CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761156Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA-761156
Drug Name:	Somapacitan
Indication(s):	Growth Hormone – in adults
Applicant:	Novo Nordisk
Date(s):	Submit Date: 8/28/2019
	PDUFA Date:8/28/2020
	Review Due Date: 4/28/2020
Review Priority:	Standard
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Keywords: Placebo, Active Control Study

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1 EXECUTIVE SUMMARY

Novo Nordisk is seeking approval for efficacy and safety of Somapacitan (NNC0195-0092), a long acting growth hormone, delivered by weekly injection, for treatment of adults with growth hormone deficiency (AGHD).

Brief Overview of Clinical Studies

This submission encompasses one efficacy trial, Study 4054, and two safety trials, Studies 4043 and 4244. This review focuses on the results from the efficacy trial. Study 4054 was a 34-week parallel placebo-controlled (double blind) and active-controlled (open label) design comparing Somapacitan administered by weekly injections, to placebo, and to Norditropin, administered using daily injections.

In Study 4054, the primary efficacy endpoint was change in truncal fat percentage (%) from baseline to week 34. The treatment difference was –1.41 with 95% confidence intervals of (-2.61, -0.22), which achieves statistical significance.

Major Statistical Issues

The following are some statistical issues identified during the review.

- This BLA relies on a single efficacy study to support efficacy.
- The treatment difference appears small (less than 60% of the assumed effect of 2.5%, used for the sample size calculation), and a determination of clinical meaningfulness is needed.
- There are Section 14 tables in the proposed label for many secondary efficacy endpoints that were not pre-specified, and there was no multiple testing procedure to control Type 1 error for these endpoints.
- The treatment effect in the North America region goes in the opposite direction as the overall effect and has the same magnitude.
- Somapacitan is statistically inferior to Norditropin, and the magnitude of the difference is almost as much as the difference between Somapacitan and Placebo.

Please refer to Section 3.2 and Section 4.1 for further details.

1.1 Conclusion and Recommendations

Study 4054 demonstrated statistical superiority of the study drug in reducing percent of truncal fat in comparison with placebo. However, there was only one study with this efficacy endpoint, and the magnitude of treatment effect is small and may not be clinically meaningful. Somapacitan was also statistically inferior to Norditropin. The magnitude of difference between Somapacitan and Norditropin (1.28 for percent truncal fat primary endpoint) is almost as much as the difference between Somapacitan and Placebo (-1.41 for the same endpoint). No

randomized treated patients on the Somapacitan arm discontinued treatment due to an adverse event. This treatment may be beneficial for some patients who do not tolerate daily injections or who prefer weekly injections. Discussions regarding clinical meaningfulness are ongoing at the time of this review.

2 INTRODUCTION

2.1 Overview

Somapacitan is a modified rhGH (recombinant long-acting human growth hormone) and is proposed to be administered using weekly injections. The proposed indication for this BLA submission is for adults with growth hormone deficiency (AGHD). From sponsor protocol, Section 3.1.1:

> …AGHD usually results from pituitary or peripituitary tumours and the associated treatments and has been recognized as a syndrome with distinct features, such as increased body fat mass, decreased lean body mass (LBM), reduced exercise capacity, reduced bone mineral density (BMD), disturbed lipoprotein metabolism and decreased psychological wellbeing. The aim of GH replacement is to correct GHD related metabolic disturbances and optimize the therapeutic response with minimal incidence of adverse reactions…

In End-of-Phase 2 (EOP2) correspondence, signed into DARRTS on 6/12/2014 under IND 116327, FDA agreed to the primary endpoint of percent truncal fat.

FDA included extensive comments concerning prevention of missing data. In addition, there was the following FDA comment concerning addressing missing data in analysis:

> We recommend that your primary analysis be like your sensitivity analysis, which uses multiple imputation that imputes, with respect to the placebo arm, missing values from subjects who discontinue therapy. This analysis may not be conservative, if subjects on the experimental arm who discontinue therapy experience a "wash out" of their truncal fat percentage.

Novo Nordisk stated that they had considered this but did not agree that it should be the primary analysis:

> Novo Nordisk has considered this but does not find that the multiple imputation (MI) analysis would be the preferred primary analysis as it is seen more as a sensitivity analysis method where different effect trajectory assumptions can be evaluated as worst case scenarios to support the evaluation of the result from the primary analysis. Furthermore recent work indicates that the coverage of the confidence interval (CI) obtained by MI is larger than the nominal coverage.

Discussion in the meeting included the following (from EOP2 Meeting Minutes):

> *We did not agree with your approach. You should conduct analyses in line with the ITT principle. Missing at Random or Missing Completely at Random assumptions are unlikely to hold. Your primary analysis of change in truncal fat percentage should take*

> *into account that patients with missing data are different from those who do not have missing data. You agreed that you would follow the approach described in our preliminary comments.*

FDA comment concerning sponsor's proposed comparison between Somapacitan and Norditropin:

> In addition, clarify the purpose of the secondary comparison (NNC0195-0092 vs. Norditropin® FlexPro®) for the main trial. If it is intended for a labeling claim, multiplicity issues need to be addressed. Also, it is not clear whether the secondary comparison is a superiority or non-inferiority test since you mentioned that 95% CI and p-value will be calculated.

Novo Nordisk response:

> The purpose of the second comparison (NNC0195-0092 vs. Norditropin® FlexPro®) for the main trial is to support the clinical judgment of the clinical relevance of the estimated treatment difference between NNC0195-0092 and placebo as mentioned in the protocol under section 17.3. The inclusion of the Norditropin® arm has been agreed to with CHMP during an advice in 2013.
> In order to not confuse the purpose of the second comparison Novo Nordisk intends to report the estimate and the corresponding confidence interval and not report p-value for the secondary comparison of the primary endpoint.
> The comparison of NNC0195-0092 vs. Norditropin® FlexPro® is not intended for a labelling claim. It is however the intention to describe the clinical trial results in the labelling.

FDA also stated that

> … Your analysis population for efficacy is essentially a completer population. You should conduct analyses based on a population that is in line with the ITT principle.

This submission included one confirmatory efficacy trial, Study 4054 (Figure 1), and two trials for safety (Studies 4043 and 4244). Both safety studies were for previously treated AGHD patients: Study 4043 was for previously treated AGHD patients, and Study 4244 was for previously hGH-treated Japanese AGHD patients. The efficacy trial, Study 4054, was for treatment-naïve patients. From protocol inclusion criteria for Study 4054:

> hGH treatment naïve or no exposure to hGH or GH secretagogues for at least 180 days prior to randomisation with any registered or investigational hGH or GH secretagogue product (if only used in connection with stimulation tests for diagnosis of GHD, subjects can be included)

This review focuses on the efficacy trial, Study 4054. The study was double-blind for the Somapacitan and placebo arms, and open-label for the active control and Norditropin arm. A double dummy design involving the Norditropin arm would confound comparisons of injection site reactions between Somapacitan and Norditropin.

From Section 5.2 of Protocol for Study 4054:

The randomized, placebo-controlled, partly double-blind, active controlled, multicentre design is based on regulatory scientific advices. The inclusion of the active controlled arm in an open design is to compare efficacy and safety including local tolerability of NNC0195-0092 to daily Norditropin® FlexPro® treatment.

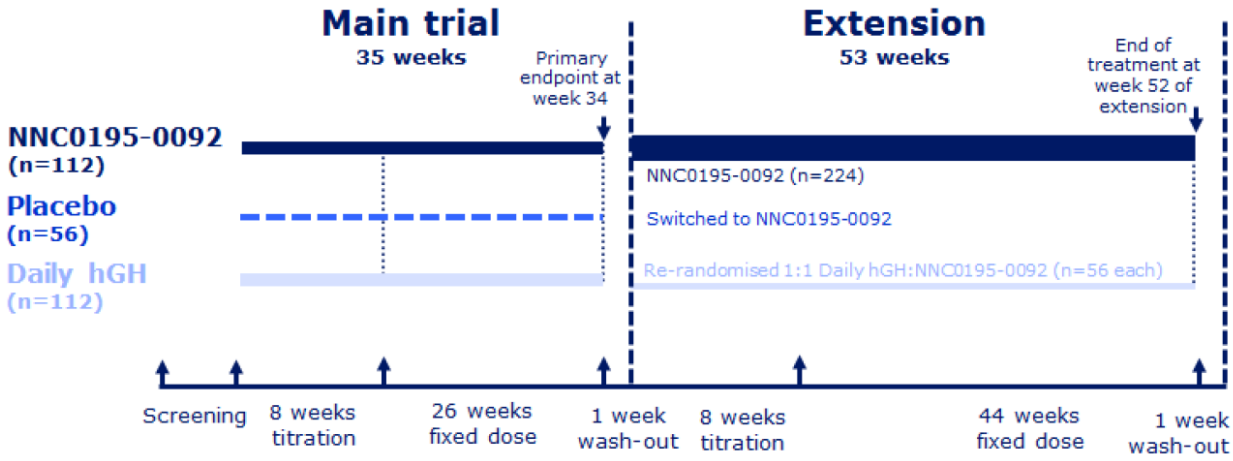

Figure 1: Design for Study 4054
Source – protocol for Study 4054, Figure 5-1; Abbreviations: hGH- human growth hormone; Two hundred and eighty (280) subjects will be randomized in a 2:2:1 ratio to receive Somapacitan, Norditropin, or placebo during a 35-week period (8 weeks of titration, followed by 26 weeks of treatment and 1 week of washout). The randomization will be stratified by region (Japan and all other countries), sex (male and female) and diabetic status. All subjects completing the 35-week period will continue their active treatment with Somapacitan weekly injection or Norditropin daily injection in a non-placebo-controlled design for an additional 53-week extension period (8 weeks of titration, followed by 44 weeks of treatment and 1 week of washout). Placebo subjects will be switched to Somapacitan treatment and Norditropin patients will be re-randomized 1:1 to Somapacitan or Norditropin within the same strata as used for the first randomization. During the extension period subjects will be assessed "on a regular basis" for adverse events, safety laboratory measurements, and efficacy.

2.2 Data Sources

The data and final study report for BLA 761156 were submitted electronically as an eCTD submission. The submission is archived at the following link.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SDTM and ADaM data sets are located in the proper sections of the submission, and analysis reviewer guides are provided which define variables and their locations. I also checked for data quality issues and found the data quality to be satisfactory.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary and secondary endpoints for Study 4054 are shown in Table 1 below. All endpoints are assessed at 34 weeks. There is no pre-specified hierarchical testing procedure. Secondary endpoints included truncal fat mass and truncal lean body mass.

Table 1: Primary and Secondary Endpoints

Endpoint Type	Study	Description
Primary	4054	Change from baseline in % Truncal Fat Week 34
Secondary*	4054	Truncal fat mass -Week 34
Secondary*	4054	Truncal lean body mass – Week 34
Primary	4043	Incidence of adverse events, including injection site reactions from baseline to the end of the treatment period – Week 26
Primary	4244	Incidence of adverse events, including injection site reactions from first administration of trial product to end of the trial period (53 weeks including follow-up)

*Body composition measured by DXA (Dual-energy X-ray absorptiometry); bone mineral density measured using spectral imaging truncal fat percentage is defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass (kg) and truncal lean body mass (kg); there was no testing hierarchy for secondary endpoints

Multiple Testing Procedure

No multiple testing procedure was pre-specified for secondary endpoints.

Non-Inferiority Margin

A non-inferiority margin was not specified for Somapacitan vs. Norditropin for percent truncal fat. However in Section 17.1 of the protocol (Sample Size Calculation), it states:

> …The assumptions of a true mean difference of 2.5% between active treatment and placebo and a SD of 4.5% is slightly conservative to what is observed in similar trials. In a secondary comparison of the primary endpoint, it will be possible to expect with probability 0.87 that half the length of the 95% confidence interval (CI) constructed for the difference between NNC0195-0092 [Somapacitan] and Norditropin® FlexPro® will be at most 1.3% if additional 104 subjects are enrolled in the Norditropin® FlexPro® treated group, resulting in a total of 260 subjects to be included in the trial. Expecting at most 7% drop-out from the trial, 280 subjects should be included in the trial.

It also states, in Section 17.3 of the protocol (Primary Endpoint) that:

> …The secondary comparison, comparison of NNC0195-0092 [Somapacitan] with Norditropin® FlexPro®, will be used to assist the clinical judgment of the clinical relevance of the estimated treatment difference between NNC0195-0092 and placebo.

From this information, it appears that the comparison of Somapacitan vs. Norditropin is a secondary comparison of the primary endpoint meant to assist in determining the clinical meaningfulness of the difference between Somapacitan and Placebo. Therefore these results for

this secondary comparison are presented along with analysis results for the other endpoints in Section 3.2.4 (Results and Conclusions).

3.2.2 Statistical Methodologies

3.2.2.1 Sponsor Approach

The sponsor's primary analysis population is the Full Analysis Set (FAS) consisting of all randomized subjects who received at least one dose of randomized treatment. The sponsor's defined primary analysis approach for continuous endpoints, including the primary endpoint of change in percent truncal fat, is ANCOVA. A method similar to Copy Reference is used to address missing data. Baseline percent truncal fat is included as a covariate in the ANCOVA model, and treatment, GHD onset type (adult or child), sex, region, diabetes status, and sex by region by diabetes status interaction are included as factors. Missing final assessments (regardless of treatment discontinuation) are multiply imputed using an ANCOVA model, based on trajectory in placebo arm. From protocol:

> … the trajectory after a withdrawn subject's last observation is imputed based on data from the placebo arm…

For patients who have no intermediate or final assessments, this approach is similar to a washout multiple imputation, where final assessments of patients on the treatment arm (or placebo arm) are multiply imputed based on final assessments on the placebo arm. For patients who do have intermediate assessments, a time-weighted approach is used, based on a patient's last observed assessment, and the proportion of time from randomization this represents of the 34 week efficacy period. From sponsor's program code comments for primary endpoint:

> If a truncal fat assessment for a subject has been performed after baseline at intermediate time t (e.g. in connection with the end-of-trial visit for withdrawn subjects) this information will be combined with the time-normalized model based estimate so that the final imputed value for the subject is a sum of the observed value at time t and the model based estimated change multiplied by (34 weeks -t) / (34 weeks) minus the baseline value.

3.2.2.2 Reviewer Approach

Estimand

The preferred estimand is the treatment policy estimand which includes all data within the final assessment window (34 weeks +/- 4 weeks) regardless of intercurrent events such as treatment discontinuation or initiation of alternative therapy. The analysis population is all randomized subjects who have been exposed to treatment and have a baseline measure. The preferred analysis method is an ANCOVA with the same covariates and factors as proposed by the sponsor. Results using this ANCOVA method with a defined final assessment window were similar to the sponsor's analysis results. Due to the unequal randomization ratio between Somapacitan and placebo, an ANCOVA allowing unequal variances between treatment groups

was also conducted as a sensitivity analysis. Results using this method were consistent with the preferred analysis. The missing data and discontinuation rates were very low. Section 3.2.2.3 and Section 3.2.4 provide more detail.

3.2.2.3 Patient Disposition

A total of 457 patients were screened, and 301 of these patients were randomized: 121 were randomized to Somapacitan arm, 61 to Placebo arm, and 119 to Norditropin (Table 2). One patient randomized to Somapacitan was not treated and is not included in Table 2. No treated patient on the Somapacitan arm discontinued due to an adverse event; four patients on the Norditropin arm, and one patient on the Placebo arm discontinued due to an adverse event. There was no rescue medication mentioned in the protocol except for subjects diagnosed with diabetes. From Section 8.5.6 of the protocol, second paragraph:

> Rescue criterion for subjects diagnosed with diabetes mellitus before inclusion into the trial: If the HbA1c increases clinically significantly during the trial, the investigator should consider adjusting the anti-diabetic medication according to local practice.

Characterization of Missing Data

Missing Rates, Discontinuation Rates, and Rescue Rates

All subjects that had no assessment at the Week 34 window (within 34 +/- 4 weeks from randomization) are counted as having missing data for the final assessment. Missing rates, and study treatment discontinuation rates are shown in Table 2. For the population of randomized treated patients with a baseline measure, the rate of missing primary efficacy data was very low: 1.7% on Somapacitan, 3.6% on Norditropin and 3.5% on Placebo.

Table 2: Descriptive statistics for patients having primary efficacy data, and patients discontinuing treatment.

Treatment	Patients Rand. / Treated	Patients Rand. Treated With BL	Rand. Treated With BL, No Imputed BL*	Disc. Treatment Early**	Disc. Treatment Early, and Missing	Did not Disc. Treatment Early, Missing	Missing	% Missing
Somap.	120*	117*	116	4	2	0	2***	1.7
Nord.	119	111	111	3	3	1	4	3.6
Placebo	61*	57*	56	2	2	0	2	3.5

Abbreviations: Somap.-Somapacitan; Nord. – Norditropin; Rand-randomized; BL-baseline measure; Disc-Discontinued; Treat.-treatment; *Subjid (b) (6) (on Somapacitan arm) and (b) (6) from Turkey (on placebo arm) had imputed baseline values - these two subjects were not included in following columns (columns to the right); **Based on discontinuing 4 weeks early (210 days or earlier). ***Patient (b) (6) (on Somapactian arm) discontinued treatment early due to move out of state; they were no longer able to continue in trial – this probably would not happen if the drug were approved and generally available - so this can be considered an artifact of the approval process– not related to drug itself. This patient can therefore be considered as missing completely at random; two or three other patients had similar reasons for withdrawing (Patient (b) (6) on Norditropin – "relocated to native land…", patient (b) (6) (Somap - patient has gone abroad, no study visits could be performed). Patient (b) (6) (Somapacitan) was "included in trial in violation of inclusion and/or exclusion criteria". Patient (b) (6) on placebo died – this was assessed as being unlikely related to drug product.

3.2.3 Demographic and Baseline Characteristics

The distributions of baseline demographic characteristics for Study 4054 is shown in Table 3. Study 4054 is the only efficacy study, and the only study to evaluate the primary endpoint of percent truncal fat. Characteristics, including baseline truncal fat percentage, seem evenly distributed between treatments arms. The baseline percent truncal fat was 39.0% for Somapacitan, 37.9% for Norditropin, and 37.4% for the placebo arm. Patients were mostly from the regions of Asia, North America, and Europe; for the Somapacitan and Placebo arms, the Asian race group consisted of 48 Asians from Asia and one Asian from North America. There were five Black/African American patients; two randomized to Somapacitan, one randomized to Placebo, and two randomized to Norditropin.

Table 3: Demographics and Baseline Characteristics by Treatment Arm - Study 4054

Treatment Group	**Somapacitan**	**Placebo**	**Norditropin**
N per Group	**116**	**56**	**111**
Sex, n (%)			
F	61 (53)	31 (55)	56 (50.5)
M	55 (47)	25 (45)	55 (49.5)
Race, n (%)*			
Asian	34 (29)	15 (27)	34 (30.6)
Black/AA	2 (2)	1 (2)	2 (2)
White	78 (67)	39 (70)	71 (64)
Haw/Pac.	1 (1)	0 (0)	0 (0)
Other	1(1)	1 (2)	4 (4)
Ethnicity, n (%)			
Hispanic or Latino	6 (5.2)	4 (7.1)	8 (7.2)
Age			
Mean (SD)	44.9 (14.3)	45.1 (15.4)	46 (15.6)
Median (min - max)	44 (23 - 75)	46 (23 - 72)	46 (23 – 77)
>=65, n (%)	13 (11)	9 (16)	18 (16.0)
< 65, n (%)	103 (89)	47 (84)	93 (84)
Region, n (%)			
Europe	36 (31.0)	20 (35.7)	37 (33.3)
Asia	46 (39.7)	22 (39.3)	40 (36.0)
North Am.	30 (25.9)	14 (25.0)	30 (27.0)
Africa	4 (3.5)	0 (0.0)	4 (3.6)
Baseline Truncal Fat (%)			
Mean (SD)	39.0 (8.8)	37.4 (8.9)	37.9 (9.5)
Median (min - max)	38.8 (15.0 – 60.5)	36.8 (21.6 - 57.3)	37.9 (13.5 – 58.5)
BMI (kg/m^2)			
Mean (SD)	27.9 (6.4)	26.4 (6.4)	27.6 (6.4)
Median (min - max)	26.9 (17.6 -47.2)	25.6 (17.7 – 44.3)	27.0 (17.0-41.4)
Diabetes Status, n (%)			
Y	7 (6.0)	3 (5.4)	6 (5.4)
N	109 (94)	53 (64.6)	105 (94.6)
GH Onset, n (%)			
Adulthood Onset	79 (68)	39 (70)	80 (72)
Childhood Onset	37 (32)	17 (30)	31 (28)

* Abbreviations/Definitions: GH-Growth Hormone; Black/AA – Black or African American; Haw/Pac.-Native Hawaiian or Other Pacific Islander; North Am. -North America; BMI Body Mass Index

3.2.4 Results and Conclusions

The primary efficacy endpoint was available on only one of the three studies – Study 4054. The primary endpoint of change from baseline in percent truncal fat (%) (Somapacitan vs. Placebo) demonstrated superiority using the sponsor's Copy Reference (CR) analysis (Table 4), and using my ANCOVA model (Table 5). I used the same covariates and factors as the sponsor (Section 3.2.2.1). However, for region, I included Europe, North America, Asia, and Africa, whereas the sponsor included only Japan and "Rest of World". Because of the low missing data rate (1.7% for Somapacitan and 3.5% for Placebo for randomized treated patients with a baseline measure), the reasons for discontinuation (Table 2), and the fact that no patient on the Somapacitan arm discontinued treatment early due to an adverse event, I did not use a method to address missing data. The treatment difference in percent truncal fat was -1.53% using the sponsor's CR method (Table 4), -1.41% using my ANCOVA in Table 5, and -1.61% median difference using ANCOVA with unequal variances (also Table 5). Of note, there was an increase in percent truncal fat on the Placebo arm (0.47% using the sponsor's method and 0.31 % using my ANCOVA model). This positive change from baseline for Placebo arm may indicate that, without treatment, percent truncal fat, (and perhaps the AGHD condition) on average, is likely to increase/worsen over time.

At the same time, the sponsor's secondary comparison of the primary endpoint of percent truncal fat, intended to be used to help assess the clinical meaningfulness of the primary comparison of the primary endpoint, demonstrated statistical inferiority of Somapacitan vs. Norditropin, (though statistical non-inferiority was not pre-specified or required). The magnitude of the difference between Somapacitan and Norditropin is almost as much as the difference between Somapacitan and Placebo, but in the opposite direction. The treatment difference (Somapacitan vs. Norditropin) was 1.28% (95% CI: 0.29%, 2.26% - Table 5). The change in % truncal fat for Somapacitan was less than half that for Norditropin: -1.10% for Somapacitan vs. -2.38% for Norditropin – Table 5.

There was no multiple testing procedure for the secondary endpoints of change in truncal fat mass and change in truncal lean body mass. Change in truncal fat mass was not statistically significant (Tables 4 and 5). These two secondary endpoints are components of the primary endpoint and are therefore correlated with it. From protocol, Section 17.3:

> …truncal fat percentage is defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass (kg) and truncal lean body mass (kg).

Table 4: Primary and Secondary Endpoints – Sponsor's Copy Reference/ Analysis Results*

Endpoint*	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val
Change in % Truncal Fat	-1.06	0.47	-1.53	-2.68	-0.38	0.009
Change in Truncal fat mass (g)	-123	373	-496	-1049	57	0.075
Change in Truncal lean body mass (g)	804	352	452	25	880	0.038

.*All endpoints are assessed at Week 34 – . No multiple testing procedure was used to control Type 1 error over primary and secondary endpoints; Abbreviations: g – gram; Exp.-Experimental Arm; Ctr.-Control Arm; Diff.-Treatment Difference;–LCL-Lower Confidence Limit; UCL Upper Confidence Limit ; P-Val-P-Value.

Table 5: Primary and Secondary Endpoints – My ANCOVA Results

Endpoint	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val
Change in % Truncal Fat *	-1.10	0.31	-1.41*	-2.61	-0.22	0.02
ANCOVA, Unequal Var.**			-1.56**	-2.51	-0.62	
Change in Truncal fat mass (g)	-145	343	-488	-1015	39	0.069
Change in Truncal lean body mass (g)	811	381	430	-0.4	860	0.0502
	Soma.	Nord.	Diff	LCL	UCL	P-Val
Change in % Truncal Fat	-1.10	-2.38	1.28	0.29	2.26	0.011

.*All endpoints are assessed at Week 34 – . No multiple testing procedure was used to control Type 1 error over primary and secondary endpoints; Abbreviations: g-gram; Exp.-Experimental Arm; Ctr.-Control Arm; Diff.-Treatment Difference; LCL-Lower Confidence Limit; UCL Upper Confidence Limit; P-Val-P-Value; Var.-Variance; SOMA. – Somapacitan; Nord.-Norditropin; *If the three-way interaction is taken out, the treatment difference between Soma and Placebo is -1.50, and p-value is 0.01; **In this analysis, residuals are derived from ANCOVA model including all factors/covariates except treatment. Then Hodge-Lehman method is conducted on residuals to ascertain treatment effect shown in table; -1.56 is the confidence interval midpoint; -1.61 is the location shift (median difference).

3.3 Evaluation of Safety

There were no randomized treated patients on the Somapacitan arm who discontinued treatment due to an adverse event during the 34-Week efficacy assessment period. There were four patients on the Norditropin arm, and one patient on the Placebo arm who discontinued due to an adverse event.

There were very few patients with injection site reactions in either of the two safety studies (one to two on each arm- all mild in severity). In Study 4054, there were two patients on Somapacitan and six on Norditropin who had an injection site reaction possibly/probably related to trial product. These adverse events were also rated as mild/moderate in severity. From the Summary of Clinical Safety for the three studies, there was a numerically smaller rate of injection site reactions for Somapacitan than for Norditropin. However the rate was small for both arms (two to 6 adverse events per 100 patient years.

Please refer to the review of Dr. Geanina Roman-Popoveniuc for a thorough safety evaluation.

3.4 Benefit-Risk Assessment

Somapacitan shows a small benefit for change in percent truncal fat, compared to placebo, though this benefit is not as large as that for Norditropin. The risks due to adverse events, including adverse events related to injection site reactions, are also small for Somapacitan, as they are for Norditropin. However, for some patients there may still be a preference for weekly injections over daily injections, even if they do not experience an injection site adverse event on Norditropin. These patients may be able to tolerate Somapacitan treatment for a longer period of time (or they may switch from Norditropin to Somapacitan and be able to continue treatment for a longer period of time than they would had they had not had that choice). There may be a favorable benefit risk for a subset of patients who do not tolerate, or do not prefer daily injections. Please see the clinical review of Dr. Geanina Roman-Popoveniuc for a more thorough benefit-risk assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

To assesses the effect of Somapacitan compared to Placebo within sex, race, age, and region, subgroup analyses were conducted for the primary endpoint using the preferred ANCOVA analysis defined in Section 3.2.2.2. These are shown in Table 6. Subgroups such as Black/African American were not included in Table 6 due to inadequate sample size. Change in percent truncal fat was the outcome variable with baseline value as a covariate, and GHD onset type (adult or child), sex, region, diabetes status, and sex by region by diabetes status interaction are included as factors.

Table 6: Treatment Differences in Change in Percent Truncal Fat, by Subgroup

Subgroup	Sample Size*	Estimate	Lower 95%	Upper 95%
Overall	172	-1.41 (0.61)	-2.61	-0.22
Female	92	-0.77 (0.83)	-2.42	0.88
Male	80	-2.47 (0.88)	-4.22	-0.72
White	117	-1.20 (0.74)	-2.67	0.27
Asian**	49	-2.04 (1.26)	-4.56	0.47
Age $\geq$ 65	22	-1.55 (1.27)	-4.15	1.06
Age < 65	150	-1.66 (0.68)	-3.01	-0.31
North Am.***	44	1.41 (0.96)	-0.52	3.33
Europe	76	-2.91 (1.09)	-5.08	-0.74
Asia**	48	-1.97 (0.94)	-3.84	0.09

Abbreviations: North Am.-North America;*Sample Sizes for subgroups include only patients on Somapacitan and Placebo arms. The Norditropin arm was included in analysis, but only Somapacitan vs. placebo was evaluated for treatment difference; ** 48 of the 49 Asian race group were from the Asia region; one Asian was from North America. Therefore region was included in the frequentist analysis, but not in the shrinkage analysis. ***All patients in the North American region were from the US.

In the traditional frequentist subgroup analysis shown in Table 6, there are random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derived shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates in Table 6. The total variability in the sample estimates is the sum of the within-subgroup variability of the sample estimator and the across-subgroup variability in the underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows

information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and the overall estimate. The weights are based on the ratio of the between-subgroup variability to the within-subgroup variability. The greater the ratio, the smaller the weight on the overall estimate (the less the shrinkage). We used the same flat prior distribution to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:
For $i = 1, 2\ldots$, Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for the subgroup sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 40)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001)

The results of the sample estimates and the shrinkage estimates of treatment effects/treatment differences in the subgroups, are presented in Figure 2. Due to high correlation between the Asian race group and Asian region group, region was not included in the shrinkage analysis shown in Figure 2. However shrinkage analysis including region is in the Appendix (Figure A1), and the frequentist estimates for region are also shown in Table 6.

The North America region was the only region with a positive treatment difference in change in percent truncal fat; this region also has high variability due to the relatively small sample size of 44 patients: 30 on Somapacitan and 14 on placebo: the estimated treatment difference is 1.41 (Somapacitan vs. Placebo), with 95% CI of (-0.52, 3.33) using the frequentist approach (Table 6) and 0.65, with corresponding intervals of (-1.54, 2.73) from the shrinkage analysis (Figure A1 in Appendix). The shrinkage analysis brings the North America region closer to the other region effects, but it still has a positive treatment effect which stands out somewhat from other regions and other subgroup effects. This treatment difference in the North America region is due both to a high negative placebo effect in the North America region of -1.70 (the Asia and Europe regions have positive placebo effects of 0.26 and 1.85 respectively), and a small treatment effect for Somapacitan in the North America region of -0.29, compared to -1.70 and -1.06 in the Asia and Europe regions respectively. Similar patterns are found for Appendicular Skeletal Muscle Mass (ASMM) and Visceral Adipose Tissue (VAT) endpoints (Tables not shown). These endpoints were selected to further explore the North America treatment difference.

However the North America placebo group sample size is only 14, and while results are suggestive, it is difficult to make firm conclusions with such a small sample size for the placebo effect. For example, the sponsor conducted sensitivity analysis excluding three patients from the North American region, all from the same site. These three have the most negative change from baseline in percent truncal fat of all 14 North America placebo patients (and all placebo patients as well). These three patients also had BMI (Body Mass Index) at baseline ranging from 28 to 44 kg/m^2. Two of the three were given alternative therapies that could have contributed to decreased percent truncal fat, and one developed clinically significant hepatic disease and did not complete treatment. The sponsor conducted sensitivity analysis excluding these three patients. If these three patients are excluded from analysis, the overall treatment difference between Somapacitan and Placebo increases from -1.41 to -1.85, and the North American subgroup effect goes from 1.41, to 0.10. These are post-hoc analyses, but they do suggest possible reasons for differences in the North American region.

It is well known that obesity is higher in the US region than in other regions. Descriptive statistics for BMI and percent truncal fat at baseline, are shown by region in Table 7 below. The North America region has the highest average BMI (31.2 kg/m^2 for North America vs. 26.9 kg/m^2 or less for the other regions). It also has the highest average baseline percent truncal fat of all regions. However, the difference between regions is more pronounced for baseline BMI than for baseline percent truncal fat. Therefore, to explore whether BMI could be a treatment effect modifier, I conducted analysis with change in percent truncal fat as response, treatment as a factor, baseline BMI as a covariate, and treatment by BMI as an interaction effect. The p-value for the interaction effect was 0.002. (The purpose of this model is not to assess treatment effect/difference itself, but to determine if an increase or decrease in the BMI covariate could change the treatment difference). Using this model, the treatment effect for Somapacitan vs. Placebo was -1.57 (95% CI: -2.73, -0.41) and -2.80 for Norditropin vs. Placebo (95% CI: -3.97, -1.64). For the North American region, it was 0.64 for Somapacitan vs. Placebo – still positive, but much less than 1.41. Perhaps Somapacitan is not a suitable (or is a less effective) treatment for patients with very high BMI levels, or with severe comorbid conditions, since the treatment effect for Somapacitan is small (unless it can be used as an add-on or in combination with other treatments). For example, if using the same covariates/factors for the primary analysis for the primary endpoint, but only including patients with BMI $\geq$ 27 kg/m^2, the treatment difference is -0.97 instead of -1.41.

Table 7: Baseline Values for BMI and Percent Truncal Fat by Region

Region	N	Mean	SD
BMI at Baseline			
Africa	8	26.9	9.5
Asia	108	25.6	5.0
Europe	93	26.8	5.7
North Am	74	31.2	6.9
% Truncal Fat at Baseline			
Africa	8	36.7	8.9
Asia	108	36.5	8.1
Europe	93	38.8	9.4
North Am	74	40.1	9.8

Abbreviations: BMI-Body Mass Index (kg/m^2). SD-Standard Deviation

All patients in the North America subgroup were from the United States. The Black/African American group, which was not included in Table 6 due to small sample size (two on the Somapacitan group and one on the Placebo group), has a difference in unadjusted raw means of -1.37.

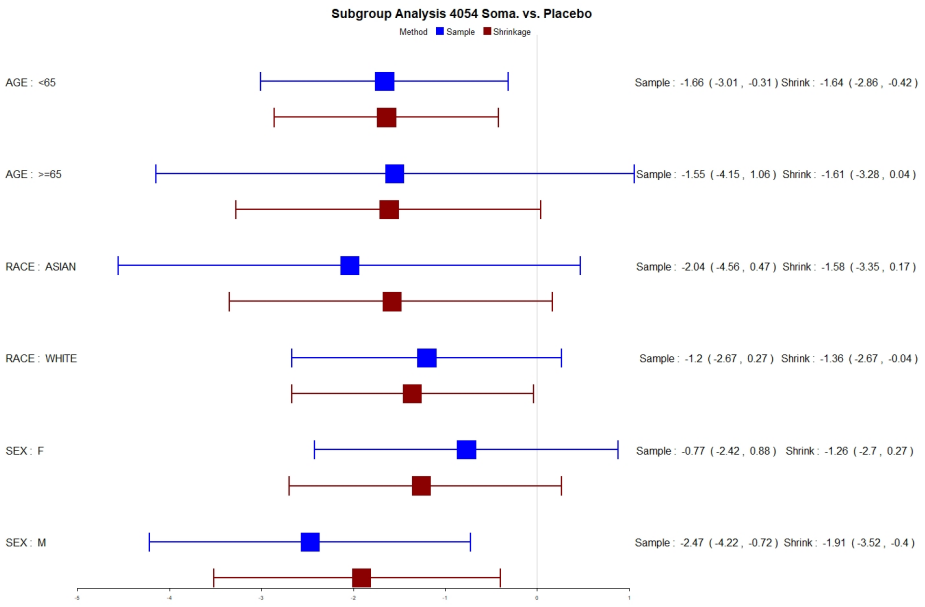

Figure 2: Forest Plot Comparing Frequentist Subgroup Analysis to Bayesian Shrinkage Analysis
48 of the 49 Asian race group were from the Asia region; one Asian was from North America. Therefore region was included in the frequentist analysis (Table 6), but not in the shrinkage analysis in this figure due to the high correlation between region and race in the Asian group. Shrinkage analysis including region is in the Appendix.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The following are some potential statistical issues identified during the review.

- Study 4054 is the only of the three studies in this BLA which includes the primary efficacy endpoint of change in percent truncal fat.
- This primary endpoint is statistically significant in favor of Somapacitan in Study 4054. However the treatment difference is small, and a determination of clinical meaningfulness is needed.
- There are Section 14 tables in the proposed label for many secondary efficacy endpoints that were not pre-specified, and there was no multiple testing procedure to control Type 1 error for secondary endpoints.
- The treatment effect in the North America region goes in the opposite direction as the overall effect, and it has the same magnitude.
- Somapacitan is statistically inferior to Norditropin, and the magnitude of the difference is almost as much as the difference between Somapacitan and Placebo.

5.2 Collective Evidence

The primary endpoint of percent truncal fat was statistically significant in favor of Somapacitan in comparison to placebo in Study 4054. The missing data and discontinuation rate were very low. No major safety issues have been identified. The secondary endpoints were also numerically in favor of Somapacitan. Though Somapacitan was statistically inferior to Norditropin, non-inferiority was not pre-specified and is not a requirement for approval.

5.3 Conclusions and Recommendations

Somapacitan is statistically superior to Placebo, and it is statistically inferior to Norditropin. Issues such as clinical meaningfulness are currently still being discussed at the time of this review, and a determination has not yet been made. If it is determined that the results are clinically meaningful, the once weekly injections for Somapacitan may be beneficial for those patients who do not prefer, or have difficulty tolerating daily injections using Norditropin. However, since the treatment effect of Somapacitan is small, it might not be adequate for patients with a serious AGHD condition, and/or with severe obesity/BMI, unless it can be used in combination with other therapies.

5.4 Labeling Recommendations

If the drug is approved, Section 14 of the label should include only descriptive results for secondary endpoints, if it is determined that they provide useful information for patients and prescribers. Labeling discussions are still ongoing while this review is being finalized.

6 APPENDIX

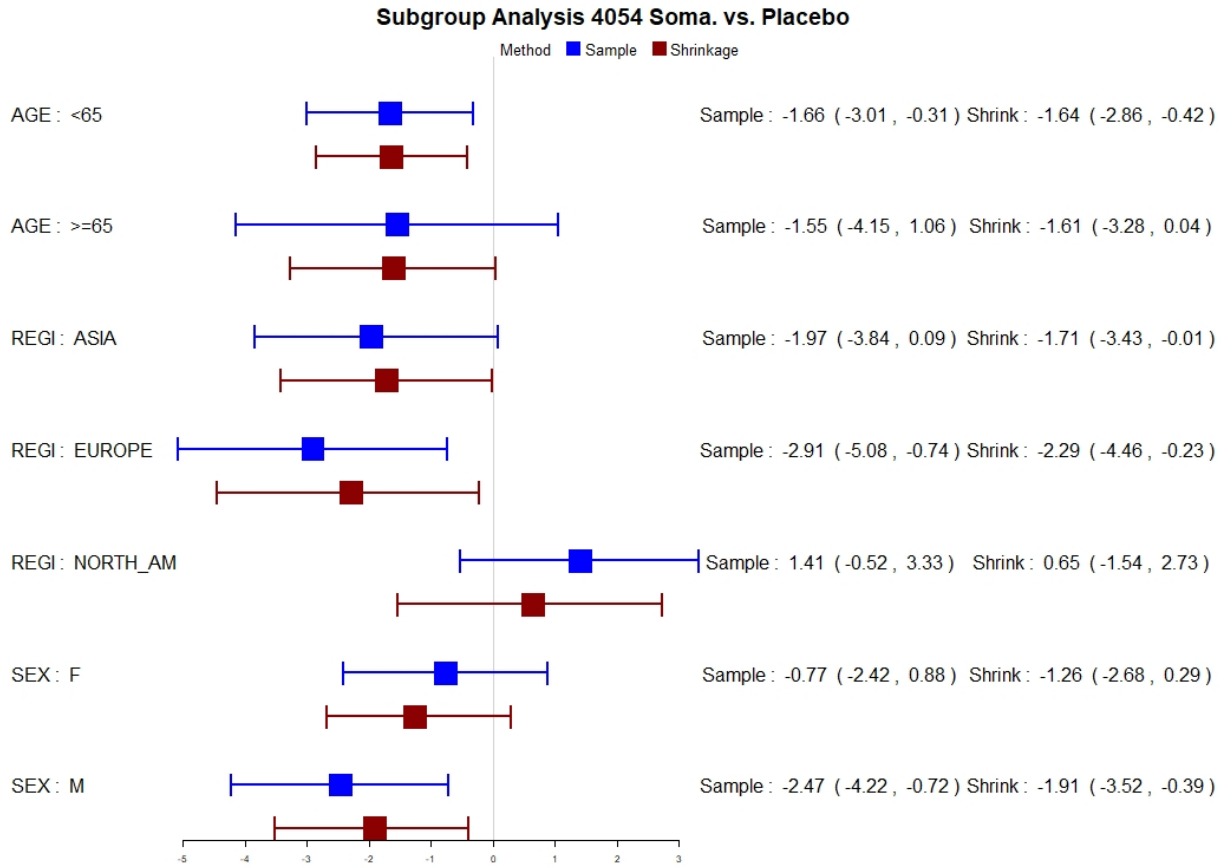

Figure A1: Shrinkage Analysis Including Region (and Excluding Race due to Correlation with Region).

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