Figure 3-17, Clinical Summary 2.7.2.

Medical officer's comments: The evaluation of the TFP changes in the pre-defined subgroup analyses confirmed the known better response to GH in males compared to females, with current results showing a greater reduction in the estimated change from baseline in TFP in male patients compared to female patients after 34 weeks of treatment with somapacitan [ETD: males: -2.49 (95%CI -4.19; -0.79); females: -0.92 (95%CI -2.5; 0.66)]. The lower treatment effect of somapacitan in females vs males was further evaluated in a post-hoc analysis which further stratified the results based on oral estrogen status use in females, and demonstrated a further lower effect of somapacitan on TFP in females on oral estrogen, which was caused by a suboptimal titration of somapacitan in the females on oral estrogen, and a higher percentage of females using oral estrogen in somapacitan group compared to the other 2 treatment arms. Modelling analysis performed by the Applicant demonstrated that target IGF-1 SDS levels can be achieved in the female patients on oral estrogen using within approved dose ranges of somapacitan. Therefore, the observed effect of oral estrogen on the dose-response relationship of somapacitan may be mitigated in clinical practice by adequate individual dose titration based on clinical and biochemical response.

Also, the subgroup analysis by region depicted an opposite effect of somapacitan on TFP in N-A subgroup compared to the other regions. Explanations for the findings could be a small subset of patients in the N-A subgroup (14 placebo-treated N-A patients), and, according to Applicant's report, there were 3 patients with a reduction in TFP of > 5%, with one of them being inadvertently on a weight loss medication (liraglutide), who largely influenced the overall reduction in TFP in N-A placebo subgroup.

7.1.3. Dose and Dose-Response

For a detailed evaluation of the Dose and dose-response relation evaluation please refer to Clinical Pharmacology review.

Dose

The clinical practice guidelines⁵ for GH therapy state that GH therapy dosing should be individualized, start with low doses and titrate according to clinical response, side effects, and IGF-1 levels, while taking into consideration age, gender, and estrogen status. The starting doses and dose increments used during the phase 3 trials were in accordance with clinical practice guidelines and also based on the multiple dose finding trial (3947) in AGHD patients. The trial showed that at steady state, the IGF-I profiles for the somapacitan doses of 0.02 and 0.04 mg/kg/week matched the IGF-I level of the average Norditropin treatment-dose of 0.004 mg/kg/day, indicating that the weekly dose of somapacitan should be approximately 5 to 10-fold higher than the daily Norditropin dose. Therefore, the selected starting doses and dose increments for somapacitan in the phase 3 trials were based on this scaling of dose relative to the dose of Norditropin.

During the phase 3 trials (trial 4054, 4244, and 4043), a fixed dose titration period was implemented for feasibility purposes, followed by a fixed dose treatment period. The dose was adjusted for each individual patient during the dose titration period, with the aim of achieving a pre-specified IGF-1 SDS target for somapacitan and Norditropin.

In the phase 3 trials, patients started on the following doses of somapacitan: 1.5 mg/week for patients ≤60 years of age, 1.0 mg/week for patients >60 years of age and 2.0 mg/week for female patients on oral estrogen followed by the titration period. In trial 4054 (treatment-naive patients), the majority of the patients either increased (59.6%) or did not adjust (30.7%) their somapacitan dose during the titration period, and these findings were consistent across the three starting dose groups. A similar pattern was observed in previously treated patients in trials 4244 and 4043, as well.

A maximum dose of somapacitan of 8 mg/kg was chosen for all phase 3 trials, based on results from trial 3947, which showed that doses up to a mean max dose of 9.6 mg/week of somapacitan were well tolerated.

After dose titration, the mean somapacitan dose in treatment-naive patients was 2.5 mg/week (trial 4054), and in previously GH treated patients was 1.8 mg/week and 2.0 mg/week, respectively (trials 4244 and 4043), while the doses of somapacitan ranged up to 8 mg/week. The mean fixed dose level of somapacitan after titration was 1.4 mg/week for patients older than 60 years, 2.1 mg/week for patients younger than 60 years and 3.8 mg/week for females on

oral estrogen, across all phase 3 trials, confirming the need for differential starting dosing regimen, based on age, gender and estrogen status.

Modelling analysis of the phase 3 trial data performed by the Applicant, using a starting dose of 1.5 mg/week for patients older than 60 years, 2.0 mg/week for patients younger than 60 years and 4.0 mg/week for female patients on oral estrogen could have provided a mean IGF-1 SDS closer to the upper normal range prior to titration, with only 5% of patients with IGF-1 SDS < -2SDS and < 5% of patients with IGF-1 SDS > 2 SDS.

Therefore, the Applicant is proposing that for patients switching treatment from daily GH to once-weekly somapacitan and who have been exposed to GH therapy previously and therefore are less likely to experience treatment related AEs, a starting dose closer to an ideal maintenance dose (b) (4)

(b) (4) may be reasonable in order to reduce the time period with doses that are below therapeutic range.

For GH-treatment naive patients, a lower starting dose, similar to the doses used during the clinical trial, is proposed by the Applicant and in line with the current clinical practice guidelines.

Medical officer's comments: The low mean doses of somapacitan used during the fixed dose period of the phase 3 trials (range 1.8 mg/week – 2.5 mg/week) relative to the maximum dose of somapacitan (8.0 mg/week) are likely due to a rather conservative dose titration scheme and IGF-1 SDS titration target of -0.5, as set by the Applicant. One could argue that in clinical practice the effect on body composition parameters may be greater once somapacitan is adequately titrated based on clinical response and IGF-1 levels, while maintaining the recommended dose ranges of somapacitan.

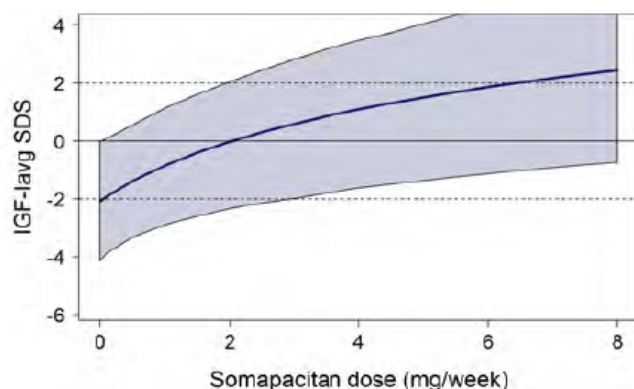
This MO proposes that somapacitan starting doses in AGHD patients to be representative of the doses used in the phase 3 clinical trials, namely 1.5 mg/week for patients ≤60 years of age, 1.0 mg/week for patients >60 years of age and 2.0 mg/week for female patients on oral estrogen, regardless of the previous use of GH therapy status. This MO does not agree with Applicant's proposal for patients switching treatment from daily GH to once-weekly somapacitan to start at a dose closer to an ideal maintenance dose ((b) (4)

(b) (4) as this dosing paradigm was not studied during the clinical trials, and therefore the safety profile of the proposed approach is not known.

Dose-response

The dose response relationship was evaluated against IGF-1 SDS biomarker during clinical pharmacology trial 3947 and the phase 3 trials, showing that IGF-1 increased with increasing somapacitan dose (Figure 15).

Figure 15: Estimated IGF-1_{avg} SDS versus somapacitan dose across the phase 3 trials



Abbreviations: IGF-I_{avg} SDS = insulin-like growth factor - I average standard deviation score.

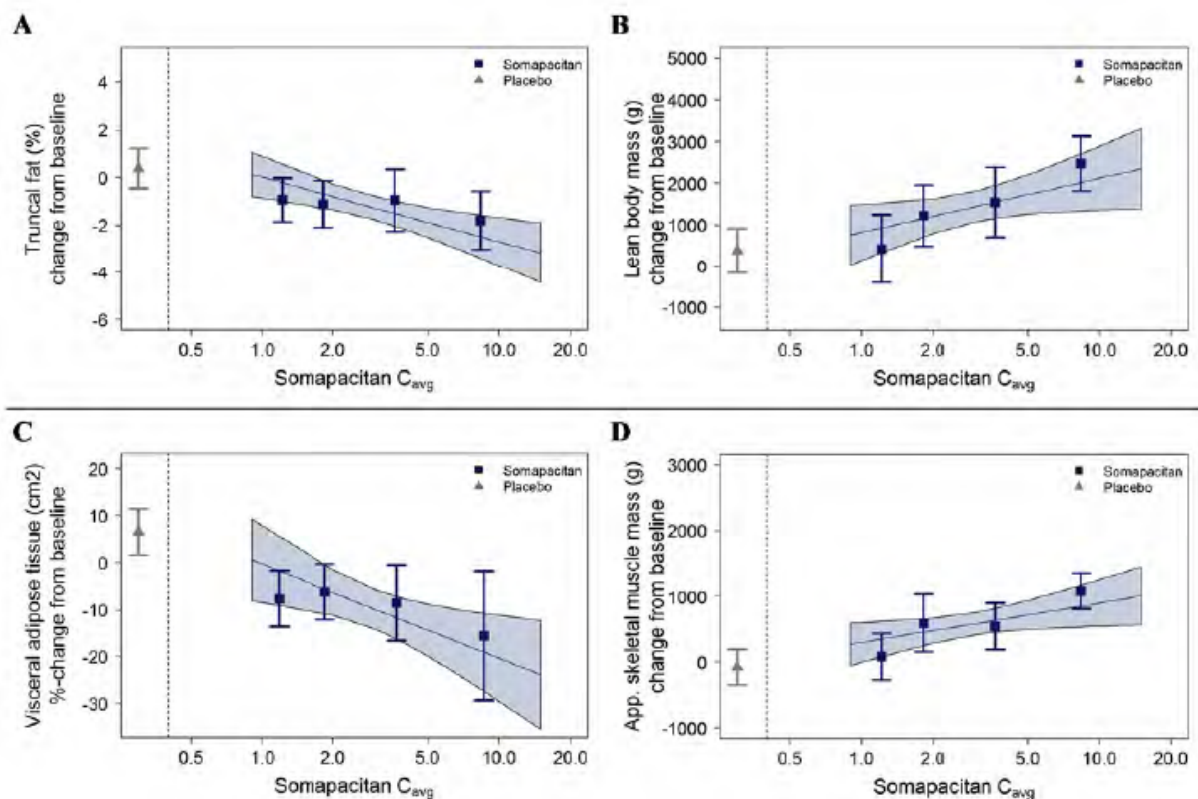
Notes: Data represent mean with 90% ranges of the individual dose-response relationships across the dose range 0.1–8 mg.

Source Figure 4-1, SCE, p. 69

The Applicant has not performed any formal analyses of dose-response with regards to body composition endpoints during pivotal trial 4054, as the dose required to achieve a similar IGF-I SDS target varies within different patient subgroups and between individual patients.

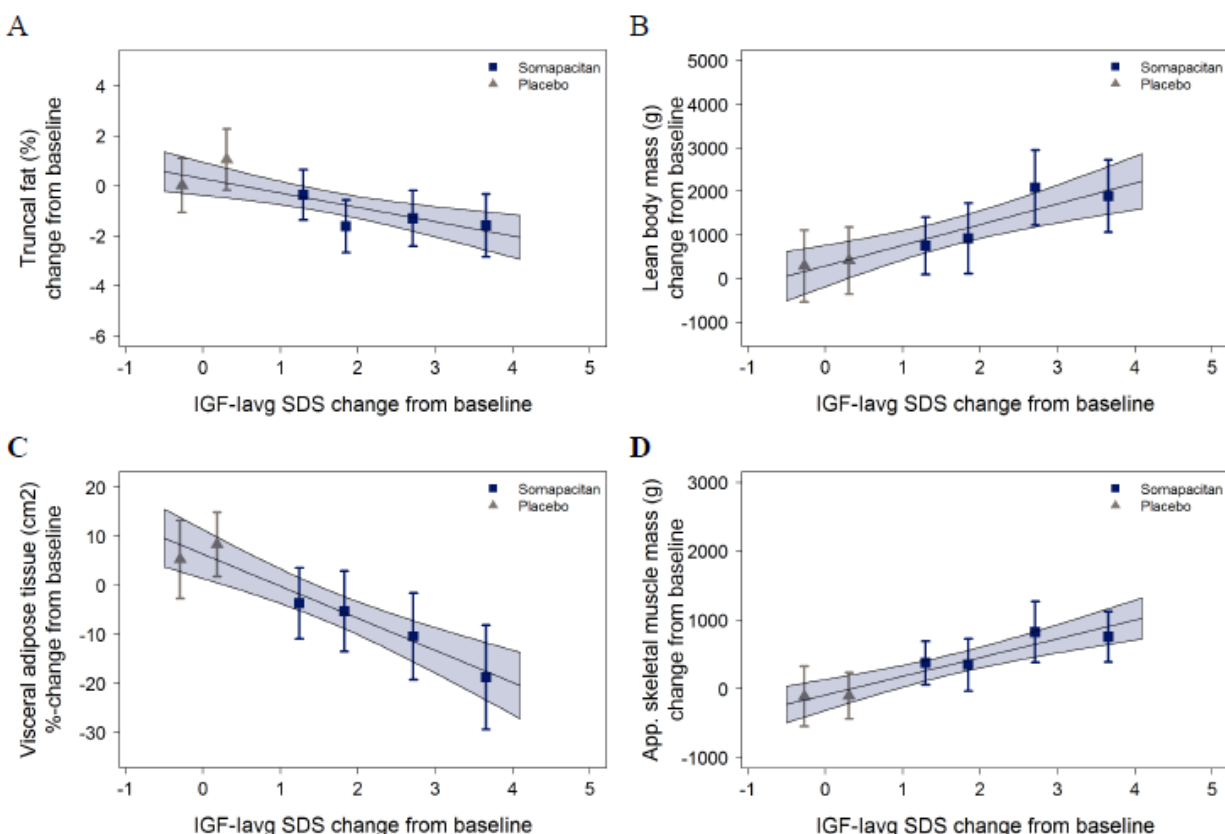
The Applicant performed population PK (C_{avg})/PD (IGF-1_{avg}) modelling on data from trial 4054, with exposure-response analysis showing that body composition endpoints improved with increasing somapacitan exposure (Figure 16) as well as with increased IGD-I SDS (Figure 17) following somapacitan treatment.

Figure 16: Change from baseline in body composition parameters versus somapacitan exposure (C_{avg})



(A) Truncal fat %, (B) total lean body mass, (C) visceral adipose tissue and (D) appendicular skeletal muscle (D) change from baseline. Symbols with error bars are mean observed response values with 95% CIs for each quantile of somapacitan C_{avg} . Lines with shaded areas are population predicted exposure-response relationships with 95% CIs. Data from trial 4054 main period.
 Source: Figure 4-2, SCE, p. 70

Figure 17: Change from baseline in body composition parameters versus IGF-1_{avg} change from baseline



Symbols with error bars are mean observed response values with 95% CIs for each quantile of IGF-1_{avg} change from baseline. Lines with shaded areas are population predicted exposure-response relationships with 95% CIs. Data from trial 4054 main phase with placebo data included in the model.

Source: Figure 5-18, Modelling report (M 5.3.3.5), p. 60

Dosing in special populations

Results from the clinical pharmacology trials and population PK analysis of data from Phase 3 studies indicate that dose adjustment of somapacitan is not required for patients based on intrinsic factors of sex, body weight, race, ethnicity or renal function. Since the somapacitan exposure and IGF-1 SDS response were lower in female patients receiving oral estrogen, a higher starting dose is recommended. On the other hand, a lower starting dose is recommended in patients >60 yrs. of age due to the observed higher exposure. This dosing recommendations are consistent with clinical practice and Applicant studied these patients accordingly in the Phase 3 trials, in which 1.0 mg/week and 2.0 mg/week starting doses were used in patients >65 yrs. and in females on oral estrogen, respectively. Considering the higher somapacitan exposure in patients with moderate hepatic impairment, a lower starting dose (1.0

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mg/week) is recommended, while the maximum dose should not exceed 4.0 mg/week. No dose adjustment is needed for patients with mild hepatic impairment. Somapacitan was not studied in patients with severe hepatic impairment. For details of Clinical Pharmacology studies refer to Section 4.5.

Onset, Duration, and Durability of Efficacy Effects

Please refer to Section 6.1.2, Durability of the response.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

None

7.2.2. Other Relevant Benefits

(b) (4)

Integrated Assessment of Effectiveness

The substantial evidence of effectiveness of somapacitan in the intended population is obtained from the single well-controlled pivotal study 4054 conducted in a treatment-naïve population with AGHD. The trial also had an active-controlled treatment arm, which brings further information regarding the efficacy of somapacitan compared to current available therapy and to help assess the clinical meaningfulness of the primary endpoint. A statistical non-inferiority margin was not pre-specified or required for this analysis in the SAP protocol.

Supportive efficacy data comes from trial 4244 which was primarily a safety trial, but compared the efficacy of somapacitan to active therapy in patients previously exposed to hGH therapy as a secondary endpoint.

Trial 4054 met its primary endpoint, demonstrating that the estimated mean change in TFP in somapacitan group was superior to placebo after 6 months of therapy. The estimated mean treatment difference in TFP reduction between somapacitan and placebo was -1.53% [95% CI: -2.68; -0.38, $p = 0.009$]. The results were confirmed by the Agency's statistical reviewer, with an additional efficacy analysis specified by the Agency's statistical reviewer (which allowed for a slightly larger assessment window, excluded patients with missing assessment values at baseline, and used a missing at random multiple imputation approach for patients who discontinued treatment drug not due to AEs or lack of efficacy) showing similar results to the pre-specified analysis.

The comparison between somapacitan and active treatment drug (Norditropin) of the primary endpoint showed a greater effect of Norditropin compared to somapacitan on the TFP reduction, with an estimated treatment difference of 1.17% [95% CI: 0.23; 2.11]. An additional analysis performed by the Applicant at the FDA's request (using FDA- specified analysis method described above), comparing the TFP reduction between Norditropin and placebo, showed an estimated treatment difference of - 2.82% [95% CI -4.0; -1.63], which is higher than the difference observed between somapacitan and placebo (-2.82% vs. -1.58%).

The results of the secondary endpoints were supportive of primary analysis results. Favorable treatment differences between somapacitan and placebo were seen in truncal fat mass and total fat mass [-496 gm (95% CI: -1049; 57), and -266 gm (95% CI: -1197; 664), respectively]. However, similar to the results of primary analysis, when the changes from baseline in these fat mass parameters were compared between somapacitan and Norditropin, they were in favor of

the latter: -123 gm vs. -534 gm, respectively, for truncal fat mass, and -32 gm vs. -755 gm, respectively, for total body fat mass.

Lastly, the changes from baseline in VAT parameter between somapacitan and placebo were largely in favor of somapacitan [treatment difference -14 cm² (95% CI: -21; -7, p = 0.0001)], and similar between somapacitan and Norditropin [treatment difference -1cm² (95% CI: -7; 4)]. However, interpretation of the changes in VAT parameters should be made with caution, since DXA is not a reliable and commonly used instrument to assess the VAT changes, with CT and MRI being preferred and used in clinical studies having VAT as efficacy endpoint.

The changes from baseline in lean body mass parameters (truncal lean body mass, total lean body mass, and ASMM) were all favorable to somapacitan compared to placebo [treatment difference 454 (95% CI: 25; 880, p = 0.038), 1144 (95% CI: 459; 1829, p = 0.0011), and 679 (95% CI: 340; 1019, p = 0.0001), respectively]. Also, the changes from baseline in all lean body mass parameters in the somapacitan and Norditropin groups were similar (804 gm vs. 843 gm, 1394 gm vs. 1345 gm, and 558 gm vs. 462 gm, respectively), confirming the effect of somapacitan on lean body compartments in the current trial.

Lastly, the improvement in the body composition parameters positively correlated with normalization in IGF-1 SDS for both somapacitan and Norditropin groups.

The less pronounced effect of somapacitan compared to Norditropin observed for most of the adipose tissue parameters after 34 weeks of treatment deserves further discussion. This effect could not be explained by different response in IGF-1 SDS between the treatment groups, as the distribution of IGF-1 SDS levels after 34 weeks of treatment was similar between somapacitan and Norditropin. However, there was an observed uneven random distribution of females on oral estrogen in trial 4054, with a higher percentage in the somapacitan group (31.7%, 38 of 120 patients) as compared to the Norditropin (19.3%, 23 of 119 patients) and placebo (16.4%, 10 of 61) groups.

The further post-hoc analysis evaluating the effect of somapacitan compared to placebo and Norditropin on the TFP reduction in the subgroup of female patients on oral estrogens demonstrated that the reduction in TFP from baseline in somapacitan group compared to placebo was similar to the effect seen for the entire population [ETD: -1.44% (95%CI: -3.97; 1.09) vs. -1.53% (95%CI: -2.68; -0.38)]. However, the effect was more pronounced with Norditropin compared to somapacitan [ETD: 2.21% (95%CI: 0.29; 4.141)], indicating that Norditropin may potentially be more efficacious than somapacitan in this subgroup. The post-hoc analysis for the rest of the trial population excluding female patients on oral estrogen showed a less pronounced treatment difference between somapacitan and Norditropin for the change from baseline in TFP [ETD: 0.84% (95% CI: -0.28; 1.96)] compared to the treatment difference observed for the entire trial population [ETD: 1.17% (95% CI: 0.23; 2.11)], and for the subgroups of females on oral estrogen (see above).

Further analyses to evaluate the observed differences revealed a suboptimal titration of somapacitan in females on oral estrogen. According to the Applicant, 42% (16 out of 38) of females on oral estrogen in somapacitan group did not reach the pre-defined IGF-1 SDS post-

titration target of -0.5 IGF-1 SDS, compared to 17% (4 out of 24) of females not on oral estrogen.

Lastly, the estimated treatment difference in TFP for somapacitan vs placebo differed between males and females [ETD: -2.49% (male) vs -0.92% (female)] in trial 4054.

Clinical data shows that women with GHD have a lower response to GH replacement than GHD men in terms of increased serum IGF-1 concentration, loss of body fat mass and changes in lipid profile levels, to support the importance of the interactions between GH and sex steroids.³⁵ In addition, oral estrogen replacement therapy suppresses lipid oxidation and IGF-1 synthesis even more, compared to transdermal estrogen, resulting in an increased fat mass and a reduction of lean body mass, respectively.³⁶ Indeed, it has been demonstrated that in AGHD hypogonadal female patients, oral but not transdermal administration of estrogen impairs the metabolic action of GH in the liver, causing a fall in IGF-I production and fat oxidation, thus attenuating the beneficial effects of GH therapy.³⁷

In conclusion, the numerically lower reduction in TFP and the other fat parameters in somapacitan group compared to Norditropin in the entire trial 4054 population may be driven by a lower dose-response effect in females on oral estrogens exposed to somapacitan, augmented by the random higher distribution of females on oral estrogens in somapacitan group compared to the other 2 treatment arms. Modelling analysis performed by the Applicant demonstrated that target IGF-1 SDS levels can be achieved in the female patients on oral estrogen using within approved dose ranges of somapacitan. Therefore, the observed effect of oral estrogen on the dose-response relationship of somapacitan may be mitigated in clinical practice by adequate individual dose titration based on clinical and biochemical response.

Another explanation for the lower efficacy of somapacitan on body fat parameters compared to Norditropin, may be related to a possible lower affinity of somapacitan for the GH receptors in certain tissues (i.e. adipose tissue). Non-clinical data showed a 3-fold lower affinity to GH receptor of somapacitan compared to native hGH, however, the comparison to daily exogenous hGH was not reported. In addition, it is known that GH-related lipolytic effects in the adipose tissue are primarily mediated directly via GH action, whereas the anabolic effects on muscle growth and protein synthesis are both IGF-1 and GH mediated.³³

The durability of the response of somapacitan treatment was demonstrated after 86 weeks of treatment through continued improvement in all body composition parameters and maintained

³⁵ Burman P, et al. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. *Journal of Clinical Endocrinology & Metabolism*. 1997;82: 550-555

³⁶ O'Sullivan AJ, et al. Route of estrogen replacement confers divergent effects on energy metabolism and body composition in postmenopausal women. *J Clin Invest*. 1998. 102: 1035-1040

³⁷ Wolthers T et al. Oral estrogen antagonizes the metabolic actions of GH in GHD women. *Am J Physiol Endocrinol Metab*. 2001; 281: 1191-1196

IGF-1 SDS levels. An estimated mean change from baseline to week 86 in TFP of -1.52% vs. -1.06% after 34 weeks of treatment was observed in subjects exposed to somapacitan. In addition, the effect of somapacitan on the body composition parameters was supported by the observed somapacitan-induced changes in all body composition parameters in subjects assigned to the placebo group in the main period of the pivotal trial who were re-allocated to 52 weeks of somapacitan treatment in the extension period. At week 87, 52 weeks of somapacitan treatment resulted in reductions from baseline in TFP of -2.28%. Of note, the reported estimated changes from baseline to week 87 in the body composition parameters did not account for any changes in body composition parameters in the placebo group from baseline to week 34, therefore any deterioration in body composition parameters occurring while on placebo was masked for this analysis.

Additional supportive evidence of efficacy of somapacitan on body fat mass parameters comes from trial 4244, where cross-sectional TAT compartments, SAT, and VAT determined by quantitative CT scans were measured after 12 months of exposure to somapacitan compared to Norditropin therapy in AGHD patients previously treated with hGH replacement therapy. Based on the observed values, the pre-trial TAT, SAT and VAT compartments values were maintained for both the somapacitan and Norditropin arms from baseline to end of trial period and there was no statistically significant difference between treatment arms for any of the abdominal adipose tissue endpoints, as expected.

There was no effect of somapacitan on other secondary efficacy endpoints assessed in pivotal trial 4054, such as body weight, waist circumference, lipid profile and cardiovascular markers (i.e. IL-6 and hsCRP).

Lastly, the results of the COAs using the various PROs instruments did not demonstrate clinical meaningful effects of somapacitan on patients well-being. It should be noted that none of the instruments used during somapacitan CDP have been validated in AGHD patients to date, thus the interpretability of any potential PRO findings is challenging, and no meaningful conclusions can be drawn.

In conclusion, based on totality of the evidence, somapacitan represents another treatment option in the armamentarium of hGH therapies of demonstrated clinical effectiveness based on demonstrated superiority over placebo in reducing the TFP after 6 months of therapy, additional benefit on lean body mass parameters, and durability of the effect up to 18 months of therapy in treatment naive patients with AGHD. In addition, treatment with somapacitan maintained the body fat parameters at 12 months in AGHD patients previously treated with daily GH therapy. The degree of changes in body composition parameters are also in line with those observed with other rhGH formulations. The lower efficacy profile of somapacitan compared to daily Norditropin therapy observed during the current CDP is likely due a lower somapacitan efficacy observed in the subgroup of female patients on oral estrogen, which was

driven by suboptimal titration of somapacitan dose and by an uneven random distribution of females on estrogen with a higher percentage in somapacitan arm, compared to Norditropin (and placebo). The oral estrogen effects in antagonizing GH therapy actions in hypogonadal females with AGHD are well described in the literature, with mitigation strategies in clinical practice including proper somapacitan dose titration to optimal IGF-1 levels, as well as clinician awareness of the effect, and potential alternate route (i.e. transdermal) for estrogen therapy administration to maximize GH effect in this patient population, as well. Adequate mitigation strategies (i.e. need for higher starting and maintenance doses of somapacitan in females on oral estrogen than general population, due to oral estrogen's antagonizing effect on GH actions) should be included in the proposed label as well.

The newness of somapacitan as a GH replacement therapy is represented by its weekly schedule of administration, whereas all other commercially available GH products require daily injections. This characteristic may be of importance for some patients who do not tolerate daily injections, or for patients who find daily injection therapy burdensome and therefore prevents them from initiating, or maintaining the therapy with hGH. From a clinical practical perspective, I believe the availability of a GH therapy that requires a less than daily injection schedule is important and necessary, to satisfy varied patients' needs and preferences.

From a clinical efficacy standpoint, I recommend approval of somapacitan as a GH replacement therapy in adult patients with GHD.

8. Review of Safety

Safety Review Approach

The safety data was derived from the 3 completed phase 3 trials (trials 4054, 4244 and 4043) and 5 clinical pharmacology trials (trial 3915, 4237, 3947, 4297 and 4298).

The safety analysis set (SAS) was derived from the FAS population, defined as all subjects who were enrolled and treated with at least 1 dose of study drug. The Applicant presented safety data by trial, as well as by pooled analyses, which included pooled global data and Norditropin/somapacitan pool. The simple pooled global data consisted of all AGHD patients enrolled in the phase 3 trials, while the Norditropin/somapacitan pool comprised the subjects from the phase 3 trials, except the placebo arm and the data from the extension part of trial 4054, which made possible to use a standard adjustment method for trial effect when comparing subjects in somapacitan and Norditropin groups. In addition, the Applicant used the Cochran-Mantel-Haenszel (CMH) weighting method for AEs analysis in the Norditropin/somapacitan pool, which further provided adjustments for study differences (i.e.

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study duration, randomization ratio, etc.). This latter safety analysis was called ‘adjusted Norditropin/somapacitan (N/S) pool’.

This medical reviewer used the safety data originating from the main phase of the pivotal trial (4054) as the primary source of safety assessment, as it was the only trial with a double blind design that included a placebo arm. Supportive safety data was further obtained from the comparison to the active arm (Norditropin) in trials 4054, 4244 and 4043 using the ‘adjusted Norditropin/somapacitan pool’ , and from the extension phase of trial 4054 to evaluate long-term safety. Where appropriate, trial specific safety findings were described as well. This medical reviewer did not use the simple pooled global safety dataset for safety evaluation and reporting, due to differences between trials design [i.e. trial 4054 was blinded to study drug and placebo arms, had different randomization ratios amongst the treatment arms, and was conducted in a different patient population (treatment-naïve patients) than the other trials].

This review includes Applicant’s analyses, as well as analyses generated by this medical reviewer using the JMP and MAED software.

8.2. Review of the Safety Database

Table 34: Safety population

Study	Population	Subjects exposed to somapacitan	Subjects exposed to placebo	Subjects exposed to Norditropin	Study duration
Total single dose		39	8	0	
3915	healthy volunteers	32	8	0	single dose
4237	healthy volunteers	7	0	0	single dose
Total repeat doses^d		489	74	174	
3915	healthy volunteers	52	13	0	3 weeks
4297 ^a	healthy volunteers	44	0	0	
4298 ^b	healthy volunteers	34	0	0	3 weeks
3947	AGHD	26	0	8	4 weeks
4054 main	AGHD	120	61	119	34 weeks
4054 ext. ^c	AGHD	226	0	52	52 weeks
4043	AGHD	61	0	31	26 weeks
4244	AGHD	46	0	16	52 weeks

^a study in patients with renal impairment

^b study in patients with hepatic impairment

^c exposed patients to somapacitan in 4054 ext. refers to subjects who were previously on somapacitan, placebo, or Norditropin in study 4054 main; 104 subjects exposed to placebo or Norditropin in main trial were exposed to somapacitan in extension trial

^d patients exposed to somapacitan and Norditropin in trial 4054 main and ext. are counted only once

Throughout the somapacitan clinical development program, 319 were exposed to somapacitan for > 6 months, 253 patients were exposed for > 6 months, and 109 patients were exposed for > 18 months (see Table 35 for details).

Table 35: Exposure in 3 months intervals (pooled global data)

	placebo N (%)	Norditropin N (%)	somapacitan N (%)
Number of subjects	61	166	333
Exposure period			
>0 months	61 (100.0)	166 (100.0)	333 (100.0)
>3 months	60 (98.4)	158 (95.2)	326 (97.9)
>6 months	55 (90.2)	151 (91.0)	319 (95.8)
>9 months	0	67 (40.4)	257 (77.2)
>12 months	0	66 (39.8)	253 (76.0)
>15 months	0	50 (30.1)	110 (33.0)
>18 months	0	47 (28.3)	109 (32.7)

N: Number of subjects, %: Percentage of subjects.

Subjects from 4054 switching treatment after main trial period are included for each treatment.

Exposure to placebo was only done in 4054 and for no more than 35 weeks. Month = 30 days.

Source: Table 1-11, SCS, p. 32

The number of AGHD patients exposed to somapacitan in the completed phase 3 clinical trials is further summarized by trial [including patient years of exposure (PYE)] in Table 36.

Somapacitan exposure was evaluated up to 86 weeks in AGHD patients in trial 4054, up to 52 weeks in trial 4244 and up to 26 weeks in trial 4043.

Table 36: Mean exposure by trial by treatment in AGHD in phase 3 trials

Phase 3 (trial IDs)	Placebo		PYE	somapacitan		PYE	Norditropin®		PYE
	n	mean mg/week		n	mean mg/week		n	mean mg/day	
Trial 4054	61	2.20	38.2	226	2.59	288.8	119	0.33	123.2
Trial 4043	.	.	.	61	2.06	29.6	31	0.20	14.6
Trial 4244	.	.	.	46	1.78	45.4	16	0.20	14.8
Total patients	61	.	38.2	333	.	363.7	166	.	152.6

Source: Table 1-8, SCS, p. 30, modified

In pivotal trial 4054, approximately 220 subjects were exposed to somapacitan for 52 weeks (12 months) and 114 subjects were exposed for 86 weeks (18 months).

After IGF-1 SDS based dose titration period, the mean somapacitan dose was 2.59 mg/week for trial 4054 (full trial), 2.06 mg/week for trial 4043 and 1.78 mg/week for trial 4244.

Medical Officer's comments: The level of exposure to the study drug during the clinical development program satisfies the ICH E1 guidelines for chronically administered medications for safety assessment, which requires exposure data for 300-600 patients at 6 months and 100 patients at 1 year.

8.2.1. Relevant characteristics of the safety population:

The baseline characteristics of the AGHD patients were similar in between the individual phase 3 trials, as outlined in Table 37.

Table 37: Baseline characteristic for AGHD patients in the phase 3 trials

	Trial 4054^b	Trial 4043	Trial 4244
Number of patients	300	92	62
Treatment naive	Yes	No	No
Age (years), mean (SD)	45.1 (15.0)	49.3 (16.5%)	52.8 (12.1%)
Age group 18–64 years, n (%) (trial 4054: 23–64 years)	259 (86.3%)	73 (79.3%)	48 (77.4%)
Age group ≥65 years, n (%)	41 (13.7%)	19 (20.7%)	14 (22.6%)
Sex			
Men	48.3%	54.3%	53.2%
Women	51.7%	45.7%	46.8%
Race ^a			
White	66.7%	58.7%	NA
Asian	28.7%	19.6% (hereof 17 Japanese patients)	100% (Japanese patients)
Black or African American	2.3%	NA	NA
BMI (kg/m ²)	27.4 (6.3)	28.6 (5.2)	26.0 (6.1)
Diabetes, n (%)	16 (5.3%)	1 (1.1%)	0
GHD adult onset, n (%)	209 (69.7%)	58 (63.0%)	51 (82.3%)
GHD childhood onset, n (%)	91 (30.3%)	34 (37.0%)	11 (17.7%)

^a Race and ethnicity were not reported for 20 patients in France due to local regulations.

^b Baseline characteristics by treatment for trial 4054 is provided in [Appendix 7.1 Table 137](#).

Source: Table 1-16, SCS, p. 41

The demographic characteristics, medical histories and concomitant medications of the individual phase 3 trials were previously described in Section 6.1.2. The baseline demographics and disease characteristics were in general well balanced between the placebo and treatment

groups.

8.2.2. Adequacy of the safety database:

The safety database was adequate for the proposed indication.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall data integrity and submission quality were adequate to perform an effective safety review.

8.3.2. Categorization of Adverse Events

The applicant's definitions of AEs and SAEs in the protocol(s) were accurate.

- Treatment emergent adverse events (TEAEs) referred to adverse events that occurred after the first dose of the investigational product was administered regardless of whether or not the AE was considered drug related.
- The Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0 or later, was used to code all AEs.
- All AEs were followed until the outcome of the event was "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.
- Severity categorization (e.g., mild, moderate, severe) of AEs by the Applicant was appropriate.
- Verbatim terms were included in the data files and were appropriately categorized in the AEDECOD (dictionary-derived term) data file.
- The description and evaluation of common AEs and SAEs focused on proportions of patients having the AEs, AE rates and/or numbers of events as appropriate, severity, types of events, relation to trial product and outcome.
- TEAEs were summarized by System Organ Class (SOC) and Preferred Term (PT) with data reported for terms with at least 5% of subjects in either treatment group. This medical reviewer analyzed and reported TEAEs occurring with a frequency of at least 2%, and

also performed separate analyses of the safety data from the pivotal trial 4054 (main phase) looking at all levels of MedDRA hierarchy and using both broad and narrow Standard MedDRA Queries using the MAED software.

- Medical events of special interest (MESI) were presented in the section concerning analysis of specific AEs by SOC

Medical officer's comment: The Applicant's process for recording, coding, and categorizing AEs, as well as their approach to safety analyses was reasonable and appropriate.

8.3.3. Routine Clinical Tests

Clinical laboratory evaluation included hematology, biochemistry, hormonal profile (thyroid function, testosterone, fasting serum cortisol, ACTH stimulation test), glucose metabolism parameters (fasting plasma glucose, fasting insulin, and Hba1c), IGF-1 SDS, vital signs (systolic and diastolic blood pressure, pulse), ECG, weight, and immunogenicity were assessed throughout the trials for safety assessments (see Appendix 6.1 for Schedule of events for pivotal trial 4054). The assessments were taken at different visits across the trials (see the Schedule of events table for each particular trial for details).

8.4. Safety Results

Deaths

There were 5 deaths during trial 4054 (main + extension), with 2 deaths occurring while on somapacitan therapy, 2 deaths while on Norditropin therapy, and 1 death while on placebo (Table 38). As per Applicant, all deaths were not related to the trial products .

Table 38: Deaths in 4054 trial (main + extension)

Treatment arm Main/extension	Subject ID	Sex/Age/ BMI	Preferred term	Main/extension	AE onset after exposure
Placebo/somapacitan	(b) (6)	M/68/32.4	Ventricular fibrillation. Cardiogenic shock. Pneumonia aspiration	Extension	Week 51 (Day 363)
Norditropin®/somapacitan		M/74/39.9	Death (Reported term: Unknown cause)	Extension	Week 65 (Day 458)
Norditropin®/Norditropin®		M/72/25.8	Pneumonia	Extension	Week 51 (Day 360)
Norditropin®/-		M 60/28.0	Influenza	Extension	Week 70 (Day 493)
Placebo		F/76/29.9	Adrenocortical insufficiency acute	Main	Week 23 (Day 163)

Abbreviations: M= Male; F= Female; Age in years; BMI: Body Mass Index (kg/m²) at baseline

Source: Applicant's Summary of Clinical Safety (SCS), Table 2-10 , page 63

The narratives of the subjects who died during the study are summarized below:

Somapacitan group

Subject (b) (6), 68 years old male with GHD, and past medical history of type 2 diabetes mellitus, hypertension, angina pectoris, transsphenoidal and transcranial hypophysectomy, benign pituitary tumor, panhypopituitarism (with growth hormone deficiency, secondary hypoadrenalism, hypothyroidism, and hypogonadism). Medication history was not provided. The subject was from placebo/somapacitan arm, on somapacitan treatment from (b) (6), when somapacitan dose was 2.0 mg weekly. On (b) (6), (trial day 363), the patient complained of difficulty breathing and then fainted at home. The patient was admitted to intensive care unit in cardiogenic shock. The patient aspired and had aspiration pneumonia. The trial product was discontinued temporarily during hospitalization, with last dose administered on (b) (6). The patient died on (b) (6), due to ventricular fibrillation, cardiogenic shock and aspiration pneumonia.

Subject (b) (6), a 74 years old male with GHD and past medical history (PMH) of pituitary macroadenoma surgically resected twice with small remainder post-surgery, panhypopituitarism (hypoadrenalism, hypothyroidism, hypogonadism, growth hormone deficiency), blindness, chronic renal impairment, incisional hernia, peripheral vascular disease, cataract, nuclear sclerosis, optic atrophy (left), visual field defect (left), cellulitis with abscess (abdominal wound), ventral hernia, pain in joint involving shoulder region, hyperlipidemia, anxiety, depressive disorder, erectile dysfunction, atrial fibrillation, deafness, obesity, peripheral neuropathy. Concomitant medications included cabergoline, Alprazolam, Atenolol

and Simvastatin. The patient was in Norditropin/somapacitan arm, who was treated in the main part of the trial with Norditropin from (b) (6), and with somapacitan from (b) (6) (somapacitan dose 2.5 mg weekly), when patient discontinued study drug due to pituitary tumor re-growth in the absence of cabergoline treatment, with tumor size reduction demonstrated post cabergoline re-initiation. The patient died on (b) (6) while at home, of unknown cause. Family refused autopsy. The patient was off study drug for approximately 5 months prior to the event of death.

Norditropin group

Subject (b) (6), a 72 years old male with GHD and PMH of panhypopituitarism, pituitary adenoma and oculomotor nerve paralysis. No concomitant medications were provided. The patient was in Norditropin/Norditropin arm, on the treatment from (b) (6) (b) (6) (main and extension). On (b) (6) the patient fell at home and he was taken to the hospital, and had events of vomiting and sleeping all day the day prior. He was diagnosed with pneumonia at the hospital and died on the same day, (b) (6), due to pneumonia. An autopsy was not performed.

Subject (b) (6), a 62 years old male, with GHD and PMH of panhypopituitarism, thalamic hemorrhage, hyperuricemia, hypertension, hyperlipidemia, numbness of right-sided upper and lower extremities, after effects of thalamic hemorrhage. Concomitant medications include oseltamivir and hydrocortisone. The patient received Norditropin during the main part of the trial, and discontinued trial drug before extension part of the trial. He took Norditropin from (b) (6). Patient developed cold-like symptoms on (b) (6), was diagnosed with influenza on (b) (6) during an emergency room visit, and started oseltamivir and increased the dose of hydrocortisone the same day. The patient died on (b) (6) while found unresponsive at home, with the cause of death reported as influenza. The patient was off trial drug for 9 months before the event.

Placebo group

Subject (b) (6), a 76 years old female with GHD and PMH of Sheehan's syndrome, chronic gastritis and hypertension. Concomitant medications included prednisone. She was on the placebo drug during the main period of the trial. After 23 weeks of exposure, the patient developed flu-like symptoms and diarrhea. The patient did not increase prednisone as recommended by the medical practitioner during the time of illness, and died of adrenocortical insufficiency 4 days later.

Medical officer's comments: This reviewer concluded that all the cases of death were not related to the trial drug considering relationship between time of exposure and event occurrence, underlying medical conditions and acute illnesses (i.e. pneumonia, influenza), which were the likely contributors in all cases. In addition, deaths are expected in the age group of the population being studied.

No deaths were reported in trials 4043 and 4244, or in the clinical pharmacology trials (trials 3915, 3947, 4237, 4297 and 4298).

8.4.2. Serious Adverse Events

Study 4054 main period

A total of 32 SAEs occurred in 23 (7.7%) patients during the study, with 12 events in 7 patients (5.8%) in somapacitan group, 13 events in 11 (9.2%) patients in Norditropin group, and 7 events in 5 (8.2%) patients in placebo group (Table 39). The event rate was similar across treatment groups: somapacitan: 15 SAEs/100 pt. years; Norditropin 16.8 SAEs/100 pt. years; placebo: 17.6 SAEs/100 pt. years. With the exception of 1 SAE (hemoconcentration) in Norditropin group, none of the SAEs were likely related to the study drug, as assessed by the investigator. The SAEs that occurred more frequently in somapacitan arm were in SOC Infections and Infestations (somapacitan 3.3%, Norditropin 1.7% and placebo 1.6%), and Gastrointestinal disorders (somapacitan 2.5%, Norditropin 0.8%, placebo 3.3%), and the cases occurring in somapacitan arm were summarized below. The PT Adrenal Insufficiency, which is a known class effect of GH therapy, occurred in 1 patient per treatment arm, with the case occurring in somapacitan arm being summarized below.

Table 39: Serious Adverse Events (SAEs) by System Organ Class (SOC), preferred term (PT) and treatment group

	NORDITROPIN	PLACEBO	SOMAPACITAN	Total
SOC (n)/PT (e)	Count (%)	Count (%)	Count (%)	Count (%)
Total	N=119	N=61	N=120	N=300
All SAEs (n)	11 (9.2%)	5(8.2%)	7 (5.8%)	23 (7.7%)
<i>Blood and lymphatic system disorders</i>	1(0.8%)			1(0.3%)
Hemoconcentration	1 (0.8)			1 (0.3)
<i>Endocrine disorders</i>	1(0.8%)	1(1.6%)	1(0.8%)	3(1%)
Adrenocortical insufficiency	1 (0.8)	1 (1.6)	1 (0.8)	3 (1)
<i>Gastrointestinal disorders</i>	1(0.8%)	2(3.3%)	3(2.5%)	6(2%)
Abdominal pain	1 (0.8)			1 (0.3)
Diarrhea		1 (1.6)		1 (0.3)
Pancreatitis acute		1 (1.6)		1 (0.3)
Inguinal hernia			1 (0.8)	1 (0.3)
Stomatitis			1 (0.8)	1 (0.3)
Vomiting		1 (1.6)	1 (0.8)	2 (0.7)
<i>General disorders and administration site conditions (n/r)</i>			1(0.8%)	1(0.3%)
Pyrexia			1 (0.8)	1 (0.3)
<i>Infections and infestations</i>	2(1.7%)	1(1.6%)	4(3.3%)	7(2.3%)
Clostridium difficile infection	1 (0.8)			1 (0.3)
Appendicitis	1 (0.8)		1 (0.8)	2 (0.7)
Gastroenteritis			2 (1.7)	2 (0.7)
Gastroenteritis viral		1 (1.6)	1 (0.8)	2 (0.7)
Herpes simplex			1 (0.8)	1 (0.3)
Sepsis			1 (0.8)	1 (0.3)
Viral upper respiratory tract infection			1 (0.8)	1 (0.3)

N: subjects exposed; n: number of subjects having an event in the given SOC at least once; e: number of adverse events reported; %: percentage of exposed subjects having the event;

MedDRA version 20.0

Source: JMP, medical officer generated report

Table 39: Serious Adverse Events (SAEs) by System Organ Class (SOC), preferred term (PT) and treatment group (cont.)

	NORDITROPIN	PLACEBO	SOMAPACITAN	Total
SOC (n)/PT (e)	Count (%)	Count (%)	Count (%)	Count (%)
Total	N=119	N=61	N=120	N=300
All SAEs (n)	11 (9.2%)	5(8.2%)	7 (5.8%)	23 (7.7%)
<i>Injury, poisoning and procedural complications</i>	2(1.7%)			2(0.7%)
Drug dispensing error	1 (0.8)			1 (0.3)
Fall	1 (0.8)			1 (0.3)
Tibia fracture	1 (0.8)			1 (0.3)
<i>Investigations</i>	1(0.8%)	1(1.6%)		2(0.7%)
Blood testosterone increased	1 (0.8)			1 (0.3)
Electrocardiogram T wave abnormal		1 (1.6)		1 (0.3)
<i>Metabolism and nutrition disorders</i>		1(1.6%)		1(0.3%)
Hyponatremia		1 (1.6)		1 (0.3)
<i>Neoplasms benign, malignant and unspecified (including cysts)</i>	1(0.8%)			1(0.3%)
Plasma cell myeloma	1 (0.8)			1 (0.3)
<i>Renal and urinary disorders</i>	2(1.7%)			2(0.7%)
Chronic kidney disease	1 (0.8)			1 (0.3)
Nephrolithiasis	1 (0.8)			1 (0.3)
<i>Skin and subcutaneous tissue disorders</i>	1(0.8%)			1(0.3%)
Dermatitis atopic	1 (0.8)			1 (0.3)

N: subjects exposed; n: number of subjects having an event in the given SOC at least once; e: number of adverse events reported; %: percentage of exposed subjects having the event;

MedDRA version 20.0

Source: JMP, medical officer generated report

Subject (b) (6) (SAEs: gastroenteritis, AI, herpes simplex, sepsis, stomatitis, viral URI, ventricular extrasystoles, dyspnea) was a 51 years old male with h/o GHD, treated with somapacitan from (b) (6). PMH included hypothyroidism, AI, ulcerative colitis, atrial fibrillation, gastroesophageal reflux disease, chronic obstructive pulmonary disease, fatigue. Concomitant medications included Tamiflu (oseltamivir). On (b) (6), the patient presented to Emergency Room (ER) with fever, cough, body aches, and nausea. The patient was admitted for observation and was diagnosed with upper

respiratory infection, complicated by sepsis, stomatitis due to herpes simplex infection and adrenal crisis syndrome. The patient received targeted therapy in the hospital. It was reported that the sepsis and adrenal crisis resolved with symptomatic treatment and increased glucocorticoid dose. On (b) (6), the patient was discharged from hospital and considered recovered from the events "Adrenal crisis syndrome", "Sepsis" and "HSV Infection". Of note, the trial product was stopped on (b) (6) due to the wash-out period and patient had not yet started the treatment for the extension period due to scheduling issues.

Medical officer's comments: The causal relationship between somapacitan and the reported SAEs is unlikely due to the temporal relationship between study drug discontinuation and occurrence of the SAEs.

Subject (b) (6) (SAE gastroenteritis) was a 46 years old male with h/o GHD treated with somapacitan from (b) (6). Additional PMH included left lumbar hernia (L5-S1), pituitary macroadenoma, gonadotropin insufficiency, chronic venous insufficiency, overweight, poliglobulia, hyponatremia.

Concomitant medications were not reported. On (b) (6) the patient was admitted to hospital due to chills, nausea, headache, diarrhea and abdominal pain. The patient received symptomatic treatment during hospitalization and his evolution was favorable. No underlying cause for the gastroenteritis was detected. On (b) (6) the patient was discharged from hospital, and the event of acute gastroenteritis was recovered.

Subject (b) (6) (SAE appendicitis) was a 29 years old female with h/o GHD treated with somapacitan, who on (b) (6) experienced gradual right iliac pain, not relieved by analgesic medication. On (b) (6), the patient presented to the ER and was admitted for surgery with a diagnosis of suspected acute appendicitis. No other analyses performed. On the same date the patient underwent exploratory surgery by laparoscopy with appendectomy, with pathologic diagnosis of phlegmonous acute appendicitis. Additional PMH diabetes insipidus, hypocalcemia, thyroglossal cyst operated - left thyroid lobectomy, empty sella syndrome, panhypopituitarism, dyslipidemia, deficiency anemia. Concomitant medications were not reported. On (b) (6) the outcome for the event "phlegmonous acute appendicitis" was recovered and the patient was discharged from hospital.

Medical officer's comment: the causal relationship between somapacitan and the reported SAEs for subjects (b) (6) is possible due to temporal relationship, however, no firm conclusion can be made at this time due to the limited information provided, and the fact that the described infections are common in general population. Thus, in this MO opinion the likelihood that the events are drug related is low.

Subject (b) (6) (SAE gastroenteritis viral) was a 48 years old male with h/o GHD who was treated with somapacitan from (b) (6). Additional PMH included

pineal tumor, hydrocephalus (secondary to pineal tumor), insertion of ventriculo-peritoneal (V-P) shunt for hydrocephalus, asthma, osteoporosis, Dupuytren's contracture, panhypopituitarism, secondary hypothyroidism, secondary hypogonadism, diabetes insipidus. Concomitant medications were not reported. On [REDACTED] (b) (6) the patient started to experience stomach cramps, stomach pain with vomiting and frequent diarrhea. On the same date the patient was taken to the ER and he was subsequently admitted to hospital. The patient underwent the following relevant tests: abdomen x-ray, chest x-ray and computerized tomogram (CT) of abdomen and pelvis. Results were not reported. The patient was diagnosed with viral gastroenteritis. The patient received treatment with antiemetic therapy and acetaminophen for stomach pain. On [REDACTED] (b) (6) the patient was discharged from hospital as recovered. At the time of this SAE the patient was between the main and extension part of the trial - last dose of study drug in the main part was on [REDACTED] (b) (6) and the first dose of the extension part was after the SAE, on [REDACTED] (b) (6).

Medical officer's comment: the causal relationship between somapacitan and the reported SAEs is unlikely due to the temporal relationship between study drug discontinuation and occurrence of the SAEs.

Subject [REDACTED] (b) (6) (SAE inguinal hernia) was a 56 years old female with h/o GHD who was treated with somapacitan since [REDACTED] (b) (6). Additional PMH included central thyroid insufficiency, hypercholesterolemia, central gonadal insufficiency, central adrenal insufficiency, menopause. Concomitant medications were not reported. On [REDACTED] (b) (6), the patient experienced inguinal hernia. Prior to the event the patient had some hard physical activity (she picked up a child). On [REDACTED] (b) (6) she was hospitalized for inguinal hernia surgery. The patient recovered well after the surgery and she was discharged from the hospital on [REDACTED] (b) (6).

Medical officer's comment: the causal relationship between the study drug and SAE is unlikely and the assessment is further complicated by confounding factors (e.g., physical activity) and limited information provided.

Subject [REDACTED] (b) (6) (SAE vomiting) was a 54 years old female with h/o GHD who was treated with somapacitan from [REDACTED] (b) (6). Additional PMH included hypopituitarism, anxiety, osteopenia, postmenopausal. Treatment medications included - hydrocortisone(hydrocortisone). The patient had completed the main trial, and had not yet initiated treatment in the extension part of the trial. On [REDACTED] (b) (6), the patient experienced nausea and vomiting for 4 days. Nausea was reported as non-serious event. Patient had taken no standard of care medication for this time. On [REDACTED] (b) (6), the patient was admitted for assessment of AI, intravenous therapy and Hydrocortisone. On [REDACTED] (b) (6) the patient was discharged as recovered.

Medical officer's comments: The etiology of the symptoms of vomiting and nausea are unclear, but most likely is due to AI caused by omitting hydrocortisone therapy in the setting of the gastrointestinal symptoms.

Overall, the incidence of SAEs in somapacitan group (and the other groups) was low, with events occurring in more than 2% of subjects noted in SOC Infections and infestations (3.3%, compared to 1.6% in placebo and 1.7% in Norditropin groups, respectively) and SOC Gastrointestinal disorders (2.5%, compared to 3.3%, in placebo and 0.8% in Norditropin groups, respectively). However, upon detailed review of SAEs case narratives, this MO agrees that none of the events in somapacitan group were likely related to the study drug.

All safety data obtained from study 4054 till cutoff date (main + extension):

A total of 37 (12.3 %) patients experienced 68 SAEs, all but 2 [1 case (subject (b) (6)) of bladder cell carcinoma (see detailed narrative in Section 8.5 below) in somapacitan arm; 1 case (subject (b) (6)) of hemoconcentration in Norditropin arm (main phase) with causality being assessed by the Investigator as probable, while confounding factors included history of smoking and use of testosterone replacement therapy, and the outcome was recovered] being evaluated as unrelated to the study drug by investigator. All narratives were reviewed by this MO who agrees with the Investigator's and Applicant's conclusions. The percentage of patients reporting SAEs was similar for somapacitan (9.3%), Norditropin (11.8% patients) and placebo (8.2% patients). A similar percentage of patients reported SAEs in the somapacitan/somapacitan arm (10.8%) and in the Norditropin/Norditropin arm (9.6%).

Adjusted Norditropin/somapacitan pool

The SAE profile using the CMH adjusted approach for N/S pool showed similar proportions (somapacitan 6.4% vs Norditropin 7.4%) and event rates per 100 patient years (somapacitan 13.5 vs Norditropin 14.1) for the SAEs between treatment arms. None of the SAEs in 4043 and 4244 trials were considered related to study drug. SAEs in somapacitan group in these trials consisted of patella fracture, procedural complications, mammoplasty, cholelithiasis, inguinal hernia, large intestine polyp, gastroenteritis and head injury. The majority of the SAEs were recorded as single events in 1 or 2 patients across different SOC amongst all phase 3 trials.

Medical officer's comments: The SAE rates per 100 patient years between treatment groups was similar in the trial 4054 (main period) (somapacitan 15.0 vs Norditropin 16.8) and adjusted N/S pool (somapacitan 13.5 vs Norditropin 14.1). The proportion of patients experiencing SAEs was lower in somapacitan group compared to Norditropin group in both trial 4054 main + extension period (9.3% vs 11.8%), and adjusted N/S pool (6.4% vs 7.4%) the lower rate observed in adjusted N/S pool compared to 4054 main+extension trial likely being explained by differences in the exposure time per trial, and per treatment arm.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 4054 main and extension

A total of 12 AEs led to permanent study drug discontinuation in 11 patients. Of the 12 AEs, 3 were SAEs (plasma cell myeloma in Norditropin/somapacitan arm, hemoconcentration and dermatitis atopic in Norditropin/- arm).

In the main phase of trial 4054, no patients in somapacitan group discontinued the trial drug due to AEs. Four (0.9%) patients in Norditropin group and 1 (0.5%) patient in placebo group permanently discontinued the trial product due to AEs during the main phase of the 4054 trial, with 2 events (diabetes mellitus and hemoconcentration) likely being related to trial product (both in Norditropin group).

In the extension phase of study 4054, 6 patients in somapacitan group discontinued the study drug due to AE: 1 patient (subject (b) (6)) in somapacitan/somapacitan arm developed hepatic steatosis and HbA1c increased (7.6%) on study day 457, both assessed as mild, 1 patient (subject (b) (6)) in Norditropin/somapacitan arm experienced fatigue on day 330, 2 patients (subjects (b) (6)) in Norditropin/somapacitan, and placebo/somapacitan, respectively were diagnosed with benign pituitary tumors on study days 298, and 558, respectively, 1 patient (subject (b) (6)) in somapacitan/somapacitan arm had thyroid disorder (unspecified follicular lesion) and 1 patient (subject (b) (6)) in Norditropin/somapacitan arm had plasma cell myeloma, which developed during the main phase of the trial while on Norditropin, but it was diagnosed in the extension phase of the trial while on somapacitan. No discontinuations from Norditropin were reported in the extension phase of the trial. The events of neoplasms are described in details in Section 8.5.

Trials 4043 and 4244

Two patients discontinued somapacitan in trial 4043, 1 in somapacitan group and 1 in Norditropin group, both due to asthenia, on day 1, and 2 respectively.

In trial 4244 there was only 1 reported discontinuation of the study drug due to AE of DM in Norditropin group.

Medical officer's comments: The overall rate of study drug discontinuation during the phase 3 trials was low, while no subjects in somapacitan group discontinued the study drug due to AE in the main phase of pivotal trial 4054. The incidence of study drug discontinuation was similar across the study groups. The AEs leading to study drug discontinuation were generally non-serious and of mild severity.

8.4.4. Significant Adverse Events

Severe TEAEs occurring in main phase of the pivotal study 4054 were reported in 5.8% of subjects in somapacitan group, compared to 7.6% in Norditropin group and 6.6% in placebo group (Table 14.3.1.7, page 460 of CSR 4054, main). Headache was the only severe AE that was more common in the somapacitan treatment group compared to placebo and Norditropin groups and occurred with a frequency of 1.7% (2 patients) vs 0% vs 0%, respectively. Severe TEAEs in the Norditropin/somapacitan adjusted pool were reported in 5.6% of subjects in somapacitan group vs 6.3% subjects in Norditropin group (Appendix 7.1, Table 105, SCS, page 294). In study 4043 there were no severe TEAEs that occurred in more than 1 patient in somapacitan, or Norditropin treatment groups, with similar overall frequency reported (somapacitan 8.2% vs. Norditropin 6.5%) (Table 14.3.1.7, page 198 of CSR 4043). No severe TEAEs were reported in study 4244.

Medical officer's comments: Overall, the frequency of severe TEAEs was similar between somapacitan, placebo and active comparator groups. Headache was the only severe AE that occurred in more than 1 subject (2 subjects) in somapacitan group compared to no subject in placebo, or Norditropin group in study 4054. Headache is a labeled AE of GH therapy, with the reported severity in the Norditropin group possibly being influenced by the fact it was open label study group.

Related TEAEs in the pivotal trial 4054 were reported in 24% of subjects in Somapacitan group, 21% in placebo, and 30% in Norditropin groups (Table 14.3.1.10, page 484, of the CSR). Related AEs that were more common in the somapacitan treatment group compared to placebo and Norditropin groups include, in order of frequency, headache 5.0% vs. 3.3% vs. 2.5%, lipohypertrophy/lipodystrophy 2.5% vs. 0% vs. 0%, upper abdominal pain 1.7% vs. 0% vs 0%, adrenal insufficiency 1.7% vs. 0% vs. 0%, all labeled GH-related AEs.

Medical officer's comments: The fact that treatment relation is determined at the discretion of the study investigators must be considered when trying to draw conclusions from these data.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Trial 4054 (main phase)

TEAEs by Preferred Term (PT) that occurred in > 2% of subjects and occurred more frequently in the Somapacitan treatment group are listed (and highlighted) in Table 40. PTs that occurred ≥ 1% more commonly in the somapacitan treatment group compared to placebo, during the initial 26 week placebo-controlled study period are in order of frequency relative to placebo

(i.e. somapacitan - placebo): back pain (6.0%), arthralgia (5.1%), lipohypertrophy/lipodystrophy (3.3%), blood creatinine increase (3.3%), weight increased (3.3%), UTI (2.6%), abdominal pain (2.6%), pyrexia (2.5%), tonsillitis (1.7%), vomiting (1.7%), dizziness (1.7%), adrenal insufficiency (1.7%), peripheral edema (1.7%), hypertension (1.7%), gastroenteritis (1%).

Table 40: Adverse reactions by PT with > 2% overall incidence in AGHD patients treated with somapacitan compared to placebo and Norditropin during main phase of pivotal 4054 study

	Somapacitan (N = 120)			Norditropin (N = 119)			Placebo (N = 61)		
Preferred term	N	(%)	E	N	(%)	E	N	(%)	E
Back pain	11	9.2	11	4	3.4	4	2	3.2	2
Arthralgia	8	6.7	8	10	8.4	10	1	1.6	1
Abdominal pain	7	5.8	9	4	3.4	4	2	3.2	2
Gastroenteritis	5	4.2	6	3	0.8	4	2	3.2	2
UTI	5	4.2	5	1	0.8	1	1	1.6	1
Oropharyngeal pain	5	4.2	5	1	0.8	1	2	3.3	2
Tonsillitis	4	3.3	4	2	1.7	2	1	1.6	1
Peripheral edema	4	3.3	6	9	5.8	11	1	1.6	1
Lipohypertrophy/lipodystrophy acquired	4	3.3	4	0	0	0	0	0	0
Vomiting	4	3.3	4	4	3.4	5	1	1.6	2
Dizziness	4	3.3	5	4	3.4	7	1	1.6	1
Adrenal Insufficiency	4	3.3	4	2	1.7	2	1	1.6	1
Hypertension	4	3.3	4	4	3.4	4	1	1.6	1
Blood creatine phosphokinase increase	4	3.3	6	0	0	0	0	0	0
Weight increased	4	3.3	4	1	0.8	1	0	0	0
Pyrexia	3	2.5	4	1	0.8	2	0	0	0
Sleep disorder	3	2.5	3	0	0	0	1	1.6	1

N= number of patients having the event, (%) = proportion of patients having the event, E = total number of events
Table generated using JMP clinical software, with number of events (E) selected from Applicant's CSR,
Table 14.3.1.4. page 440

Of note, TEAEs of headache, fatigue/asthenia, paresthesia and injection site reaction, which are known class effects of the growth hormone drugs, were not reported in Table 8.3 , due to occurrence of those events with lower frequency in somapacitan arm compared to placebo arm, as follows: headache (8.3% vs 16.4%), fatigue/asthenia (4.2 % vs 6.6 %), paresthesia (2.2% vs 3.3%) and injection site reaction (2.5 % vs 6.6%), respectively. The incidence of these AEs in somapacitan group compared to Norditropin was similar: headache (8.3% vs 8.4%),

fatigue/asthenia (4.2% vs 5.8%), paresthesia (2.5% vs 0.8%), injection site reactions (2.5% vs 2.5%).

A MedDRA-Based Adverse Event Diagnostics (MAED) analysis of the main phase of the pivotal trial 4054 sorted by Relative Risk (RR) of 3.0 or greater with respect to treatment with somapacitan is shown in Table 41. While peripheral edema, arthralgia, and adrenal insufficiency are expected AE associated with the GH drugs class, new AEs with a high relative risk (RR) include 'blood creatinine phosphokinase increased', pyrexia, weight increased, 'lipohypertrophy/lipodystrophy' and back pain with relative risk of 5.6, 4.6, 4.6, 4.6, 3.05, respectively and p-values of 0.169, 0.3, 0.3, 0.3, 0.145, respectively.

Table 41: MAED Analysis of the AEs data of study 4054 (main phase) sorted by Relative Risk (RR) ≥ 3 for Somapacitan vs. Placebo

	Somapacitan (N = 120)			Placebo (N = 61)						
PT	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	Relative risk (RR)	RR C.I. (lower bound)	RR C.I. (upper bound)	P-value
Blood creatine phosphokinase increased	7	5	4.17	0	0	0	5.636	0.317	100.29	0.169
Edema peripheral	7	5	4.17	0	0	0	5.636	0.317	100.29	0.169
Pyrexia	5	4	3.33	0	0	0	4.612	0.252	84.287	0.302
Weight increased	4	4	3.33	0	0	0	4.612	0.252	84.287	0.302
Lipohypertrophy/lipodystrophy acquired	4	4	3.33	0	0	0	4.612	0.252	84.287	0.302
Arthralgia	9	9	7.5	1	1	1.64	4.575	0.593	35.286	0.168
Adrenal insufficiency	3	3	2.5	0	0	0	3.587	0.188	68.346	0.552
Back pain	12	12	10	2	2	3.28	3.05	0.705	13.197	0.145

In **bold** are AEs that are not known to be associated with GH drug class

A similar MAED analysis looking at AEs which generated the lowest p-values up to a maximum value of 0.169 is shown in Table 42. Only back pain, arthralgia, 'blood creatinine phosphokinase increased', and peripheral edema had a positive relative risk, meaning they were more common in the somapacitan treatment group. Of note, neither of these calculated p-values was < 0.05.

Table 42: MAED Analysis of the AEs data of study 4054 (main phase) sorted by Calculated p-values ≤ 0.169 Ranked from Lowest to Highest

PT	Somapacitan (N = 120)			Placebo (N = 61)			RR	RR C.I. (lower bound)	RR C.I. (upper bound)	P-value
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)				
Headache	48	10	8.33	16	11	18.03	0.462	0.208	1.027	0.083
Bronchitis	1	1	0.83	3	3	4.92	0.169	0.018	1.595	0.112
Dermatitis	0	0	0	2	2	3.28	0.102	0.005	2.102	0.112
Dysmenorrhea	0	0	0	2	2	3.28	0.102	0.005	2.102	0.112
Eczema	0	0	0	2	2	3.28	0.102	0.005	2.102	0.112
Respiratory tract infection	0	0	0	2	2	3.28	0.102	0.005	2.102	0.112
Upper respiratory tract infection	7	6	5	7	7	11.48	0.436	0.153	1.24	0.132
Back pain	12	12	10	2	2	3.28	3.05	0.705	13.197	0.145
Diarrhea	5	4	3.33	8	5	8.2	0.407	0.113	1.46	0.167
Arthralgia	9	9	7.5	1	1	1.64	4.575	0.593	35.286	0.168
Blood creatine phosphokinase increased	7	5	4.17	0	0	0	5.636	0.317	100.29	0.169
Edema peripheral	7	5	4.17	0	0	0	5.636	0.317	100.29	0.169

The preferred terms of “back pain”, “arthralgia”, “blood creatine phosphokinase increase”, “peripheral edema”, “pyrexia”, “weight increased”, and “lipohypertrophy/lipodystrophy” were consistently more common TEAEs compared to placebo based on analysis performed in Tables 40, 41 and 42. While arthralgia, peripheral edema, weight increased and lipohypertrophy/lipodystrophy are GH class effects recognized as medical events of special interest (MESI) that are further analyzed and discussed in Section 8.5, the AEs of “back pain”, “blood creatine phosphokinase increase”, and “pyrexia” were analyzed below.

Medical Officer Comments:

Back pain: was noted in 11 (9.2%) patients in somapacitan group, compared to 4 (3.4%) patients in Norditropin group and 2 (3.2%) patients in placebo group. In somapacitan group, the duration of event varied from 2 - 88 days (duration not available in 2 cases), was mild in all cases, with causality to study drug being considered unlikely in all, but 2

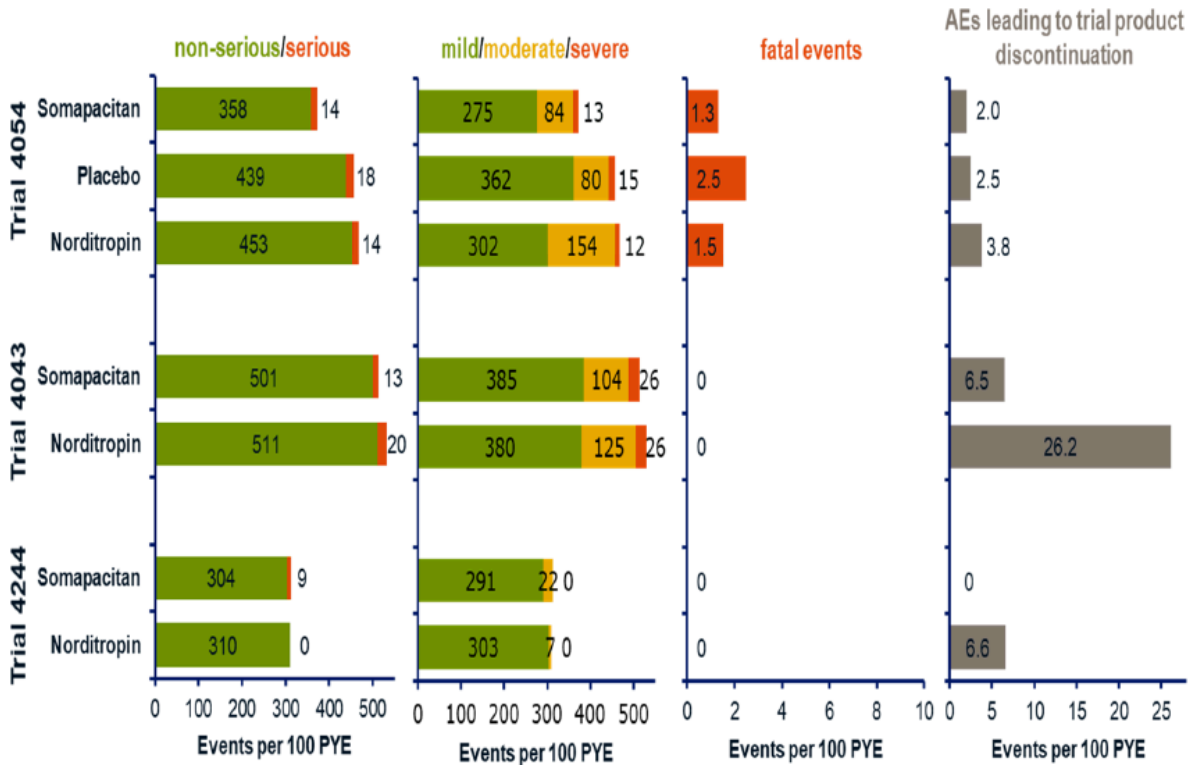
cases, by the study investigators. The AE recovered in all, but one case, and no dose reduction was required due to AE. It is possible that back pain could be another clinical manifestation of fluid retention with subsequent spinal nerve compression, which is a known class effect of growth hormone products. It is reassuring that the event was mild and recovered in majority of patients, suggesting a transient nature of the drug effect. Of note, back pain was reported in 4.3% (somapacitan) vs 6.3% (Norditropin) of the patients in trial 4244, and 4.9% (somapacitan) vs 3.2% (Norditropin) of the patients in trial 4043, respectively. However, both trials were open label, and conducted in patients previously exposed to hGH therapy.

“Blood creatine phosphokinase increase” was noted in 4 patients in somapacitan group compared to no patients in placebo, or Norditropin groups. The duration of event ranged from 11 - 23 days (no duration reported in 1 subject), all, but 1 case (classified as severe) were mild in severity, and all, but 1 case recovered. There were no associated symptoms, or conditions (i.e. myalgia, myositis) reported. The clinical significance of the event is not immediately evident, but it should be noted in the label, for physician awareness.

Pyrexia was reported in 3 patients in somapacitan group, 1 patient in Norditropin group and no patients in placebo. In somapacitan group, the duration of event lasted 2-5 days, and in 2 subjects other underlying causal effects were present, namely, viral infection and diarrhea, which makes the causal relationship between the somapacitan and the event unlikely.

Figure 18 shows an overview of all the event rates per 100 patient years by trial. Subjects who received placebo, or Norditropin in the main phase of study 4054 and received somapacitan when they enrolled into the extension phase of study 4054 are included in both the placebo, or Norditropin groups and somapacitan treatment group depending on when the adverse event occurred. Overall, similar or lower AE reporting rates were observed for somapacitan compared to placebo, or Norditropin. Lower overall event rates were observed in trial 4244, compared to trials 4054 and 4043.

Figure 18: Overview of AEs by trial



Cross-reference: [Appendix 7.1 Table 139](#) (Trial 4054, full trial), [Trial 4043 \(M 5.3.5.1\) Table 12-4](#) and [Trial 4244 \(M 5.3.5.1\) Table 12-1](#).

Source: Figure 2-1, SCS, page 45

8.4.6. Laboratory Findings

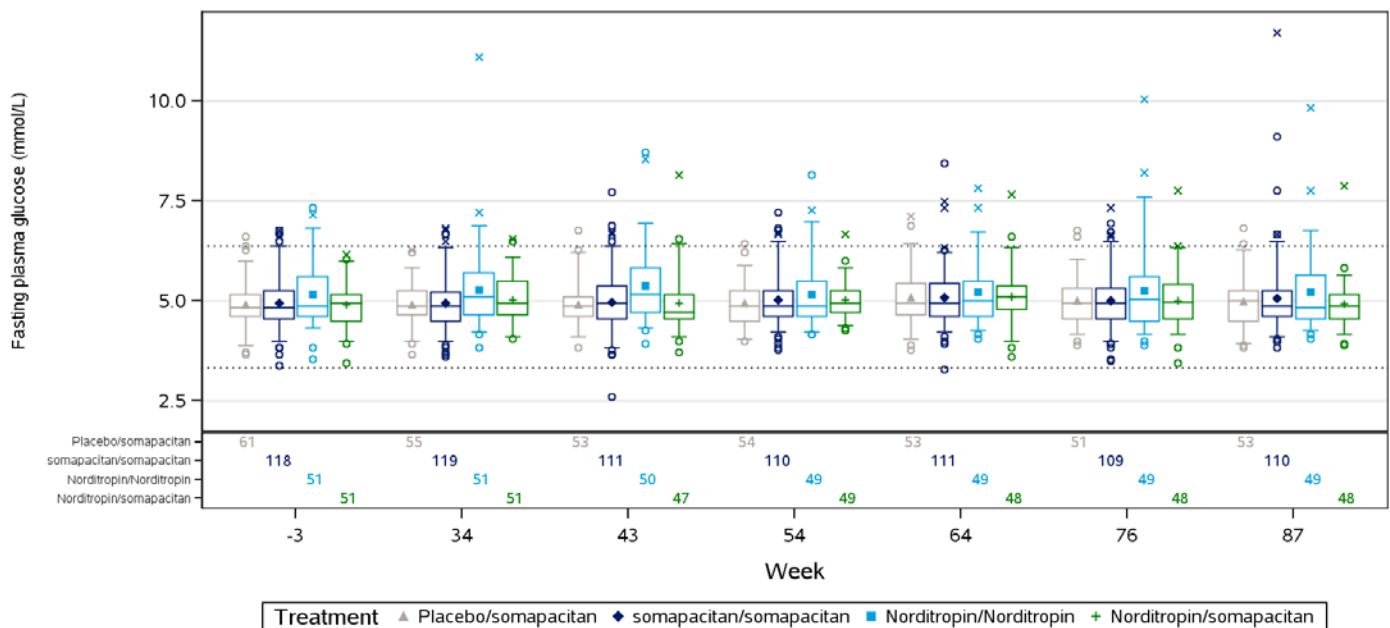
Glycemic control

Glucose metabolism may be affected by growth hormone therapy due to a decreased insulin sensitivity resulting from the GH direct insulin antagonistic effects in the liver and other tissues and is a known class AEs of rhGH formulations. Therefore, fasting blood glucose, fasting insulin and HbA1c were assessed in all phase 3 trials. The results are presented as shift tables/figures, by trial due to different timing of assessments across trials.

Trial 4054 (main + extension)

There were no clinically relevant changes in the mean fasting blood glucose and HbA1c from baseline to 86 weeks somapacitan exposure (gray triangles after week 34, dark blue diamond week -3 to 87, green plus after week 34), nor were any changes observed in these parameters following placebo or Norditropin exposure (Figure 19 and Figure 20). The mean fasting blood glucose ranged from 4.9 to 5.2 mmol/L and mean HbA1c ranged from 5.4% to 5.5% across all treatment groups from baseline to after 86 weeks of exposure (refer to Tables 14.3.5.6 and 14.3.5.21, Trial 4054, pages 1644 -1645 and 1671-1672).

Figure 19: Mean fasting plasma glucose (mmol/L) in AGHD patients (trial 4054)



Mean (triangle, square, plus and diamond); median (centre line); 25th and 75th percentiles (box); 5th and 95th percentiles (whiskers).

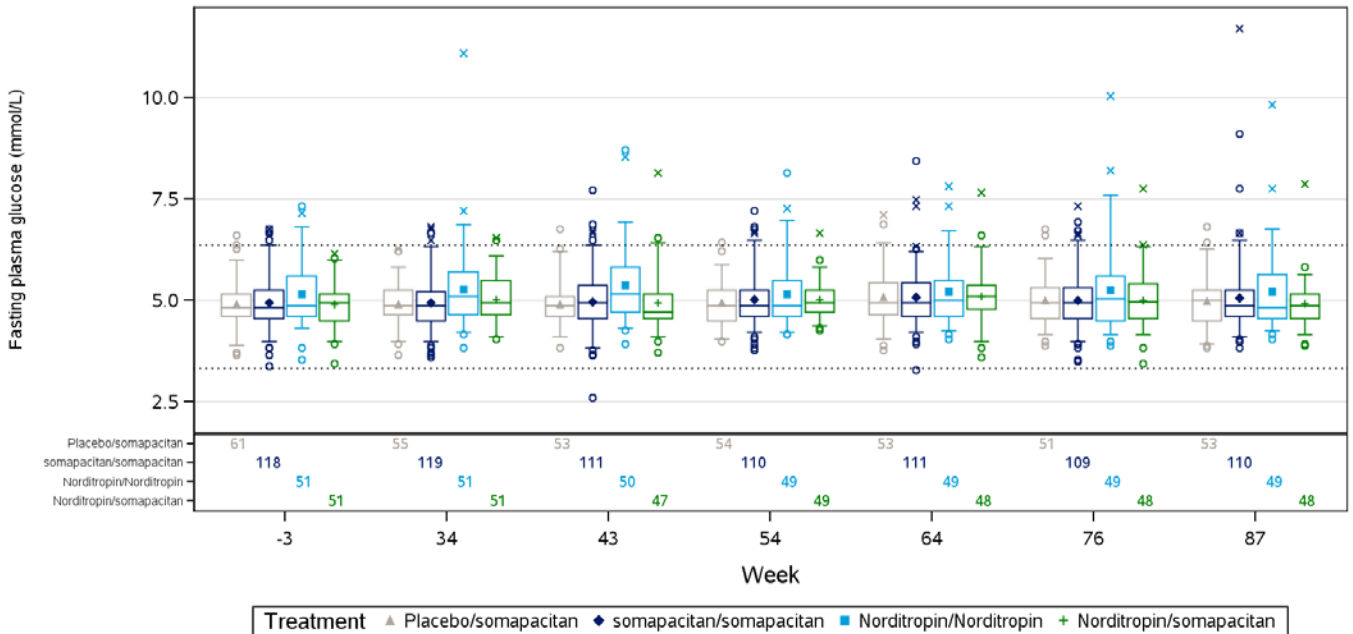
Outliers non-diabetic at baseline (circles) and diabetic at baseline (x).

Number of subjects contributing to the data points appear in the bottom panel

Normal range (mmol/L): 3.33-6.38).

Source : SCS, Fig 3-1, p. 111

Figure 20: Mean HbA1c (%) in AGHD patients (trial 4054)



Mean (triangle, square, plus and diamond); median (centre line); 25th and 75th percentiles (box); 5th and 95th percentiles (whiskers).

Outliers non-diabetic at baseline (circles) and diabetic at baseline (x).

Number of subjects contributing to the data points appear in the bottom panel

Normal range (%):F age 18-125 [4 - 6], M age 18-125 [4 - 6].

Source : SCS, Fig 3-2, p. 112

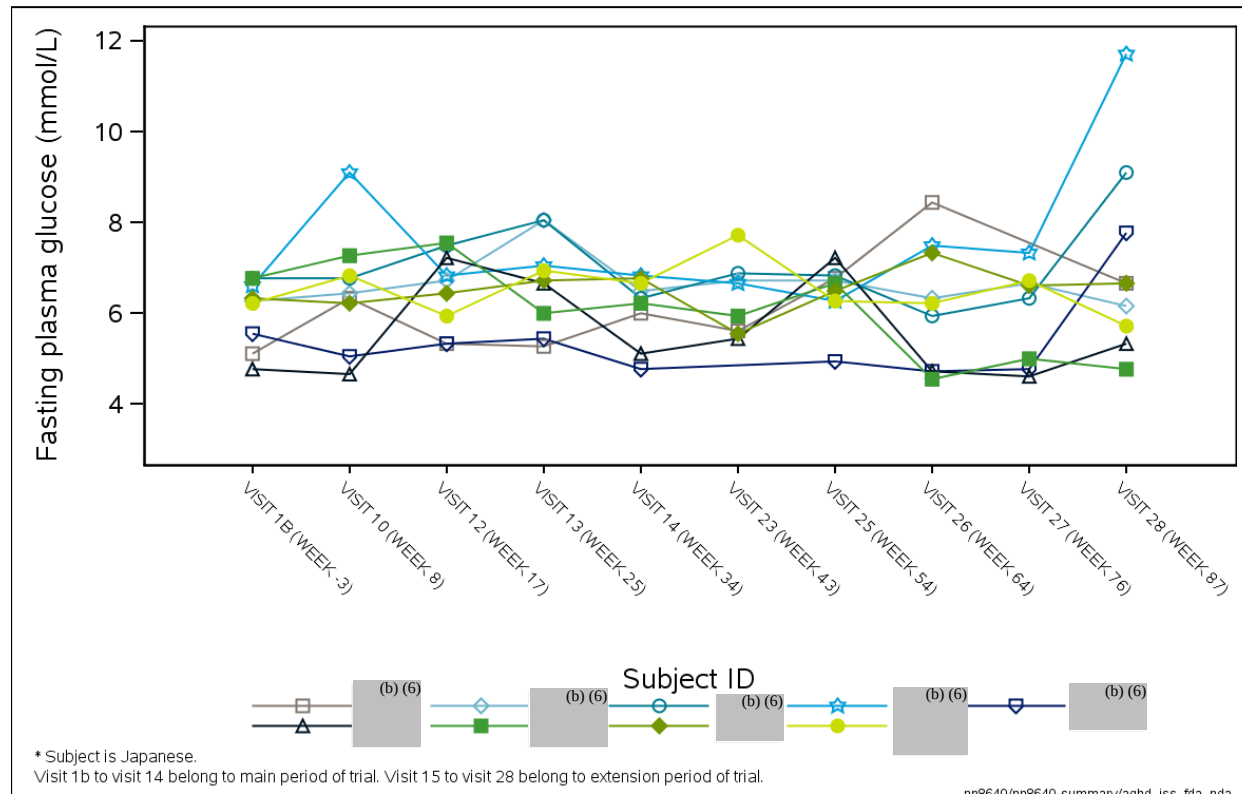
Also, the mean fasting insulin levels were within reference ranges in all groups through the entire duration of trial.

In trial 4054, 12 patients had a diagnosis of diabetes at baseline, based on fasting plasma glucose ≥ 7.0 mmol/L and/or HbA1c $\geq 6.5\%$ (somapacitan/somapacitan: 5 patients; Norditropin/Norditropin: 3 patients; Norditropin/somapacitan: 2 patients; placebo: 2 patients), which are consistent with the American Diabetes Association (ADA) criteria for diagnosis of diabetes.³⁸

In total there were 9 patients in somapacitan/somapacitan group and 6 patients in the Norditropin/Norditropin (including Norditropin/-) group who had one or more visits with either fasting glucose ≥ 7.0 mmol/L and/or HbA1c $\geq 6.5\%$ throughout the trial, compared to 2 patients in the placebo group (Figure 21 and Figure 22)

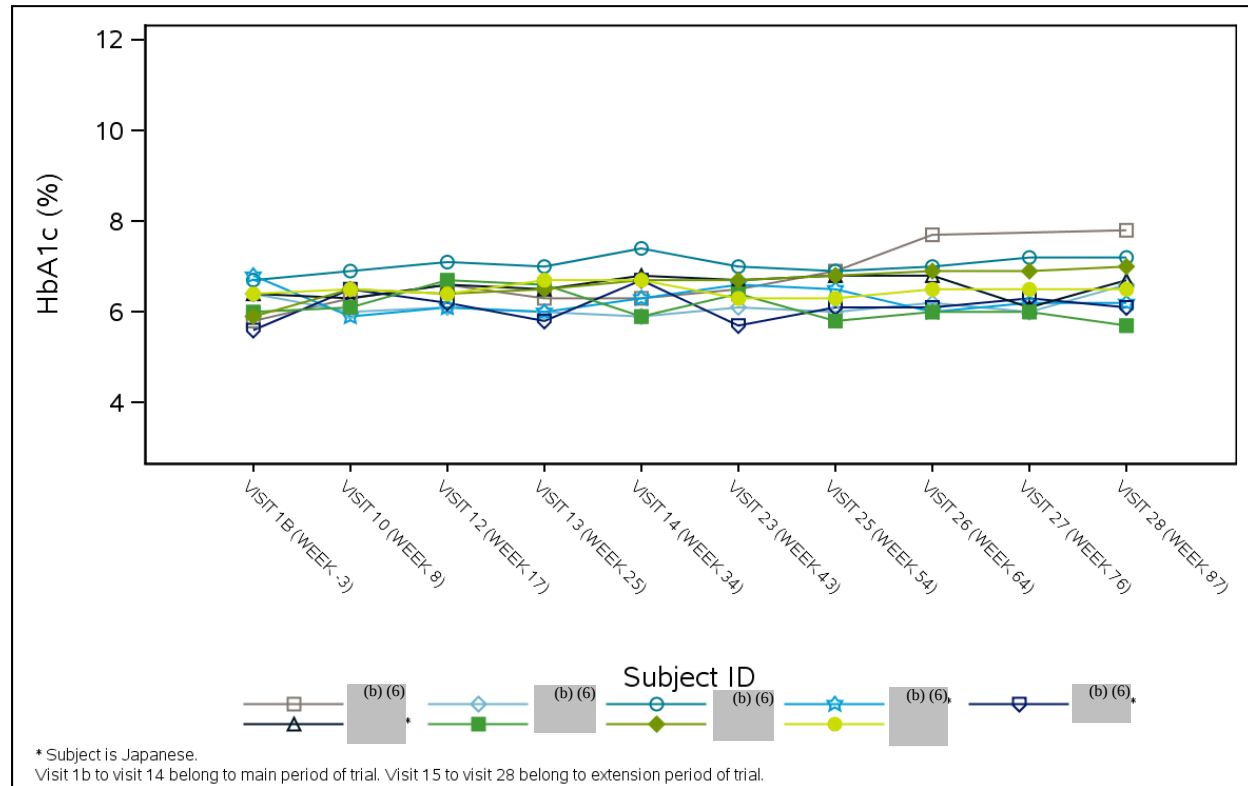
³⁸ Chamberlain JJ, et al. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med. 2016; 164: 542-552.

Figure 21: Patients with fasting plasma glucose ≥ 7.0 mmol/L during trial 4054 – somapacitan/somapacitan arm



Source: SCS, Fig 3-4, p. 115

Figure 22: Patients with HbA1c (%) $\geq 6.5\%$ during trial 4054 – somapacitan/somapacitan arm



Source: SCS, Fig 3-5, p. 116

The majority of patients with increased fasting plasma glucose values also had increased Hba1c and fasting insulin levels.

There were no new patients diagnosed with diabetes after exposure to somapacitan during the main phase of trial 4054, while 1 patient (subject (b) (6)) in somapacitan/somapacitan arm was diagnosed with diabetes in the extension phase (study day 457), with max HbA1c at 7.8%. There were 2 new patients in Norditropin arm who were diagnosed with diabetes in the main phase of trial 4054.

Three (3) patients discontinued study drug due to hyperglycemia, 2 patients in Norditropin arm (1 patients with diabetes at baseline, and 1 patient with newly diagnosed diabetes) and 1 patient in somapacitan arm (extension phase, see above), all events being considered non-serious, mild, or moderate in severity.

Trials 4043 and 4244

No clinically relevant changes from baseline in fasting plasma glucose and HbA1c levels were noted in trials 4043 and 4244 in either treatment arm (somapacitan or Norditropin). No new cases of diabetes following somapacitan exposure were reported in trials 4043 and 4244, while 1 patient in trial 4244 developed diabetes while on Norditropin therapy, and discontinued the study drug, according to the protocol.

Clinical pharmacology trials

There were no clinically relevant changes in glucose metabolism parameters observed in trials 3915 and 4237 in healthy subjects, while in trial 3947 (dose finding trial) in AGHD patients more frequent high mean fasting insulin values were observed in somapacitan 0.12mg/kg group.

In trial 4297 (renal impairment), changes in fasting plasma glucose and serum insulin were observed in some subjects across various renal function groups, most likely due to pre-existing conditions of type 1 and type 2 diabetes, or BMI and age which could predispose to some degree of insulin resistance.

In trial 4298 (hepatic impairment), observed changes in serum and insulin parameters occurred in patients with pre-existing conditions of glucose intolerance or type 2 diabetes.

Medical officer's comments: Overall, the mean fasting plasma glucose and HbA1c levels were stable throughout the trials, without significant glucose excursions noted, while the abnormalities in glucose levels and the number of patients with newly diagnosed diabetes were low and similar among the active treatment arms during the phase 3 trials. No significant glucose excursions were noted in the 12 patients with a history of diabetes at baseline either. No SAEs, or symptomatic manifestations of hyperglycemia were reported. Three patients discontinued the study drug (2 in Norditropin arm and 1 in somapacitan arm) as a result of hyperglycemia.

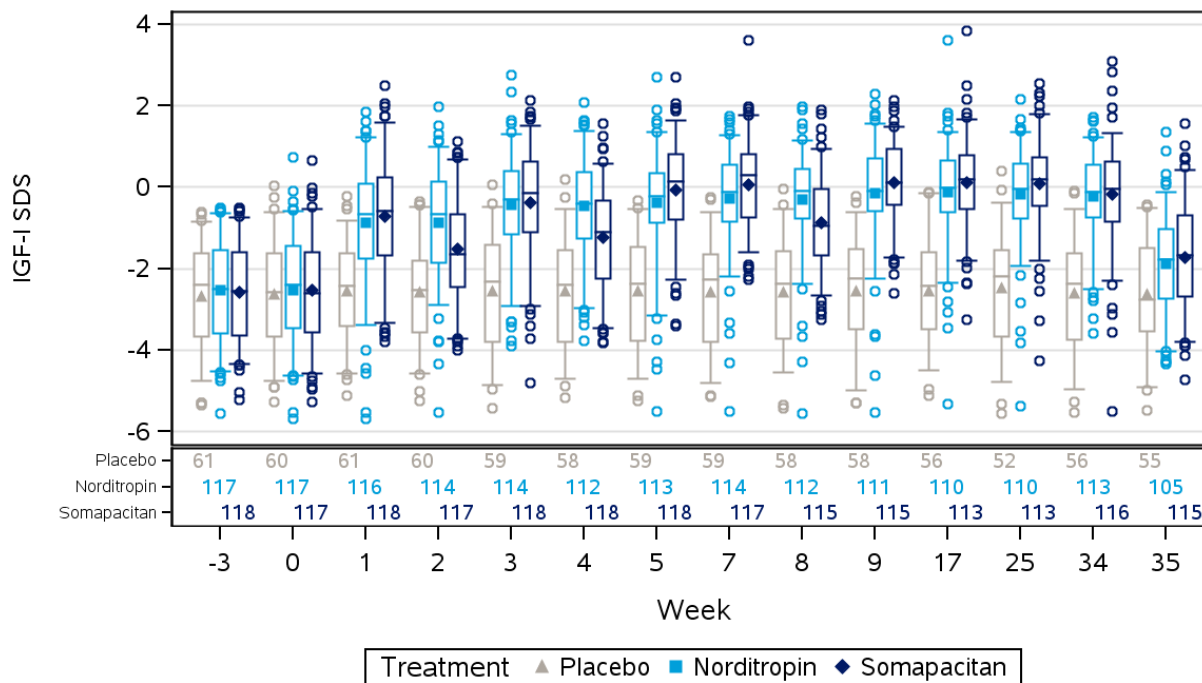
IGF-1

IGF-1 levels above normal ranges for a prolonged period of time are a potential safety concern and for that reason, individual dose titration protocols were instituted during the phase 3 trials (4054, 4043 and 4244) (see Sections 6.1.1 and 6.1.2 above, for details).

Trial 4054 (main + extension)

A mean IGF-1 SDS within the mean reference range ($-2 \leq \text{SDS} \leq +2$) was achieved throughout the 86 weeks of the trial (target IGF-1 SDS was $-0.5 < \text{IGF-1 SDS} \leq 1.75$), with similar IGF-1 SDS for somapacitan and Norditropin (Figure 23 and Figure 24).

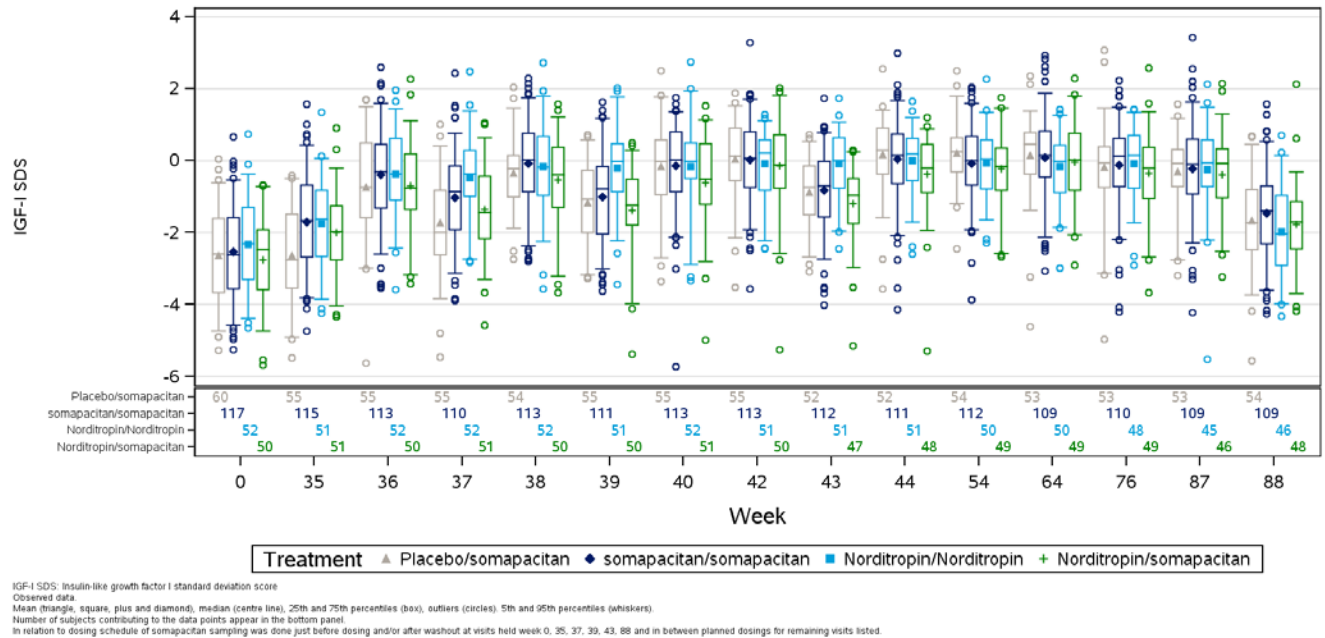
Figure 23: Box plot of IGF-1 SDS by visit during trial 4054 – main phase (FAS)



In relation to dosing schedule of somapacitan sampling done at visit 2, 4, 6, 10 and 15 just before dosing, at visit 3, 5, 7, 9, 11, 12, 13 and 14 in between planned dosings IGF-I: Insulin-like growth factor - I. Observed data, Legend: Mean (triangle, square and diamond), median (centre line), 25th and 75th percentiles (box), outliers (circles), 5th and 95th percentiles (whiskers). Number of subjects contributing to the data points appear in the bottom panel.

Source: Study 4054 main phase, Figure 14.2.61, p. 322

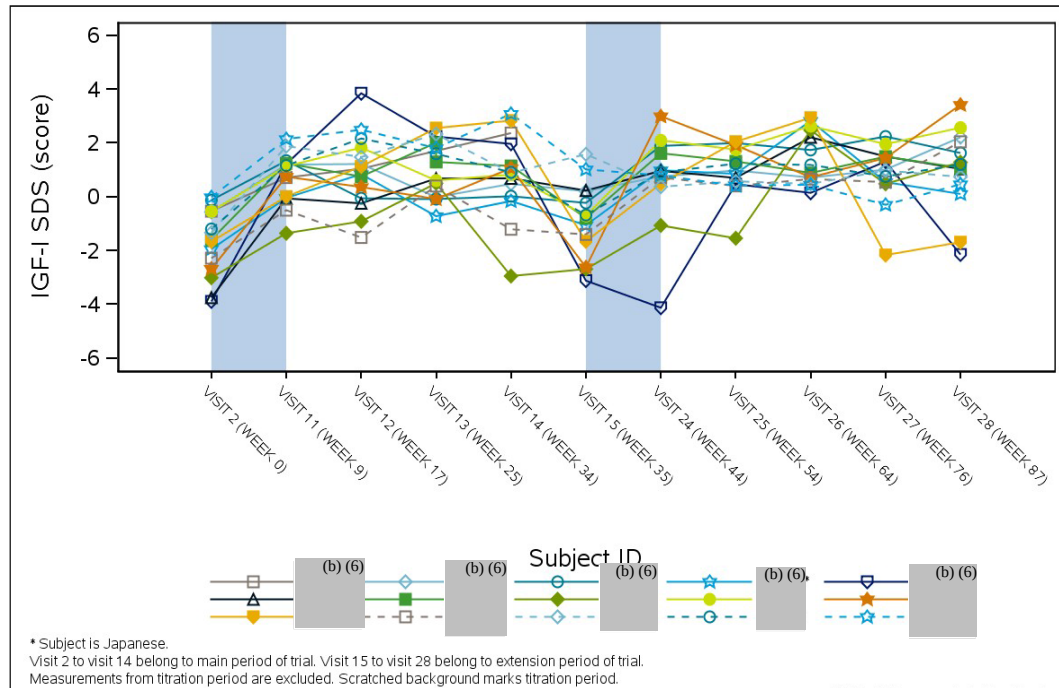
Figure 24: Box plot of IGF-1 SDS by visit during trial 4054 – extension phase (FAS)



Source: Study 4054 extension phase, Figure 11-1, p. 135

Fifteen patients in somapacitan/somapacitan arm had IGF-1 SDS above +2 during the fixed dose periods in trial 4054 (main + extension), with 5 patients having at least 2 IGF-1 SDS above 2+. However, most of these patients had IGF-1 SDS just slightly higher than upper limit of +2 (Figure 25).

Figure 25: Patients with IGF-1 SDS above +2 during fixed dose periods during trial 4054 in somapacitan/somapacitan arm.



Source: SCS, Figure 3-8, page 121

To further evaluate if the temporarily elevated IGF-1 levels were associated with adverse events, the AEs reported in the 5 patients with at least 2 IGF-1 SDS above 2+ were reviewed in detail.

Subject (b) (6) experienced UTI (study day 109), while the elevated IGF-1 SDS were reported at a later time during study period (week 44 and 87, respectively), thus making the relationship between the AE and elevated IGF-1 unlikely.

Subject (b) (6) was diagnosed with mild CPK elevation on study day 71 (lasted for 11 days) and study day 237 (lasted for 301 days). The elevated IGF-1 SDS were documented at week 17 (approx. study day 120), and week 34 (approx. study day 238), which then decreased to below normal reference range (during wash out period), then returned to normal during the extension phase. Of note, the second event of elevated CPK persisted when IGF-1 SDS declined to lower

than normal ranges during the wash-out period, suggesting an unlikely relationship between the AE and elevated IGF-1 level.

Subject (b) (6) was diagnosed with back pain and foot fracture on study day 176 and study day 181, respectively, when IGF-1 SDS was within normal ranges, thus making the relationship between the AEs and elevated IGF-1 unlikely.

Subject (b) (6) had multiple events of headache, spanning over the study days 74 to 115, and 211 to 220, while the elevated IGF-1 SDS was noted on study day 448 and 609, respectively, thus making the relationship between the AEs and elevated IGF-1 unlikely.

Subject (b) (6) was diagnosed with arthralgia on study day 51, lipohypertrophy on study day 193 (duration 68 days), and hypertension (HTN) on study day 475 (duration 127 days), while the IGF-1 SDS was noted on study days 175, 238, and 448, respectively. The IGF-1 SDS had normalized at study day 532. There is a temporal relationship noted between the events of lipohypertrophy and HTN, and the elevated IGF-1, therefore, a causal relationship between the events of lipohypertrophy and HTN, and IGF-1 elevation cannot be excluded.

There were no dose reductions associated with any of the aforementioned AEs in the 5 subjects described above.

Trial 4043

There were no patients with IGF-I SDS above +2 during the fixed dose treatment period.

Trial 4244

IGF-1 SDS above +2 was noted in 2 patients during fixed dose period of the trial, with only one occurrence in each patient. No AEs were reported in these patients at the time of the IGF-1 elevation.

Clinical pharmacology trials

According to the Applicant, no new safety issues were observed following somapacitan exposure of 117 healthy subjects (trials 3915, 4237, 4297 and 4298), 29 subjects with renal impairment (trial 4297), 18 subjects with hepatic impairment (trial 4298) or 26 AGHD patients (trial 3947).

Medical officer's comments: Overall, the peak IGF-1 levels temporarily above normal ranges were not associated with any safety issues, was of short duration and returned to normal with dose adjustments.

Other hematology and biochemistry parameters

Hemoglobin and hematocrit

Trial 4054 (main + extension)

No clinically significant changes in mean hemoglobin and hematocrit levels from baseline to end of main (week 34) and extension (week 87) trial period, respectively, were noted in any treatment group.

The number of patients who shifted from normal to high hemoglobin levels from baseline to end of main trial period (week 34) per treatment group are as follows: somapacitan: 4 (3.3 %) patients; placebo: 0 patients; Norditropin 4 (3.4%) patients.

The number of patients who shifted from normal to high hemoglobin levels from baseline to end of trial period (week 87) per treatment group are as follows: placebo/somapacitan: 2 (3.3%) patients; somapacitan/somapacitan: 7 (5.8%) patients; Norditropin/somapacitan: 2 (3.9%) patients; Norditropin/Norditropin: no patients; Norditropin/-: no patients.

The number of patients who shifted from normal to high hematocrit levels from baseline to end of main trial period (week 34) per treatment group are as follows: somapacitan: 6 (5.0 %) patients; placebo: 0 patients; Norditropin 4 (3.4%) patients.

The number of patients who shifted from normal to high hematocrit levels from baseline to end of trial period (week 87) per treatment group are as follows: placebo/somapacitan: 2 (3.3%) patients; somapacitan/somapacitan: 6 (5.0%) patients; Norditropin/somapacitan: 3 (5.9%) patients; Norditropin/Norditropin: no patients; Norditropin/-: no patients.

Trials 4043 and 4244

In the active controlled supportive trials no clinically relevant changes in the hematology parameters were observed from baseline to end of the trial in either of treatment arms.

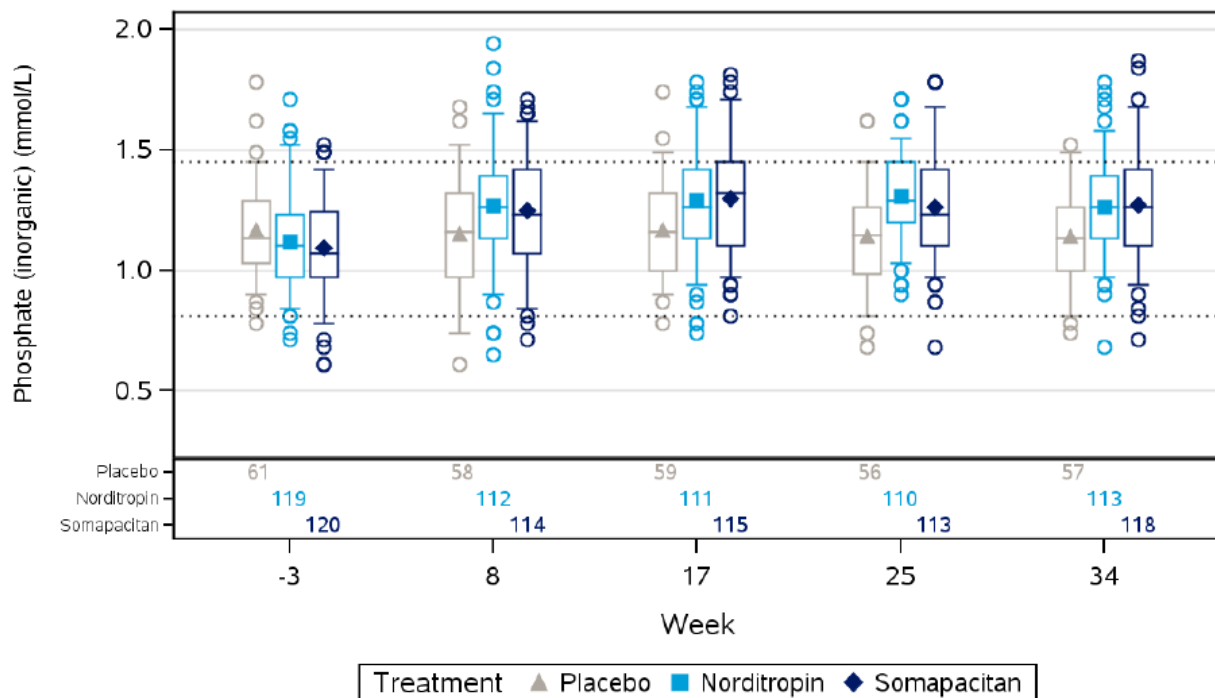
Medical officer's comments: There were no clinically meaningful changes in any of the hematology parameters. The overall number of patients with elevated hemoglobin and hematocrit levels is small and elevation in hemoglobin and hematocrit were noted to occur intermittently throughout the trial period, with no gradual increase pattern.

Phosphate

Trial 4054 (main + extension)

Mean phosphate levels were noted to be increased within reference ranges in somapacitan and Norditropin groups compared to baseline and placebo groups in the main phase of trial 4054 (Figure 26). The same pattern was observed in the extension phase of the trial.

Figure 26: Mean phosphate (inorganic) by visit trial 4054, main phase



Observed data, Legend: Mean (triangle, square and diamond), median (centre line), 25th and 75th percentiles (box), outliers (circles). 5th and 95th percentiles (whiskers). Number of subjects contributing to the data points appear in the bottom panel. Normal range (mmol/L): F age 18-125 [0.81 ; 1.45], M age 18-125 [0.81 ; 1.45].

Source: Figure 12-5, CSR trial 4054 (main), p. 167

Of note, a higher percentage of patients shifted from normal to elevated phosphate levels in the somapacitan group compared to Norditropin and placebo groups [somapacitan: 21 (17.5%) patients; placebo : 3 (4.9%) patients; Norditropin: 8 (6.7%) patients] from baseline to end of the main trial period. Similarly, the number of patients with at least 1 elevated phosphate value during main phase of trial 4054 was higher in somapacitan group (35%), compared to

Norditropin (27%), and placebo (8.2%), respectively. The changes in the phosphate levels were not associated, in general, with changes in calcium levels.

At the end of trial 4054, the number of patients who shifted from normal to high phosphate levels from baseline to end of trial period (week 87) per treatment group are as follows: placebo/somapacitan: 8 (13.1%) patients; somapacitan/somapacitan: 8 (6.7%) patients; Norditropin/somapacitan: 5 (9.8%) patients; Norditropin/Norditropin: no patients; Norditropin/-: no patients.

Amongst patients in somapacitan/somapacitan group, 7 (5.8%) patients shifted from normal to high phosphate levels from baseline to end of trial period (week 87), with 14 of the patients with elevated phosphate levels at end of main trial period (week 34) having normal phosphate levels by the end of the extension phase period of the trial.

The phosphate elevation was noted to occur on an intermittent basis in most of the patients, with 10 (8.3%) patients in the somapacitan/somapacitan group having elevated phosphate levels more than 50% of the times being tested.

Trials 4043 and 4244

A similar trend with intermittently mild phosphate levels elevation was noted in both active controlled studies.

The number of patients who shifted from normal to high phosphate levels from baseline to end of trial 4043 per treatment group are as follows: somapacitan: 5 (8.2%) patients; Norditropin 1 (3.2%) patients. The shift tables for trial 4244 were not provided by the Applicant.

Medical officer's comments: Although the elevation in phosphate levels is of unknown clinical significance, was mild, and occurred intermittently at the individual level through the duration of the trial period, there was a significant difference in the frequency of event occurrence between somapacitan group and placebo in the main phase of the pivotal trial 4054. Moreover, 8.3% patients in somapacitan group had phosphate elevation for > 50% of the time being tested. The similar findings were noted in the active controlled supportive studies, although the incidence of the event occurrence was lower. Although the noted changes were mild, and of no apparent clinical significance, it

should be considered as labeled event under Section 6.0 Adverse Reactions, for healthcare providers awareness.

Creatine phosphokinase

Trial 4054 (main + extension)

No clinically significant changes in mean creatine phosphokinase levels from baseline to end of main (week 34) and extension (week 87) trial period, respectively, were noted in any treatment group.

The number of patients who shifted from normal to high creatine phosphokinase levels from baseline to end of main trial period (week 34) per treatment group are as follows: somapacitan: 11 (9.2%) patients; placebo 4 (6.6%) patients; Norditropin 6 (5.0%) patients.

The number of patients who shifted from normal to high creatine phosphokinase levels from baseline to end of trial period (week 87) per treatment group are as follows: placebo/somapacitan: 7 (11.5%) patients; somapacitan/somapacitan: 11 (9.2%) patients; Norditropin/somapacitan: 4 (7.8%) patients; Norditropin/Norditropin: 2 (3.8%) patients; Norditropin/-: no patients.

Trials 4043 and 4244

The mean (SD) change from baseline in creatine phosphokinase level to end of trial period in trial 4043 was as follows: somapacitan 67.2 (699.4)U/L; Norditropin: -23.4 (157.5) U/L, with the mean (SD) change from baseline to end of trial period in somapacitan group shifting from normal [178.2 (215.0) U/L] to above normal [246.3 (713.1) U/L] [upper normal range 169 U/L (females) and 207 U/L (males)].

The number of patients who shifted from normal to high creatine phosphokinase levels from baseline to end of trial 4043 are as follows: somapacitan: 4 (6.6%), Norditropin 3 (9.7%). The shift tables for trial 4244 were not provided by the Applicant.

Medical officer's comments: Although elevation in creatine phosphokinase is of unknown clinical significance and was noted on an intermittent basis at the individual level, with no increasing trend at the individual subject level in all studies, overall, the frequency of the event was higher in somapacitan treated patients, compared to placebo, and Norditropin arms in the pivotal trial 4054. Creatine phosphokinase increase was also an observed AE, discussed in Section 8.4.5, above. As a result, elevated creatine

phosphokinase levels should be considered as a labeled AE, under Section 6.0, Adverse Reactions, for healthcare providers awareness.

Alkaline phosphatase

Trial 4054 (main + extension)

No clinically significant changes in mean alkaline phosphatase levels from baseline to end of main (week 34) and extension (week 87) trial period, respectively, were noted in any treatment group.

The number of patients who shifted from normal to high alkaline phosphatase levels from baseline to end of main trial period (week 34) per treatment group are as follows: somapacitan: 6 (5.0 %) patients; placebo 2 (3.3%) patients; Norditropin 12 (10.1%) patients.

The number of patients who shifted from normal to high alkaline phosphatase levels from baseline to end of trial period (week 87) per treatment group are as follows:
placebo/somapacitan: 6 (9.8%) patients; somapacitan/somapacitan: 3 (2.5%) patients;
Norditropin/somapacitan: 2 (3.9%) patients; Norditropin/Norditropin: 1 (1.9%) patients;
Norditropin/-: no patients.

“Blood alkaline phosphatase increased” was reported as an AE in 2 (0.6%) patients in trial 4054 in somapacitan group, with no reported events in the placebo, or Norditropin groups.

Trials 4043 and 4244

No clinically significant changes in mean alkaline phosphatase levels and shift tables from baseline to end of the trials period were noted.

Medical officer’s comments: The shift from normal to abnormal values in alkaline phosphatase occurred in only few patients in trial 4054, the changes were small, and not clinically relevant.

There were no clinically meaningful changes in any other biochemistry parameters assessed. Laboratory values outside reference range were observed at one or more time points during the trial, with no clear pattern, or trend, across all treatment groups.

Analysis focused on outliers or shifts from normal to abnormal did not raise any other safety concerns.

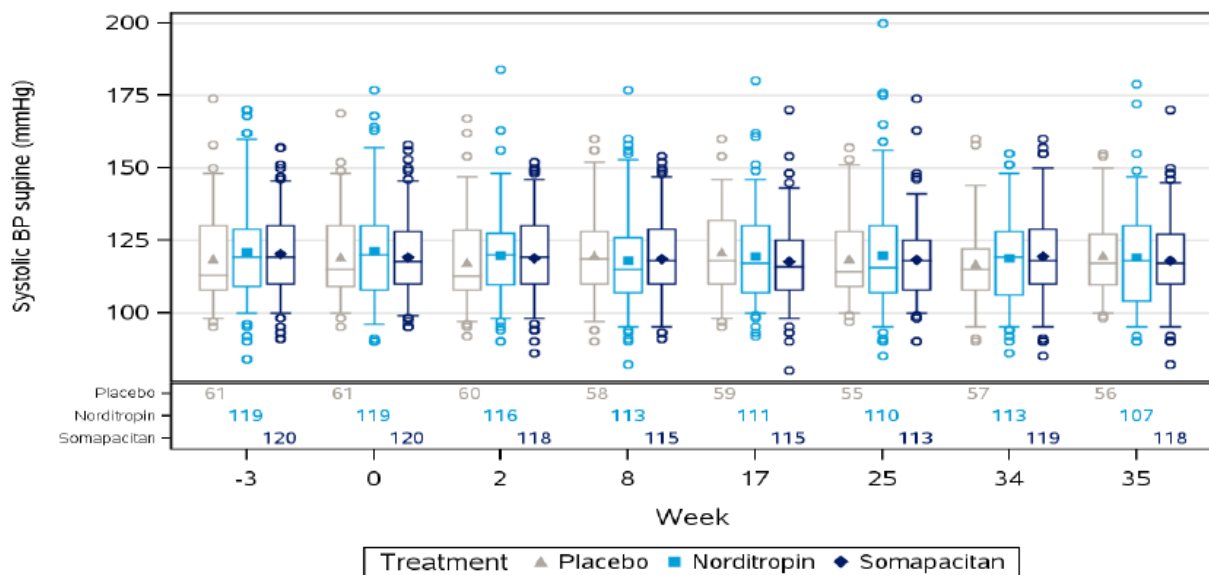
No other clinically relevant changes in other biochemistry parameters were observed in trials 4054, 4043 and 4244, respectively.

8.4.7. Vital Signs

Vital signs

There were no changes in blood pressure (BP) or pulse from baseline to end of main trial period in any study groups (see Figure 27 and Figure 28 below for systolic and diastolic BP changes).

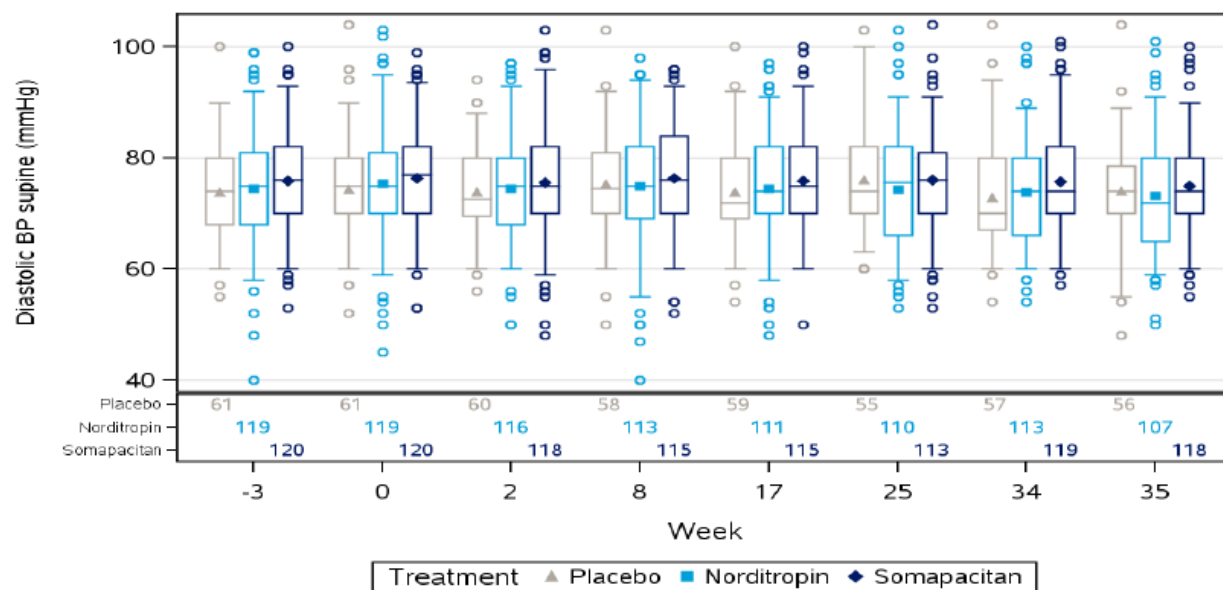
Figure 27: Systolic blood pressure (mmHg) by visit – main phase trial 4054



Observed data, Legend: Mean (triangle, square and diamond), median (centre line), 25th and 75th percentiles (box), outliers (circles), 5th and 95th percentiles (whiskers). Number of subjects contributing to the data points appear in the bottom panel.

Source: Figure 12-6, SCS, p.168

Figure 28: Diastolic blood pressure (mmHg) by visit – main phase trial 4054



Source: Figure 12-7, SCS, p.168

The mean (SD) changes from baseline in systolic and diastolic BP in all 3 phase 3 trials are summarized in Table 43.

Table 43: Changes from baseline in systolic and diastolic BP (mmHg) in the phase 3 clinical trials

Trial ID	Trial duration	somapacitan		Norditropin®	
	Weeks	Change in systolic	Change in diastolic	Change in systolic	Change in diastolic
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Trial 4054 ^a	86	0.45 (13.01)	-0.85 (9.21)	-1.35 (13.07)	-0.61 (8.71)
Trial 4043	26	-1.70 (13.69)	0.08 (9.84)	0.79 (13.77)	2.21 (8.99)
Trial 4244	52	-3.3 (11.7)	0.9 (8.7)	-3.1 (14.8)	1.1 (9.7)

^a Means (SD) are for the somapacitan/somapacitan and the Norditropin®/Norditropin® groups.

Source: Table 4-1, SCS, p. 124.

The changes in the mean systolic and diastolic blood pressure from baseline to end of individual trial periods were minor and not clinically relevant. The observed wide SD reflects the natural

variations in BP in response to stress, activity level, etc.

Body weight

Please see detailed assessment for body weight during main phase of trial 4054 in Section 6.1.2, where it was evaluated as secondary efficacy endpoint.

The changes from baseline in mean body weight in other phase 3 trials were minimal and not clinically relevant, with the largest change in mean body weight observed after 87 weeks of exposure to somapacitan in trial 4054, of 1.5 kg (see Table 44 for details).

Table 44: Changes from baseline in body weight (kg) in phase 3 clinical trials

Trial ID	Trial duration	somapacitan	Norditropin [®]
	Weeks	Mean (SD)	Mean (SD)
Trial 4054	88	1.5 (4.8)	0.0 (5.2)
Trial 4043	26	0.38 (3.14)	-0.62 (2.17)
Trial 4244	52	-0.29 (3.49)	0.66 (2.50)

^a Means (SD) are for the somapacitan/somapacitan and the Norditropin[®]/Norditropin[®] groups.

Source: Table 4-2, SCS, p. 125

The AEs concerning weight increase were addressed in Section 8.4.5.

8.4.8. Electrocardiograms (ECGs)

Trial 4054 (main+ extension)

ECG were performed at the following timepoint during trial: week -3, week 25, week 35, week 64 and week 88. The majority of the ECGs were classified as normal or abnormal not clinically significant by the investigators. Nine (9) patients had their ECGs evaluated as abnormal clinically significant by the investigator at one or more timepoints during the trial (somapacitan/somapacitan: 4 patients; placebo/somapacitan: 2 patients (1 patient while on placebo and 1 patient also when exposed to somapacitan); Norditropin/somapacitan: 1 patient (while on somapacitan); Norditropin/Norditropin: 2 patients).

The rate of AEs that may indicate potential arrhythmic effects (ECG-related AEs) did not differ between somapacitan, placebo, or Norditropin (Table 45). In total, AEs were reported in 9 (4.0%) patients in somapacitan group, 6 (5.0% patients in Norditropin group and 2 (3.3%) patients in placebo group. These AEs included 1 case of ventricular extrasystoles, 1 case of QTc prolongation and 1 case of ventricular fibrillation in the somapacitan group.

Table 45: ECG-related AEs in trial 4054

MedDRA SOC Preferred Term	Somapacitan		Placebo		Norditropin	
	N	%	N	%	N	%
All	9	4.0	2	3.3	6	3.3
Tachycardia	3	1.3	0		0	
Atrioventricular block first degree	2	0.9	0		0	
Bradycardia	0		0		1	0.8
Bundle branch block right	0		0		1	0.8
Sinus arrhythmia	0		1	1.6	0	
Ventricular extrasystoles	1	0.4	0		0	
Ventricular fibrillation	1	0.4	0		0	
Cardiac murmur	1	0.4	0		0	
ECG PR prolongation	0		0		1	0.8
ECG QT prolongation	1	0.4	0		0	
ECG T wave abnormal	0		1	1.6	0	
ECG T wave inversion	0		0		1	0.8
ECG abnormal	1	0.4	0		0	
Heart rate increased	0		0		1	0.8

N: Number of subjects having the given event, or an event in the given system organ class at least once; %: Percentage of exposed subjects having the event

Source: Appendix 7.1, Table 175, SCS, modified

The event of ventricular extrasystoles (subject (b) (6)) was reported in a 50 year old male enrolled in somapacitan/somapacitan arm, and occurred on trial day 331 during the extension phase. The event duration was 12 days, was rated as SAE of moderate severity, the study drug dose was not changed as a result of the event, and the event was listed as recovered.

The event of ECG QT prolonged (subject (b) (6)) was reported in a 35 year old female enrolled in somapacitan/somapacitan arm, and occurred on trial day 615 during the extension phase. The event duration was 7 days, was rated as mild and recovered.

The event of ventricular fibrillation (subject (b) (6)) was reported in a 66 year old male enrolled in placebo/somapacitan arm, and occurred on trial day 363 during extension phase, while on somapacitan therapy. The event duration was 12 days, was rated as SAE and severe,

and the study drug was discontinued as a result of the event. The causality between the study drug and the event was assessed as unlikely by the investigator. A detailed case narrative can be found in Section 8.4.1.

Trials 4043 and 4244

There were no ECG-related AEs reported in trial 4043 and 4244.

Clinical pharmacology trials

No clinically relevant changes in ECG were observed following somapacitan exposure in 117 healthy subjects, 29 renal and 18 hepatic impaired subjects, as well as 26 AGHD patients in the clinical pharmacology trials.

Medical officer's comments: Overall, there were no clinically relevant changes in ECG observed in healthy, hepatic, or renal impaired subjects, as well as AGHD patients in the clinical development program. The rate of ECG-related AEs in the placebo-controlled phase 3 trial was similar amongst treatment groups, occurred with a very low incidence and were unlikely to be related to the study drug.

8.4.9. QT

A dedicated QT study was not performed by the Applicant during the clinical development program. According to ICH E14, large targeted proteins (i.e. somapacitan) “have a low likelihood of direct ion channel interactions and a thorough OQ/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or non-clinical studies”.³⁹

The potential effect of somapacitan on cardiac repolarization was assessed based on ECGs collected in the phase 3 trial 4054 at the expected C_{max} for somapacitan, according to agreement correspondence between the Applicant and the Agency via e-mail on 04/23/2015. The ECGs were collected at baseline and close to the expected time of C_{max} for somapacitan (C_{max} defined as 16-32 hours after last dose) at different timepoints [at the screening visit 1B, at visit 13 (week 25) and at the wash-out visit 15 (week 35); and in the extension part at visit 26 (week 64) and at the follow-up visit 29 (week 88)] during the treatment period in accordance with ‘ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs.

³⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqt-c-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-1>

A QT-IRT consult was obtained to review the Applicant's ECG data (see review in DARRTS, dated 09/05/2019). The QT-IRT review team evaluated data from the phase-3 study 4054 and noted that the mean somapacitan dose was much lower than the maximal allowed dose of 8 mg (main phase average dose: 2.5 mg/week or 0.037 mg/kg/week and extension phase average dose: 2.3 mg/week or 0.034 mg/kg/week). They noted that the peak concentrations observed (4.9 ng/mL) were much lower than those anticipated (142.4 ng/mL) with maximum therapeutic dose (8 mg), and that at these lower somapacitan exposures, there were no large increases in the QTc interval. According to QT-IRT team, none of the patients in the somapacitan group had QTc > 480 ms or a change from baseline >60 ms. Of note, 15 subjects (12.5%) in somapacitan group had ECG assessments not done on time of Cmax, however, these protocol should not impact the interpretability of the results, since majority of patients in somapacitan group (> 100 subjects) had the ECG assessments within the appropriate timeframe. There was no formal recommendation for labeling as a result of the IRT consult.

8.4.10. Immunogenicity

According to Clin-Pharm review (see Dr. Absar's review in DARRTS, dated 05/04/2020), no anti-somapacitan antibodies were detected after treatment with somapacitan in healthy adults or AGHD patients in the five clinical pharmacology studies or the three phase 3 studies.

8.5. Analysis of Submission-Specific Safety Issues

Table 46 lists the medical events of special interest (MESI) defined by the Applicant based on the adverse drug reactions (ADRs) observed in clinical trials or publications, as well as the safety profile of the growth hormone drugs class.

Table 46: Medical Events of Special Interest

Safety areas assessed (by SOC and PT)	Reason for inclusion (e.g. class effect; competitor label; observed in trials)	MedDRA search term (SOC; SMQ)
Endocrine disorders		
Hypothyroidism	Class effect	SMQ Hypothyroidism
Adrenocortical insufficiency	Class effect	HLT Adrenal cortical hypofunctions
Gastrointestinal disorders		
Pancreatitis	Class effect	SMQ Acute pancreatitis
Generalized disorders		
Peripheral edema	Class effect	PT Edema peripheral PT Peripheral swelling
Fatigue/Asthenia	somapacitan trials ^a	HLT Asthenic conditions
Weight increased	Class effect	PT Weight increased
Immune system disorders		
Allergic reactions (non- anaphylactic reactions)	Class effect	SMQ Hypersensitivity
Hypersensitivity (Anaphylactic reactions)	Class effect	SMQ Anaphylactic reaction
Injury, procedural and adm. site conditions		
Injection site reactions	Class effect	HLT Injection site reactions
Lipohypertrophy	somapacitan trials ^a	PT Lipohypertrophy PT Injection site hypertrophy
Lipoatrophy	Class effect somapacitan trials ^a	PT Lipodystrophy acquired PT Lipoatrophy PT Injection site atrophy PT Fat tissue decreased
Investigations		
Blood alkaline phosphatase	Class effect	PT Blood alkaline phosphatase increased
increased (bone)	somapacitan trials ^a	HLT Immunology analyses NEC
Drug specific antibodies present		

Abbreviations: HLT = high level term; PT = preferred term; SOC = system organ class; SMQ = standard MedDRA queries; USPI = US Package Insert.

^asomapacitan trials includes all completed clinical trials in adults and children.

Source. Applicant's Table 1-2, Summary of clinical safety

Table 46: Medical Events of Special Interest (cont.)

Safety areas assessed (by SOC and PT)	Reason for inclusion (e.g. class effect; competitor label; observed in trials)	MedDRA search term (SOC; SMQ)
Metabolism disorders		
Hyperglycemia	Class effect	HLT Hyperglycemic conditions NEC
Type 2 diabetes	Class effect	HLT Carbohydrate tolerance analyses (inch diabetes) SMQ Hyperglycemia/new onset diabetes mellitus PT Blood insulin increased
Musculo-skeletal disorders		
Arthralgia	Class effect	PT Arthralgia
Myalgia	Class effect	PT Myalgia
Neoplasms		
Benign neoplasms	Class effect	SOC Neoplasms benign, malignant and unspecified (including cysts and polyps)
Nervous system disorders		
Headache	Class effect	HLT Headaches NEC
Paresthesia	Class effect	PT Paresthesia
Stroke	Publications	SMQ Central nervous system vascular disorders
Carpal tunnel syndrome	Class effect	PT Carpal tunnel syndrome
Benign intracranial hypertension	Class effect	HLT Increased intracranial pressure disorders
Other	N/A (Health Authority requirement)	
Rare events		

Abbreviations: HLT = high level term; PT = preferred term; SOC = system organ class; SMQ = standard MedDRA queries; USPI = US Package Insert.

^asomapacitan trials includes all completed clinical trials in adults and children.

Source: Applicant's Table 1-2, Summary of clinical safety

All MESIs were further evaluated by this MO using the safety review approach outlined in Section 8.1 above. Table 47 summarizes the number of patients, frequency and number of events of each MESI observed, in order of frequency.

Table 47: Medical Events of Special Interest (trial 4054, Norditropin/somapacitan adjusted pool)

	Somapacitan			Norditropin			Placebo		
Preferred term	N	(%)	E	N	(%)	E	N	(%)	E
Headache									
4054 main	10	8.3		10	8.4		10	16.4	15
Norditropin/somapacitan adjusted pool	21	9.1	60	18	11.1	62			
4054 main + ext	32	14.2	94	15	12.6	73			
Allergic reactions (non-anaphylactic)									
4054 main	8	6.7	9	11	9.2	13	9	14.8	10
Norditropin/somapacitan adjusted pool	11	5.2	12	18	11.5	20			
4054 main + ext	24	10.6	30	14	11.8	18			
Arthralgia									
4054 main	8	6.7	8	10	8.4	10	1	1.6	1
Norditropin/somapacitan adjusted pool	16	7.0	17	14	8.2	14			
4054 main + ext	15	6.6	16	14	11.8	15			
Fatigue/Asthenia									
4054 main	5	4.2	5	9	5.8	9	4	6.6	4
Norditropin/somapacitan adjusted pool	18	7.4	20	17	10.7	17			
4054 main + ext	20	8.8	24	11	9.2	12			
Adrenal Insufficiency									
4054 main	4	3.3	4	2	1.7	2	1	1.6	1
Norditropin/somapacitan adjusted pool	6	2.9	6	2	1.1	2			
4054 main + ext	6	2.7	6	2	1.7	2			
Peripheral edema									
4054 main	4	3.3	6	9	5.8	11	1	1.6	1
Norditropin/somapacitan adjusted pool	5	2.7	7	8	4.4	11			
4054 main + ext	15	6.6	28	8	6.7	12			
Weight increased									
4054 main	4	3.3	4	1	0.8	1	0	0	0
Norditropin/somapacitan adjusted pool	7	3.3	7	2	1.3	2			
4054 main + ext	3	1.2	3	1	0.8	1			

Source: Table generated by this medical reviewer

Table 47: Medical Events of Special Interest (trial 4054, Norditropin/somapacitan adjusted pool) (cont.)

	Somapacitan			Norditropin			Placebo		
Preferred term	N	(%)	E	N	(%)	E	N	(%)	E
Lipohypertrophy/lipodistrophy									
4054 main	4	3.3	4	0	0		0	0	0
Norditropin/somapacitan adjusted pool	4	2.2	4	0	0	0			
4054 main + ext	5	2.2	5	0	0	0			
Paresthesia									
4054 main	3	2.5	4	1	0.8	1	2	3.3	2
Norditropin/somapacitan adjusted pool	4	2.0	5	1	0.5	1			
4054 main + ext	4	1.8	5	1	0.8	1			
Injection site reactions*									
4054 main	2	1.6	5	8	6.7	8	3	4.9	5
Norditropin/somapacitan adjusted pool	3	1.4	6	9	5.2	9			
4054 main + ext	4	1.8	8	8	6.7	8			
Myalgia									
4054 main	2	1.6	4	4	3.4	4	3	4.9	3
Norditropin/somapacitan adjusted pool	2	0.9	2	5	3.2	5			
4054 main + ext	6	2.7	8	6	5.0	6			
Hyperglycemia/Type 2 DM									
4054 main	1	0.8	1	4	3.4	6	0	0	0
Norditropin/somapacitan adjusted pool	2	0.9	2	4	2.4	7			
4054 main + ext	4	1.8	7	4	3.4	8			
Hypothyroidism									
4054 main	1	0.8	1	3	2.5	1	1	1.6	1
Norditropin/somapacitan adjusted pool	2	0.9	2	6	3.8	6			
4054 main + ext	1	0.4	1	5	4.2	5			
Carpal tunnel syndrome									
4054 main	0	0	0	0	0	0	0	0	0
Norditropin/somapacitan adjusted pool	1	0.4	1	0	0	0			
4054 main + ext	1	0.4	1	0	0	0	0	0	0

*Not all injection site reactions were reported as AEs; see Injection site reactions assessment below

Table 47: Medical Events of Special Interest (trial 4054, Norditropin/somapacitan adjusted pool) (cont.)

	Somapacitan			Norditropin			Placebo		
Preferred term	N	(%)	E	N	(%)	E	N	(%)	E
Neoplasms benign, malignant and unspec.									
4054 main	0	0		2	1.7	2	0	0	0
Norditropin/somapacitan adjusted pool	5	2.2	5	4	3.4	5			
4054 main + ext	5	2.2	5	4	3.4	5			
Intracranial hypertension									
4054 main	0	0	0	0	0	0	0	0	0
Norditropin/somapacitan adjusted pool	0	0	0	0	0	0			
4054 main + ext	0	0	0	0	0	0			
Pancreatitis									
4054 main	0	0	0	0	0		1	1.6	1
Norditropin/somapacitan adjusted pool	0	0	0	0	0	0			
4054 main + ext	0	0	0	0	0				
Severe hypersensitivity									
4054 main	0	0	0	0	0	0	0	0	0
Norditropin/somapacitan adjusted pool	0	0	0	0	0	0			
4054 main + ext	0	0	0	0	0	0			

*Not all injection site reactions were reported as AEs; see Injection site reactions assessment below

Source: Table generated by this medical reviewer

The ADRs of headache, allergic reactions (non-anaphylactic), fatigue/asthenia, injection site reactions, paresthesia, and myalgia occurred less frequently in the somapacitan group than placebo group in the pivotal trial 4054, as follows: 8.3% vs. 16.4%, 6.7% vs. 14.8%, 4.2% vs. 6.6%, 1.6% vs 4.9%, 2.5% vs. 3.3%, and 1.6 % vs. 4.9%, respectively. All these ADRs occurred with similar frequency in somapacitan and Norditropin groups, when observed amongst the 3 respective datasets (Table 47). Due to the lower observed frequency of these ADRs in somapacitan group compared to placebo, and no higher frequency compared to Norditropin, the safety profile of somapacitan with respect to these ADRs is reassuring, and therefore they were not further discussed in details below.

Injection site reactions

The Applicant reported only the injection site reactions considered as clinically significant based on Investigator's judgement as AEs, and included the preferred terms 'injection site bruising', 'injection site pain', 'injection site reaction' and 'injection site hematoma' (Table 48). A total of 18 injection site reactions (in 13 patients, 4.3%) were considered clinically significant and were thus reported as AEs.

Table 48: Injection site reactions reported as AEs by preferred term (trial 4054)

MedDRA SOC Preferred term	Placebo				Norditropin				Somapacitan				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Inj site bruising	3		5		8		8		2		5		13		18	
	2	(3.3)	3	7.5	6	(5.0)	6	7.7	1	(0.8)	1	1.3	9	(3.0)	10	5.1
Inj site pain	1	(1.6)	1	2.5	1	(0.8)	1	1.3	1	(0.8)	2	2.5	3	(1.0)	4	2.0
Inj site reaction	0				1	(0.8)	1	1.3	1	(0.8)	2	2.5	2	(0.7)	3	1.5
Inj site haematoma	1	(1.6)	1	2.5	0				0				1	(0.3)	1	0.5

N: number of subjects having the event at least once

R: event rate per 100 patient years; %: percentage of exposed subjects having the event

MedDRA version 20.0

Source: CSR 4054, main, Table 12-10, page 159

However, in total, 21 (7.0%) patients experienced 33 injection site reactions during the main phase of trial 4054, with similar frequency observed between somapacitan and Norditropin groups (6.7% vs. 5.9%, respectively), whereas the frequency in the placebo group was higher (9.8%) (Table 49). The event rates for injection site reactions were overall low, with the higher event rate observed in the placebo group (somapacitan: 15.0 events/100 pts years; Norditropin 12.9 events/100 years; placebo: 27.6 events/100 pts years;). The types of injection site reactions were similar amongst the groups, and most of them were mild in intensity.

Table 49: Injection site reactions by type and treatment (trial 4054)

	Somapacitan		Norditropin		Placebo		Total	
	N(%)	R	N(%)	R	N(%)	R	N(%)	R
Subjects exposed	120		119		61		300	
Total patients years	79.88		77.54		39.82		197.24	
Injection site reactions	8 (6.7%)	15	7 (5.9%)	12.9	6 (9.8%)	27.6	21 (7.0)	16.7
Pain	1 (0.8)	2.5	2 (1.7)	2.6	0		3 (1.0)	2.0
Itching	0		1 (0.8)	1.3	0		1 (0.3)	0.5
Swelling	3 (2.5)	5.1	0		0		3 (1.0)	2.0
Redness	0		3 (2.5)	3.9	2 (3.3)	5.0	5 (1.7)	2.5
Induration	1 (0.8)	1.3	0		0		1 (0.3)	0.5
Other	5 (4.1)	6.3	4 (3.4)	5.2	5 (8.2)	22.6	18 (4.7)	9.1

N: number of subjects having the event at least once

R: event rate per 100 patient years; %: percentage of exposed subjects having the event

MedDRA version 20.0

Source: CSR 4054, main, Table 12-6, page 171-172, modified

The risk of experiencing at least one injection site reaction irrespective of the weekly number of injections was slightly higher in the somapacitan group than Norditropin group (odds ratio: 1.17). When adjusting for the weekly number of injections, the risk was even higher in somapacitan group than Norditropin (OR: 7.57) (Table 50).

Table 50: Logistic regression on the event of experiencing at least one injection site reaction (trial 4054)

	Odds ratio	[95% CI]	p-value
Irrespective of the frequency of injections			
somapacitan/placebo	0.61	[0.20; 1.87]	0.3857
somapacitan/Norditropin	1.17	[0.41; 3.37]	0.7694
Adjusting for the frequency of injections			
somapacitan/placebo	0.60	[0.19; 1.84]	0.3685
somapacitan/Norditropin	7.57	[2.62; 21.87]	0.0002

CI: Confidence interval

Source: adapted from Applicant's CSR 4054, Tables 14.3.1.22 and 14.3.1.23, pages 506-507 of 1858

Medical officer's comments: Evaluation of all injection site reactions occurring in pivotal trial 4054 revealed a higher event frequency in placebo group compared to somapacitan group, and similar frequency in somapacitan and Norditropin groups. The likelihood of experiencing at least one injection site reaction irrespective of the weekly number of injections was slightly higher in somapacitan group compared to Norditropin group, therefore the less frequent administration of somapacitan does not appear to provide a benefit in this regard, compared to daily hGH injection.

Arthralgia occurred more frequent in somapacitan group than placebo (6.7% vs. 1.6%) in the main phase of trial 4054, and with similar frequency to Norditropin groups, both in the main phase of trial 4054 and Norditropin/somapacitan adjusted pool (6.7% vs 8.4% and 7.0% vs 8.2%, respectively).

Adrenal Insufficiency occurred more frequent in somapacitan group than placebo (3.3% vs. 1.6%) in the main phase of trial 4054, and consistently more frequent than in Norditropin groups, in the main phase of trial 4054 and Norditropin/somapacitan adjusted pool (3.3 % vs 1.7% and 2.9% vs 1.7%, respectively). Three out of four events in somapacitan group in the main phase of trial 4054 were classified as mild in intensity, with the fourth one being classified as severe (case number (b) (6)). This subject experienced the event during the washout phase of the trial, 67 days after study drug discontinuation, therefore unlikely to be related to study drug.

Peripheral edema occurred more frequent in somapacitan group than placebo (3.3% vs 1.6%) in the main phase of trial 4054, but less frequent than in Norditropin groups, both in the main phase of trial 4054 and Norditropin/somapacitan adjusted pool (3.3 % vs 5.8% and 2.7% vs 4.4%, respectively). Of note, no events of peripheral edema were reported in trials 4043 and 4244.

Weight increased as reported AE by patients occurred more frequent in somapacitan group than placebo (3.3% vs. 0%) in the main phase of trial 4054, and consistently more frequent than in Norditropin groups, in the main phase of trial 4054 and Norditropin/somapacitan adjusted pool (3.3 % vs 0.8% and 3.3% vs 1.3%, respectively). During the main phase of trial 4054 "weight increased" was reported in 4 patients in somapacitan group and no patients in placebo, or Norditropin groups, the event had a duration ranging from 15-272 days, cases were mild in severity, and not associated with other events, such as fluid overload. A further detailed analysis of the weight trends in the entire population being studied can be found in Section 8.4.7.

Lipohypertrophy/lipodystrophy occurred in 4 patients (3.3%) in somapacitan group in the main phase of trial 4054, and in 1 additional patient in extension phase of 4054, with no other cases being reported in trials 4043 and 4244. No cases were reported in placebo, or Norditropin

groups of either trial. Also see discussion above, section 8.4.5. The duration of event lasted from 25- 226 days, was rated as “mild” in 3 out of 4 cases (1 case rated as moderate lipodystrophy), and all events recovered. The relationship between somapacitan and the events of lipohypertrophy (2 cases) at the site of injection is possible, considering the growth promoting effects of the drug. One event of lipodystrophy occurred in a patient with medical history of lipodystrophy (the genetic condition of abnormal distribution of subcutaneous fat tissue) and it was reported as “transient worsening of abdominal lipodystrophy”, while the other event was described as “transient ‘contusion’ at the abdominal injection site after multiple injections in the area”. The event was reported recovered after 3 weeks. Additionally, ‘lipoatrophy’ (also a GH class effect) was reported in 2 patients exposed to somapacitan in the extension phase of trial 4054 (one in placebo/somapacitan arm and one in Norditropin/somapacitan arm), and in 1 patient exposed to Norditropin group in the main phase of trial 4054.

Medical officer’s comments: The AEs of ‘arthralgia’, ‘adrenal insufficiency’, ‘peripheral edema’, ‘weight increase’ and ‘lipohypertrophy/lipodystrophy’ were noted to occur with higher frequency in the somapacitan group compared to placebo, consistent with the drug class effect. When compared to Norditropin, the incidence of these AEs was relatively similar, which confers somapacitan a reassuring safety profile. While the events of ‘lipohypertrophy’ and ‘lipoatrophy’ are mechanistically anticipated local adverse drug reactions, the event of ‘lipodystrophy’ as a local adverse reaction is not clearly defined. While the cases of lipodystrophy were likely some types local injection site reactions, their categorization as lipodystrophy reactions is uncertain.

Hyperglycemia/Type 2 diabetes mellitus events as reported AEs were not common in somapacitan groups, with 1 (0.8%) and 2 (0.9%) cases reported in the main phase of 4054 trial, and Norditropin/somapacitan adjusted pool, respectively, while no cases were reported in the placebo group of the 4054 trial. In Norditropin groups, there were 4 (3.4%) cases reported in the main phase of 4054 trial, and 1 case in trial 4244.

There was 1 patient diagnosed with diabetes (mild) after somapacitan exposure in the extension phase of trial 4054, while 2 patients were diagnosed with diabetes (mild) after Norditropin exposure in main phase of trial 4054 (see Section 8.4.6 for details).

Carpal tunnel syndrome occurred in 2 patients in the entire safety population after exposure to somapacitan (1 case in the extension phase of trial 4054, and 1 case in trial 4043), while no events were reported in Norditropin and placebo arms.

Medical officer’s comment: The ADRS of hyperglycemia/type 2 DM and carpal tunnel syndrome occurred with very low incidence in the present trials.

Other class related AEs identified in Table 46, “hypothyroidism”, “Neoplasm benign, malignant and unspec”, “intracranial hypertension”, “pancreatitis”, “severe hypersensitivity” occurred with very low frequency, or not at all, as outlined in Table 47. A detailed discussion regarding the ‘Neoplasms benign, malignant and unspec.’ class was done below.

Neoplasms benign, malignant and unspec.

There was a low incidence of ‘neoplasms’ during the clinical development program of somapacitan, with no significant difference between study groups. Twelve (12) cases of benign, malignant and unspecified neoplasms were reported, with a similar percentage of patients with neoplasms in the somapacitan (2.1% patients, 7 events) and Norditropin (2.4% patients, 5 events) groups (Table 51). There were no cases in the placebo group. Events were reported in trials 4054 and 4244, while no events were reported in trial 4043.

Table 51: Neoplasms benign, malignant and unspec.

	Somapacitan			Norditropin			Placebo		
Preferred term	N	(%)	E	N	(%)	E	N	(%)	E
Total	7	2.1	7	5	2.4	5			
Study 4054 main									
Melanocytic nevus	0	0	0	1	0.8	1	0	0	0
Pituitary tumor	0	0	0	0	0	0	0	0	0
Plasma cell myeloma	0	0	0	1	0.8	1	0	0	0
Study 4054 main + extension									
Total	5	2.2	5	5	4.2	5			
Lipoma	1	0.4	1	1	0.8	1			
Angiomyolipoma				1	0.8	1			
Basal cell carcinoma	1	0.4	1	0	0	0			
Bladder trans cell carcinoma	1	0.4	1	0	0	0			
Melanocytic nevus	0	0	0	1	0.8	1			
Pituitary tumor	2	1.6	2	0	0	0			
Plasma cell myeloma	0	0	0	1	0.8	1			
Soft tissue neoplasm	0	0	0	1	0.8	1			
Norditropin/Somapacitan adjusted pool									
Total	2	0.9	2	3	1.4	3			
Pituitary tumor	1	0.4	1	0	0	0			
Intraductal papillary mucinous neoplasm	1	0.4	1	0	0	0			

Source: Table generated by this medical reviewer

Malignant neoplasms

There were 3 cases of malignant neoplasms (basal cell carcinoma, bladder transitional cell carcinoma and plasma cell myeloma) reported, all cases occurring in the extension phase of trial 4054, in Norditropin/somapacitan arm, which were described briefly below.

Basal cell carcinoma (subject (b) (6)) was reported in a 66 years old female enrolled in trial 4054, on study day 405 (extension phase). The patient was treated with Norditropin in the main phase and with somapacitan in the extension phase. The event was assessed as possibly related to study drug and listed as recovered, without any actions taken for the study drug.

Bladder transitional cell carcinoma (subject (b) (6)) was reported in a 72 years old male in trial 4054, on study day 564 (extension phase). The patient was treated with Norditropin in the main phase and somapacitan in the extension phase. The patient had a past history of 27 years of smoking, and multiple comorbidities, including but not limited to hypercholesterolemia, aortic sclerosis, osteoarthritis, left bundle branch block, hypertension, iron deficiency. The event was assessed as possibly related to study drug, and had not yet recovered at the time of reporting.

Plasma cell myeloma (subject (b) (6)) was reported in a 68 years old male in trial 4054. Past medical history included hyperlipidemia, non-alcoholic steatohepatitis, craniopharyngioma, panhypopituitarism. The patient was diagnosed with albuminuria approximately 5 months after initiation of Norditropin. The patient completed the 34 weeks of Norditropin treatment according to the protocol and started somapacitan therapy during the extension phase of the trial, when the diagnosis of albuminuria was confirmed and further investigations lead to the diagnosis of plasma cell myeloma, 7 weeks of treatment with somapacitan was started. As a result of the diagnosis of plasma cell myeloma, the study drug was discontinued. Although the final diagnosis was made while on somapacitan therapy, the treatment drug assignment was Norditropin, given development of signs of disease while on Norditropin therapy.

Medical officer's comments: While all cases of malignant neoplasms occurred during somapacitan therapy, the causal relationship between the events and somapacitan cannot be established, considering the previous exposure to Norditropin in the cases of basal cell carcinoma and bladder transitional cell carcinoma, whereas the signs of disease in the case of plasma cell myeloma developed while patient was on Norditropin therapy. It is well documented that neoplasm development and disease manifestation is a long-term process and length of drug exposure is an important factor in this context. In addition, the number of events was small, and all occurred in the extension phase of the trial 4054, when no placebo control was available, for comparison purposes. Therefore, a causal relationship between somapacitan and malignancy cannot be determined.

Benign neoplasms – pituitary adenomas

Amongst the benign neoplasms, there were 3 cases of pituitary adenoma, which will be discussed further, given the clinical context of population being studied, which consists of adults GHD which could be acquired in the context of treatment for pituitary adenoma.

Subject (b) (6) was a 52 years old male in placebo/somapacitan arm of trial 4054, who was diagnosed with mild enlargement of the residual pituitary tumor on study day 558 (extension phase), approximately 10 months after exposure to somapacitan. PMH included hepatic steatosis, hyperuricemia, dyslipidemia, hypopituitarism, and concomitant medications included amlodipine, brotizolam, levothyroxine and testosterone enanthate. The patient was diagnosed with pituitary tumor 1.6 years before the randomization. The study drug was discontinued due to AE of residual pituitary tumor enlargement.

Subject (b) (6) was a 73 years old male in Norditropin/somapacitan arm of trial 4054, diagnosed with moderate interval increase 78% in size of residual pituitary adenoma on study day 298 (extension phase) while on somapacitan therapy. The patient had been exposed to Norditropin for 10 months during the main phase of the trial, and on Somapacitan for approximately 50 days. The patient was diagnosed with pituitary tumor benign 17.5 years before the randomization, which was resected through adenomectomy with small remainder post-surgery. The study drug was discontinued due to AE of residual pituitary tumor enlargement. Medical history included neuropathy peripheral, renal impairment, peripheral vascular disorder, anxiety, depression, hyperlipidemia, optic atrophy, visual field defect, abdominal hernia, atrial fibrillation, obesity, hypopituitarism. Concomitant medications included acetylsalicylic acid, alprazolam, atenolol, dexamethasone, gabapentin, hydrocortisone, levothyroxine, simvastatin, testosterone, vardenafil. It is not known from the case report form if therapeutic measures were administered to treat the event of PT pituitary tumor benign. The final outcome of the event was recovered.

Subject (b) (6) was a 67 years old male in somapacitan arm of trial 4244, diagnosed with “regrowth of pituitary adenoma” by MRI on study day 195 (approximately 7 months) after initiation of somapacitan. There was no information about the size of pituitary tumor regrowth, and no information if confirmatory MRI scan had been performed.

Medical officer comments: Two (subjects (b) (6)) of the three cases of residual pituitary tumor regrowth occurred after 7-10 months of therapy with somapacitan, while subject (b) (6) had been exposed for 10 months to Norditropin and approximately 50 days to somapacitan when the pituitary tumor regrowth was diagnosed, making the somapacitan causal relationship determination difficult to establish in the latter case. A causal relationship between somapacitan and pituitary tumor regrowth is possible in the first 2 cases, also considering the time of exposure,

however, the total number of cases reported was very small to further draw meaningful conclusions. Nonetheless, potential for tumor (re)growth represents a known adverse effect of growth hormone therapy class.

In conclusion, the AEs of hypothyroidism”, “Neoplasm benign, malignant and unspec”, “intracranial hypertension”, “pancreatitis”, “severe hypersensitivity”, although occurring with very low incidence, or not at all during somapacitan CDP, they should be adequately identified in the label in Section 5. Warning and Precautions, as important class AEs.

8.6. Safety Analyses by Demographic Subgroups

The Applicant reported safety analyses by demographic subgroups to include sex (male vs female), age (< 65 years vs. ≥ 65 years) and GHD deficiency onset (childhood vs adult) from the pooled global data (trials 4054, 4043 and 4244).

Safety by sex

Overall, the safety of somapacitan was consistent across sex groups. 76% of males participated in the trial reported at least one AE compared to 88% in women, whereas SAEs were more commonly reported in men (10.4%), than in women (7.1%). See Table 52 below, for details.

Table 52: AE category by sex

	placebo		Norditropin		somapacitan	
	N	(%)	N	(%)	N	(%)
Men						
Subjects exposed	29		84		164	
Total patient years	18.5		79.6		181	
All adverse events	18 (62.1)		61 (72.6)		125 (76.2)	
Serious adverse events	2 (6.9)		11 (13.1)		17 (10.4)	
Causality						
Possible	1 (3.4)		21 (25.0)		28 (17.1)	
Probable	2 (6.9)		10 (11.9)		17 (10.4)	
Treatment discontin. due to AEs*	1 (3.4)		4 (4.8)		4 (2.4)	
Women						
Subjects exposed	32		82		169	
Total patient years	21.3		81.4		196	
All adverse events	28 (87.5)		69 (84.1)		150 (88.8)	
Serious adverse events	3 (9.4)		5 (6.1)		12 (7.1)	
Causality						
Possible	8 (25.0)		13 (15.9)		37 (21.9)	
Probable	2 (6.3)		10 (12.2)		20 (11.8)	
Treatment discontin. due to AEs	0		3 (3.7)		2 (1.2)	

Source: Table 5-1, SCS, p. 133, modified

Safety by age groups

Overall, the safety of somapacitan was considered consistent across age groups. Although there was a slightly higher percentage of patients reporting AEs in patients aged ≥ 65 years (88.5%) compared to patients aged < 65 years (81.5%), the SAEs reporting was similar between the groups: 9.6% (patients aged ≥ 65 years) vs 8.5% (patients aged < 65 years) in somapacitan group. See Table 53 below, for details.

Table 53: AE category by age

	placebo		Norditropin		somapacitan	
	N	(%)	N	(%)	N	(%)
Age <65 years						
Subjects Exposed	51		138		281	
Total patient years	33.3		137		323.9	
All adverse events	37	(72.5)	110	(79.7)	229	(81.5)
Serious adverse events	4	(7.8)	10	(7.2)	24	(8.5)
Causality						
Possible	8	(15.7)	28	(20.3)	55	(19.6)
Probable	3	(5.9)	13	(9.4)	33	(11.7)
Treatment discontinuations due AEs	0		6	(4.3)	5	(1.8)
Age ≥ 65 years						
Subjects Exposed	10		28		52	
Total patient years	6.5		23.8		53.9	
All adverse events	9	(90.0)	20	(71.4)	46	(88.5)
Serious adverse events	1	(10.0)	6	(21.4)	5	(9.6)
Causality						
Possible	1	(10.0)	6	(21.4)	10	(19.2)
Probable	1	(10.0)	7	(25.0)	4	(7.7)
Treatment discontinuations due AEs	1	(10.0)	1	(3.6)	1	(1.5)

Source: Table 5-2, SCS, p. 134, modified

Safety by GHD onset

Overall, the safety of somapacitan was considered consistent across GHD onset groups. More patients with adult onset GHD reported AEs (85.2%) compared to patients with childhood onset (76.7%) after somapacitan exposure. However, the percentage of patients with SAEs was similar for both patients groups after somapacitan exposure. See Table 54 for details.

Table 54: AE categories by GHD onset

	placebo N (%)	Norditropin N (%)	somapacitan N (%)
Childhood onset			
Subjects Exposed	20	45	103
Total patient years	12.5	43.6	116.1
All adverse events	11 (55.0)	32 (71.1)	79 (76.7)
Serious adverse events	0	2 (4.4)	9 (8.7)
Causality			
Possible	2 (10.0)	6 (13.3)	24 (23.3)
Probable	1 (5.0)	3 (6.7)	11 (10.7)
Treatment discontinuations due to adverse events	0	1 (2.2)	1 (1.0)
Adulthood onset			
Subjects Exposed	41	121	230
Total patient years	27.3	117.4	261.7
All adverse events	35 (85.4)	98 (81.0)	196 (85.2)
Serious adverse events	5 (12.2)	14 (11.6)	20 (8.7)
Causality			
Possible	7 (17.1)	28 (23.1)	41 (17.8)
Probable	3 (7.3)	17 (14.0)	26 (11.3)
Treatment discontinuations due to adverse events	1 (2.4)	6 (5.0)	5 (2.2)

Source: Table 5-2, SCS, p. 134, modified

Medical officer's comments: Overall, the safety of somapacitan was consistent across the demographic subgroups by sex, age and GHD onset, and no specific safety concerns were observed in the AEs profile by the specific demographic subgroups.

Safety in patients with renal impairment

Somapacitan was evaluated in 29 patients with renal impairment and 15 patients with normal renal function in trial 4297. Across all renal function groups, 24 subjects (54.5%) had 65 AEs. There were no SAEs reported. The dose of somapacitan was not modified due to the AEs and no other action was taken regarding somapacitan due to the AEs. All subjects had recovered from the AEs. There was no apparent pattern of difference in the distribution of AEs between the renal impairment groups and the normal renal function group. The profile of reported AEs was similar to profile in pivotal placebo-controlled phase 3 trial 4054, with most common AEs reported being headache (22.7%), edema peripheral (11.4%), and arthralgia (9.1%).

Medical officer's comments: Somapacitan was well tolerated in subjects with renal impairment (ranging from mild to hemodialysis patients) after exposure to somapacitan

for 3 weeks.

Safety in patients with hepatic impairment

Somapacitan was evaluated in 18 patients with hepatic impairment (mild or moderate) and 16 patients with normal hepatic function in trial 4298. There were 9 AEs, reported in 5 subjects. Four (4) of these AEs which occurred in 2 subjects were probably related to somapacitan and both subjects were in the moderate hepatic impairment group. These adverse events were all in the category of injection site reactions and they were of mild severity. All subjects recovered from all AEs.

Medical officer's comments: Somapacitan was well tolerated in subjects with mild to moderate hepatic impairment after exposure to somapacitan for 3 weeks.

8.7. Specific Safety Studies/Clinical Trials

None

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

According to Pharm/Tox reviewer, the carcinogenic risk for somapacitan is expected to be similar to that of currently marketed hGH products, therefore standard 2-year carcinogenicity studies in rodents were not performed (see Section 4.4 for details).

A low incidence of 'neoplasms' was noted during the clinical development program of somapacitan, with no significant difference between study groups (see Section 8.5 above, for details).

8.8.2. Human Reproduction and Pregnancy

There were no exposures in pregnancies and/or no exposures in lactating women during somapacitan CDP.

According to Division of Pediatrics and Maternal Health (DPMH) review (refer to DARRTS review dated 04/21/2020, for full details), published data with short-acting rhGH over several decades

of use in pregnant women was sufficient in evaluating the safety of somapacitan in pregnant women, therefore DPMH did not recommend a post marketing pregnancy safety study for somapacitan at this time. In addition, no adverse developmental outcomes have been described in animal reproduction studies for either short-acting or long-acting rhGH. Therefore, DPMH recommends that labeling should convey that although there is no pregnancy outcome information with the use of somapacitan in pregnant women, no safety concerns or adverse pregnancy outcomes have been reported with several decades of rhGH use in pregnant women.

With regards to lactation, DPMH notes that although there is no data on the presence of somapacitan in human milk, limited published literature with short-acting hGH indicate the unlikelihood of any significant drug transfer into the milk or oral absorption by a breastfed infant, due to hGH large molecular weight and long peptide structure. Animal data did show the presence of somapacitan in rat milk at up to 50% of plasma levels. Therefore, DPMH recommends the lactation labeling to include information regarding limited published lactation data with short-acting rhGH, a statement regarding the presence of somapacitan in animal milk, and the required PLLR lactation benefit/risk statement. DPMH considers the available data are sufficient to inform the use of somapacitan during lactation, therefore a requirement for a post marketing lactation study for somapacitan is not recommended at this time.

(b) (4)

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no clinical experience with somapacitan overdose, drug abuse, or dependence, however, the proposed label adequately indicates that inappropriate use of somapacitan may result in significant negative health consequences, which is consistent with other GH products. For example, acute overdosage might lead to fluid retention and imbalance in glucose metabolism, manifested by initial hypoglycemia, followed by hyperglycemia, whereas long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess endogenous growth hormone. The potential for withdrawal and rebound effects are not known GH therapy class effects, and have not been studied in somapacitan clinical trials.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

None

8.9.2. Expectations on Safety in the Postmarket Setting

None

8.9.3. Additional Safety Issues From Other Disciplines

None

8.10. Integrated Assessment of Safety

The exposure to somapacitan during the non-clinical and clinical development programs was adequate to characterize the safety profile of somapacitan in patients with AGHD. The safety areas of special interest included primarily GH class effects, injection site reactions and antibody development, and are further summarized below.

Neoplasms

The theoretical concern regarding possible effect of GH therapy on neoplasia development has been extensively discussed in the literature and supported primarily by non-clinical data, given the GH primary mechanism of action of growth promotion via direct effect and indirectly via IGF-1 synthesis.⁴⁰ However, to date, there is no clear indication from long-term epidemiological studies that rhGH therapy is associated with an increased risk for cancer development/regrowth, or pituitary tumor recurrence/regrowth, with majority of the data for malignancy coming from studies of children treated with GH.²²⁻²⁷ Therefore, despite a large number of studies indicating no evidence of an increased cancer risk in patients treated with GH therapy, in light of the mechanistic effects of GH therapy on growth promotion, GH therapy is contraindicated in patients with evidence of active malignancy, due to the serious potential consequences of exacerbating the progression of malignancy. In addition, all rhGH therapies labels warn against a possible increased risk of second neoplasm in pediatric cancer survivors who were treated with radiation to the brain/head and subsequently developed GHD and were treated with somatropin (largely due to an increased incidence of meningioma⁴¹), and the unknown causal relationship between GH replacement therapy and CNS tumor recurrence, or occurrence of new malignant tumors in adults with GHD.

There was a low incidence of 'neoplasms' during the clinical development program of somapacitan, with no significant difference between the somapacitan, Norditropin, and placebo groups, relative to the time of exposure to each study drug (see Section 8.5 for details).

⁴⁰ Kasprzak A., et al. Insulin-like growth factor (IGF) axis in cancerogenesis. Mutation Research 2017; 772: 78–104

⁴¹ Ergun-Longmire B, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab. 2006; 91: 3494–3498

In conclusion, the current somapacitan CDP did not bring any new safety information with regards to the risk of neoplasm development, or recurrence, due to an overall low number of reported cases, with no significant difference between treatment arms.

Glucose intolerance and Diabetes Mellitus

The effect of GH therapy on insulin sensitivity and the risk of diabetes mellitus is a well-recognized effect of GH therapy class of medications. However, the effect of GH therapy on insulin sensitivity in AGHD patients is difficult to predict, because of a dual effect of GH at different receptor and cellular levels. GH therapy improves insulin sensitivity by decreasing the fat mass, and indirectly via IGF-1 receptors, while GH has a direct insulin antagonistic effect in the liver and other tissues. The insulin antagonistic effects are mostly seen when high doses of GH therapy are being used, whereas at lower doses, there are no significant changes on insulin sensitivity.⁴²

Overall, the mean fasting plasma glucose and HbA1c levels were stable during the phase 3 trials, without significant glucose excursions noted, while the abnormalities in glucose levels and the number of patients with newly diagnosed diabetes mellitus were low and similar among the active treatment arms. No significant glucose excursions were noted in the 12 patients with a history of diabetes at baseline either. No SAEs related to glucose homeostasis, or symptomatic manifestations of hyperglycemia were reported. The AEs of hyperglycemia/type DM occurred with low incidence (< 1%) after somapacitan exposure in the phase 3 trials.

In conclusion, somapacitan exposure had no significant impact on glucose homeostasis during the current CDP. However, the program included primarily a patient population without history of diabetes at baseline, with only a few patients with well controlled diabetes (4%) in the pivotal trial 4054. Presence of diabetes was an exclusion criterion in trial 4244 and Japanese patients in trial 4043. Therefore the effects of somapacitan in diabetic AGHD patients without adequate glycemic control at baseline remains unknown. Because of the known and anticipated mechanistic effects of somapacitan on glucose homeostasis in AGHD patients, adequate warning regarding the risk of glucose intolerance and DM should be provided in the label, with additional recommendations regarding need for periodic monitoring of glucose levels in all patients exposed to rhGH therapy.

Fluid retention

A relative decrease in extracellular fluid volume exist in untreated GH-deficient patients, with re-equilibration and an approximate total gain of extracellular water of 1 kg.⁴³ The mechanism for fluid retention is due to an increased tubular reabsorption of sodium in the distal nephron, which is accompanied by an increase in plasma renin activity and decreased brain natriuretic

⁴² al-Shoumer KA, et al. Effects of four years' treatment with biosynthetic human growth hormone (GH) on glucose homeostasis, insulin secretion and lipid metabolism in GH-deficient adults. Clin Endocrinol (Oxf), 1998; 48:795–802

⁴³ Johannsson G, et al. GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis. J Clin Endocrinol Metab. 2002; 87:1743–1749

peptide levels, effects that are dose dependent.⁵ The most common effects of fluid retention are manifested as peripheral edema, but other effects, such as arthralgia, weight increase, paresthesia, and carpal tunnel syndrome (latter two being a possible manifestation of nerve compression) may be a result of fluid accumulation as well.

The AEs of 'peripheral edema', 'arthralgia', 'weight increase' were indeed noted to occur with higher frequency in the somapacitan group compared to placebo (3.3% vs 1.6%, 6.7% vs 1.6%, 3.3% vs 0%), consistent with the drug class effect. When compared to Norditropin, the incidence of these AEs was either similar, or lower (3.3% vs 5.8%, 6.7% vs 8.4%, 3.3% vs 0.8%), which confers somapacitan a reassuring safety profile. Changes from baseline in mean body weight were minimal and not clinically relevant. Inclusion of these ADRs in the Adverse Reactions Section (6) of the label is recommended, whereas the general effect of fluid retention of somapacitan should be presented in the W&P section.

Adrenal Insufficiency (AI)

GH replacement causes a lowering effect of serum cortisol level due to reversal of the enhanced conversion of cortisone to cortisol during the GH-deficient state, potentially unmasking central (secondary) AI. The AE of 'adrenal insufficiency' was noted to occur with slightly higher frequency in the somapacitan group compared to placebo, and Norditropin groups (3.3% vs 1.6% vs 1.7%), with the majority of cases in somapacitan group being classified as mild in intensity. All patients recovered with somapacitan dose adjustments/treatment of AI and no adrenal crisis was reported. Overall, the incidence of AI was low, and consistent with the drug class effect.

Injection site reactions

Injection site reactions are generally expected AEs with injectable products. The overall incidence of injection site reactions during the CDP was low, with 7% of patients experiencing 33 injection site reactions during the main phase of trial 4054, with similar frequency observed between somapacitan and Norditropin groups (6.7% vs 5.9%, respectively), whereas the frequency in the placebo group was higher (9.8%). The types of injection site reactions were similar amongst the groups, and most of them were mild in intensity, which confers a reassuring safety profile to somapacitan. However, the likelihood of experiencing at least one injection site reaction irrespective of the weekly number of injections was slightly higher in somapacitan group compared to Norditropin group, therefore the less frequent administration of somapacitan does not appear to provide a benefit in this regard, compared to daily hGH injection.

Other ADRs

Other recognized ADRs associated with GH treatment, such as headache, allergic reactions (non-anaphylactic), fatigue/asthenia, paresthesia, and myalgia occurred less frequently in somapacitan group, compared to placebo (8.3% vs 16.4%, 6.7% vs 14.8%, 4.2% vs 6.6%, 2.5% vs 3.3%, and 1.6 % vs 4.9%, respectively), whereas most of them occurred with relative similar

frequency in somapacitan and Norditropin groups, conferring a reassuring safety profile to somapacitan overall.

The other GH related class effects, such as hypothyroidism, carpal tunnel syndrome, occurred with very low incidence (< 1%) during somapacitan CDP, whereas the ADRs of intracranial hypertension, pancreatitis, severe hypersensitivity, and stroke were not reported at all.

Back pain

The AE of back pain occurred with a higher frequency in somapacitan group compared to placebo, and Norditropin groups, respectively (9.2% vs 3.2% and 3.4%, respectively), in the main phase of pivotal trial 4054. Additional analysis revealed a relative risk for the back pain in somapacitan group compared to placebo of 3.05 (lower bound of C.I. of 0.705 and higher bound of C.I. of 13.2, P value = 0.145). The duration of event varied from 2 - 88 days (duration not available in 2 cases) in somapacitan group, was mild in all cases, with causality to study drug being considered unlikely in all, but 2 cases, by the study investigators. Patients recovered in all, but one case, and no dose reduction was required due to AE. It is possible that back pain could be another clinical manifestation of fluid retention with subsequent spinal nerve compression, which is a known class effect of growth hormone products. It is reassuring that the event was mild and recovered in majority of patients, suggesting a transient nature of the drug effect, similar to other clinical manifestations of fluid retention.

Changes in phosphate and creatine kinase levels

Among the laboratory tests, a higher percentage of patients shifted from normal to high phosphate and creatine kinase levels in somapacitan group, compared to placebo and Norditropin, from baseline to end of the main trial period, as follows: 17.5% vs 4.9% vs 6.7%, and 9.2% vs 6.6% vs 5.0%, respectively. However, the elevations occurred on an intermittent basis, were mild and not progressive, and of unknown clinical significance. However, due to a higher occurrence of these laboratory abnormalities in somapacitan group compared to placebo, and Norditropin groups, they should be labeled for healthcare providers awareness.

Immunogenicity

There was no evidence of development of anti-somapacitan/anti-GH antibody development during the clinical development program.

Overall, the safety of somapacitan was consistent across the demographic subgroups by sex, age and GHD onset, and no specific safety concerns were observed in the AEs profile by the specific demographic subgroups.

In summary, the safety profile of somapacitan in patients with AGHD was well characterized in somapacitan CDP, and the pattern of AEs emerging from the CDP was similar to the AEs associated with the hGH therapy class and are mechanistically anticipated pharmacodynamic effects. They include a potential increased risk of neoplasm, glucose intolerance and diabetes

mellitus, clinical manifestations of fluid retention (i.e. peripheral edema, arthralgia, nerve compression syndromes including back pain, paresthesia, carpal tunnel syndrome), headache, adrenal insufficiency, hypothyroidism, injection site reactions, lipohypertrophy/lipoatrophy, and other class effects not observed during somapacitan CDP, i.e. intracranial hypertension, severe hypersensitivity, pancreatitis, and stroke. There was no evidence of an increased risk of neoplasm, or recurrence/regrowth of existing pituitary adenomas. The clinical development program for somapacitan did not reveal any major new safety signals following somapacitan exposure in AGHD patients. In conclusion, the safety profile of somapacitan is acceptable in the view of its potential benefit, with AEs that are predictable, well known class effects of GH therapies, which can be adequately identified and managed by the health care providers.

9. Advisory Committee Meeting and Other External Consultations

Not applicable for this submission.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Agreement on the final labeling language has not been reached at the time of this review was completed. Refer to the complete labeling in the approval letter. The following sections should be addressed in the label:

- DOSAGE AND ADMINISTRATION:
 - I recommend the dosing initiation and titration schedule recommendations to reflect the doses studied during the clinical trials, as follows:
 - starting dose: 1.5 mg/week (range, 1.0 mg/week to 2.0 mg/week); the need for a lower range starting dose for elderly (> 65 years of age), and a higher starting dose for females on oral estrogen should be adequately conveyed in the label;
 - I do not agree with the Applicant's recommendation (b) (4) for patients switching from daily GH therapy, (b) (4) (b) (4) .

- I agree with the dose titration frequency and dosing increments as proposed by the Applicant, as they reflect the trials procedures, and are consistent with clinical practice guidelines
 - the maximum proposed dose is 8 mg/week, which is in accordance with the dose studied in the clinical trials.
- CONTRAINDICATIONS:
 - I agree with the Applicant's proposal to include acute critical illness, active malignancy and hypersensitivity to somapacitan in the CONTRAINDICATIONS section, according to the hGH therapy class effect
- WARNING AND PRECAUTIONS:
 - I agree with the Applicant's proposal to include 'Increased Mortality in Patients with Acute Critical Illness', 'Increased Risk of Neoplasm', 'Glucose Intolerance and Diabetes Mellitus', 'Intracranial Hypertension', 'Severe Hypersensitivity', 'Fluid Retention,' 'Hypoadrenalism', 'Hypothyroidism', 'Pancreatitis', 'Lipohypertrophy/lipoatrophy' in the WARNING AND PRECAUTIONS section, according to the hGH therapy class effect.
- ADVERSE REACTIONS:
 - In the Clinical Trial Experience subsection, I recommend inclusion of the Adverse Reactions that occurred more commonly in somapacitan group compared to placebo, and with an incidence of >2% in adult patients with GHD during the 6-month placebo-controlled portion of pivotal trial 4054
 - I recommend inclusion of laboratory tests 'elevation in phosphate and creatine phosphokinase' in the Adverse Reaction section as well. In pivotal trial 4054, a higher percentage of patients shifted from normal to high phosphate and creatine phosphokinase levels from baseline to end of main trial period in somapacitan group compared to placebo (17.5% vs 4.9% , and 9.2% vs. 6.6%, respectively); although these laboratory changes were of small magnitude overall, occurred intermittently, and were non-progressive during the trial, they should be labeled AEs, for healthcare providers awareness.
- CLINICAL STUDIES section:
 - I recommend inclusion of results from main phase of the pivotal trial 4054, in Clinical Studies section of the label, since it is the only clinical trial evaluating the safety and efficacy of the drug in an placebo-controlled, well designed study.
 - I agree with the Applicant presentation of the results for the primary efficacy endpoint (change from baseline in TFP compared to placebo) in a table format, while the results of the secondary comparison to Norditropin for the primary endpoint to be presented in either table, or text format.

- o I do not recommend presentation in the label of the secondary efficacy endpoints results related to changes in other body composition parameters, since the Applicant did not include any hierarchical testing, nor any adjustment for multiplicity testing was performed for these secondary endpoints.

11. Risk Evaluation and Mitigation Strategies (REMS)

Not required for this submission.

12. Postmarketing Requirements and Commitments

The Applicant submitted an iPSP for 2 pediatric clinical trials to be performed as part of post-marketing commitment:

1. Clinical Trial NN8640-4172, a 1 year phase 2, randomized, open-label, active-control, dose-finding trial, to investigate efficacy and safety of once-weekly somapacitan versus daily Norditropin (somatropin) in pre-pubertal children with GHD (boys ≥ 2.5 and ≤ 10 years of age, and girls ≥ 2.5 and ≤ 9 years of age) followed by a 2 year single-arm period to evaluate safety in this cohort, and a 4 year single-arm period that also enrolls cohorts of younger children with GHD (boys and girls < 2.5 years of age) and older children with GHD (boys > 10 and ≤ 17 years of age, and girls > 9 and ≤ 17 years of age) to evaluate safety in all three cohorts.
2. Clinical Trial NN8640-4263, a 1 year phase 3 randomized, parallel group, open-label trial, to evaluate the efficacy and safety of once weekly somapacitan versus daily Norditropin in pre-pubertal pediatric patients (boys ≥ 2.5 and ≤ 10 years of age, and girls ≥ 2.5 and ≤ 9 years of age) with GHD, followed by a 3 year single-arm extension period to evaluate long-term safety.

13. Appendices

Appendix 1
NN8640-4054 Trial flow chart for main period

Trial Periods		Screen	Screen	Randomisation	Titration								Treatment				Follow-up
Visit number		1a ¹⁷	1b ¹⁷	2	3	4	5	6	7	8	9	10	11	12	13	14 ¹	15 ²
Visit type		IC	Site	Site	IGF	Site	IGF	Site	IGF	Phone ³	IGF	Site	IGF	Site	Site	Site	Site
Timing of visit	Weeks	V1b to 1d min	-3 to -2 weeks	0	1+3d	2	3+3d	4	5+3d	6	7+3d	8	9+3d	16+4d	25+1d after dosing is	33+4d	35
Visit window	Days				+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	±7 ⁴	±7 ⁴	+2
PATIENT RELATED INFO/ASSESSMENTS																	
Informed consent		x															
In/exclusion criteria			x	x													
Demography			x														
Medical history and concomitant illness			x														
Randomisation				x													
Height			x														
MRI scan			x ¹³														
CT scan			x ¹³														
EFFICACY																	
Body weight			x	x		x						x		x	x	x	x*
Waist circumference				x												x	
PRO questionnaires				x ⁵											x ³	x ³	
Blood sampling for IGF-I and IGF-BP-3			x	x ⁷	x ⁷	x ⁷	x ⁷	x ⁷	x ⁷		x ⁷	x ⁷	x ⁷	x ⁷	x ⁷	x ⁷	x ⁷ *
Blood sampling for Lipids			x													x	
Blood sampling for PK				x ⁷	x ⁷	x ⁷	x ⁷	x ⁷	x ⁷		x ⁷	x ⁷	x ⁷	x ⁷	x ⁷	x ⁷	x ⁷
DXA scan			x ⁶													x ¹⁶	
Blood sampling for cardiovascular			x									x		x	x	x	
SAFETY																	
Adverse events				x		x		x		x		x		x	x	x	x
Local tolerability				x ¹²		x						x		x	x	x	x*
ECG			x												x		x
Physical examination			x	x		x						x		x	x	x	x*
Vital signs			x	x		x						x		x	x	x	x*
Blood sampling for biochemistry, haematology and hormones ⁹			x									x		x	x	x	
Blood sampling for cortisol			x								x			x	x	x	
ACTH/ITT			x ¹⁰									x ¹¹					x ^{11*}
Blood sampling for antibodies				x ⁷		x ⁷		x ⁷				x ⁷		x ⁷	x ⁷	x ⁷	x ⁷
Blood sampling for glucose metabolism			x									x		x	x	x	
Eye examination			x ¹³														x ¹³
OTHER ASSESSMENTS																	
Withdrawal criteria						x						x		x	x	x	x*
Concomitant medication			x	x		x		x		x		x		x	x	x	x

Clinical Review
Geanina Roman-Popoveniuc, MD
BLA 761156
SOGROYA/somapacitan-beco

Pregnancy test			x ³	x ³		x ³						x ³		x ³	x ³	x ³	x ³
Compliance						x						x		x	x	x	
TRIAL MATERIAL																	
Administration of trial product																	
Dosing (observed trial drug administration)				x		x						x					x*
Dispensing visit				x		x						x		x	x		x*
New dose of trial product						x ¹⁴		x ¹⁴		x ¹⁴		x ¹⁴					x ¹⁴ *
Drug accountability				x		x		x				x		x	x		x
IV/WRS call			x	x		x		x		x		x		x	x		x
REMINDERS																	
Trial conduct																	
Attend visit fasting			x	x	x	x	x	x	x			x	x	x	x	x	x
Handout and instruct in diary				x		x		x				x		x	x		x*
Training in trial product and pen handling				x		x						x					x*
Diary returning						x		x				x		x	x		x

1. If a patient discontinues treatment during the 34-week period, procedures for treatment discontinuation should be followed.
2. All assessments marked with * do not need to be performed if a patient withdraws from the trial up to and including visit 15.
3. The phone visits can be site visits instead if required by local practice or regulation or at investigators discretion.
4. Visits 12 and 13 and V25, V26 and V27 can be moved either one whole week earlier or one whole week later.
5. **FOR ALL COUNTRIES EXCEPT JAPAN:** To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample At V2 the test is mandatory and needs to be performed from a urine sample. If required locally this may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than Visit 1b and V2, optional urine pregnancy testing may be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements. **FOR JAPAN ONLY:** To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample and a urine sample. At V2 the test is mandatory and needs to be performed from a urine sample. This may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than V1b and V2, urine pregnancy test in women of childbearing potential should be performed according to the flow chart.
6. Baseline DXA should be obtained at Visit 1b however if it is not possible, it should be performed within 4 calendar days from Visit 1b since the quality of the scanned image must be confirmed by the imaging laboratory before the patient can be randomised.
7. Before trial drug administration (if dosing planned on visit day).
8. The PRO questionnaires must be performed after all fasting related activities and before all other trial-related activity at each applicable visit. TSQM-9 is not assessed at randomisation.
9. Testosterone is assessed only in male patients.
10. If patient is not being treated with glucocorticoid replacement and has not had ACTH stimulation test or ITT within past 3 months, perform ACTH stimulation test or ITT.
11. If a patient has morning cortisol below normal range, ACTH stimulation test or ITT must be performed. The morning serum cortisol sample collection, which is the basis for the ACTH stimulation test or ITT, should be performed at visit 9, 14 and 22, respectively, before 9 am when the patient is already fasting.
12. After trial drug administration.
13. Fundus photography performed in patients diagnosed with diabetes mellitus only (see inclusion criterion 10). Fundus photography performed ≤ 90 days prior to randomisation is acceptable if results are available for evaluation at randomisation.
14. Besides the IGF-I based dose adjustment during the titration period, dose reduction can be considered during the entire study period (including the two titration periods) at the investigator's discretion for safety concerns. If AEs with a probable relationship to the trial drug are persistent but continuation in the trial is acceptable as judged by the investigator and patient, dose reduction in steps of 25% can be considered.
15. Only for patients with a history of pituitary adenoma or other benign intracranial tumour. MRI/CT if an MRI or CT scan has not been performed ≤ 9 months (defined as ≤ 270 days) prior to randomisation (results must be available for evaluation at randomisation).
16. The quality of the DXA scan obtained at visit 14 must be confirmed by the imaging laboratory prior to conducting visit 15.
17. Visit 1a and visit 1b may be combined if site SOPs and IEC/IRB decision allow this, i.e. that patients as standard practice attend all visits in a fasting state.
18. Visit 13 and visit 26 and the previous dose must be scheduled according to [Appendix 16.1.1](#) (Protocol Table 8-1 or Table 8-2).

NN8640-4054 Trial flow chart for extension period

Trial Periods		Titration								Treatment					Follow-up
Visit number		16	17	18	19	20	21	22	23	24	25	26	27	28 ¹	29 ¹
Visit type		IGF	Site	IGF	Site	IGF	Phone ³	IGF	Site	IGF	Site	Site	Site	Site	Site
Timing of visit	Weeks	36+3d	37	38+3d	39	40+3d	41	42+3d	43	44+3d	53+4d	64+1d after dosing ¹⁸	75+4d	86+4d	88
Visit window	Days	+1	+1	+1	+1	+1	+1	+1	+1	+1	±7 ⁴	±7 ⁴	±7 ⁴	+2	±2
SUBJECT RELATED INFO / ASSESSMENTS															
Withdrawal criteria			x						x		x	x	x		
Concomitant medication			x		x		x		x		x	x	x	x	x
Pregnancy test			x ³						x ³		x ³	x ³	x ³	x ³	x ³
EFFICACY															
Body measurements			x						x		x	x	x	x	x
Waist circumference														x	
Body weight			x						x		x	x	x	x	x
PRO questionnaires												x ³		x ³	
Biomarkers		x ¹	x ¹	x ¹	x ¹	x ¹		x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x
IGF-1		x ¹	x ¹	x ¹	x ¹	x ¹		x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x
IGFBP-3		x ¹	x ¹	x ¹	x ¹	x ¹		x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x
Lipids															x
PK Sampling		x ¹	x ¹	x ¹	x ¹	x ¹		x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x ¹	x
DXA scan															x
Biochemistry									x		x	x	x	x	
hsCRP									x		x	x	x	x	
Protein markers															
Interleukin 6									x		x	x	x	x	
SAFETY															
Adverse events			x		x		x		x		x	x	x	x	x
Local tolerability			x						x		x	x	x	x	x
ECG												x			x
Physical examination			x						x		x	x	x	x	x
Vital signs			x						x		x	x	x	x	x
Biochemistry									x		x	x	x	x	
Haematology									x		x	x	x	x	
Hormones									x		x	x	x	x	
Cortisol								x			x	x	x	x	
Free T4									x		x	x	x	x	
TSH									x		x	x	x	x	
Total T3									x		x	x	x	x	
Total T4									x		x	x	x	x	
Total testosterone									x ³		x ³	x ³	x ³	x ³	
ACTH/ITT									x ¹¹						
Antibodies			x ¹		x ¹				x ¹		x ¹	x ¹	x ¹	x ¹	x
Glucose metabolism									x		x	x	x	x	
Fasting insulin									x		x	x	x	x	
Fasting plasma glucose									x		x	x	x	x	
HbA1c									x		x	x	x	x	
Eye examination															x ¹³
Fundusphotography															x ¹³
OTHER ASSESSMENTS															
Compliance			x						x		x	x	x	x	
TRIAL MATERIAL															
Administration of trial product															
Dosing (Observed trial drug administration)			x						x						

Clinical Review
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BLA 761156
SOGROYA/somapacitan-beco

Dispensing visit			X		X			X		X	X	X		
New dose of trial product			X ¹⁴		X ¹⁴		X ¹⁴		X ¹⁴					
Drug accountability			X		X			X		X	X	X		X
IV/TWRS call			X		X		X		X		X	X	X	X
REMINDERS														
Trial Conduct														
Attend visit fasting		X	X	X	X	X		X	X	X	X	X	X	X
Handout and instruct in diary			X		X			X		X	X	X		
Training in trial product and pen handling			X					X						
Sign off Casebook														X
ecap dispensing and training										X				
ecap returning										X				X
Diary returning			X		X			X		X	X	X		X

1. If a patient discontinued treatment during the 34-week period, procedures for treatment discontinuation were followed.
2. All assessments marked with * did not need to be performed if a patient withdrew from the trial up to and including visit 15.
3. The phone visits could be site visits instead if required by local practice or regulation or at investigators discretion.
4. Visits 12 and 13 and V25, V26 and V27 could be moved either one whole week earlier or one whole week later.
5. FOR ALL COUNTRIES EXCEPT JAPAN: Were performed in females only. At Visit 1b the test was mandatory and needed to be performed on a blood sample At V2 the test was mandatory and needed to be performed from a urine sample. If required locally this was to be supplemented by a blood sample (results of the second blood sample were not required for randomisation). During the trial for all other site visits than Visit 1b and V2, optional urine pregnancy testing were to be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements. FOR JAPAN ONLY: Were performed in females only. At Visit 1b the test was mandatory and needed to be performed on a blood sample and a urine sample. At V2 the test was mandatory and needed to be performed from a urine sample. This was to be supplemented by a blood sample (results of the second blood sample were not required for randomisation). During the trial for all other site visits than V1b and V2, urine pregnancy test in women of childbearing potential was to be performed according to the flow chart.
6. Baseline DXA was obtained at Visit 1b however if it was not possible, it was to be performed within 4 calendar days from Visit 1b since the quality of the scanned image had to be confirmed by the imaging laboratory before the patient could be randomised.
7. Before trial drug administration (if dosing planned on visit day).
8. The PRO questionnaires had to be performed after all fasting related activities and before all other trial-related activity at each applicable visit. TSQM-9 was not assessed at randomisation.
9. Testosterone was assessed only in male patients.
10. If patient was not being treated with glucocorticoid replacement and had not had ACTH stimulation test or ITT within past 3 months, perform ACTH stimulation test or ITT.
11. If a patient had morning cortisol below normal range, ACTH stimulation test or ITT had to be performed. The morning serum cortisol sample collection, which was the basis for the ACTH stimulation test or ITT, was to be performed at visit 9, 14 and 22, respectively, before 9 am when the patient was already fasting.
12. After trial drug administration.
13. Fundus photography performed in patients diagnosed with diabetes mellitus only (see inclusion criterion 10). Fundus photography performed ≤ 90 days prior to randomisation was acceptable if results were available for evaluation at randomisation.
14. Besides the IGF-I based dose adjustment during the titration period, dose reduction could be considered during the entire study period (including the two titration periods) at the investigator's discretion for safety concerns. If AEs with a probable relationship to the trial drug were persistent but continuation in the trial is acceptable as judged by the investigator and patient, dose reduction in steps of 25% can be considered.
15. Only for patients with a history of pituitary adenoma or other benign intracranial tumour. MRI/CT if an MRI or CT scan had not been performed ≤ 9 months (defined as ≤ 270 days) prior to randomisation (results had to be available for evaluation at randomisation).
16. The quality of the DXA scan obtained at visit 14 had to be confirmed by the imaging laboratory prior to conducting visit 15.
17. Visit 1a and visit 1b were to be combined if site SOPs and IEC/IRB decision allowed this, i.e. that patients as standard practice attend all visits in a fasting state.
18. Visit 13 and visit 26 and the previous dose had to be scheduled according to [Appendix 16.1.1](#) (Protocol Table 8-1 or Table 8-2).

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): 4054

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>445</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>17</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>10</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Clinical Review
Geanina Roman-Popoveniuc, MD
BLA 761156
SOGROYA/somapacitan-beco

Covered Clinical Study (Name and/or Number): 4043

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>82</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Clinical Review
Geanina Roman-Popoveniuc, MD
BLA 761156
SOGROYA/somapacitan-beco

Covered Clinical Study (Name and/or Number): 4244

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>98</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>18</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>4</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Clinical Review
Geanina Roman-Popoveniuc, MD
BLA 761156
SOGROYA/somapacitan-beco

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GEANINA ROMAN-POPOVENIUC
07/23/2020 06:14:29 PM

MARINA ZEMSKOVA
07/23/2020 06:17:42 PM
I concur.