CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761156Orig1s000

SUMMARY REVIEW
### Cross-Discipline Team Leader Review

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<th><strong>Date</strong></th>
<th>8/6/2020</th>
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<tr>
<td><strong>From</strong></td>
<td>Marina Zemskova, MD</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Cross-Discipline Team Leader Review</td>
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<td><strong>NDA/BLA # and Supplement#</strong></td>
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<td><strong>Applicant</strong></td>
<td>Novo Nordisk</td>
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<td><strong>Date of Submission</strong></td>
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<td><strong>Proprietary Name</strong></td>
<td>Sogroya</td>
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<tr>
<td><strong>Established or Proper Name</strong></td>
<td>Somapacitan-beco</td>
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<tr>
<td><strong>Dosage Form(s)</strong></td>
<td>10 mg/1.5 mL prefilled pen</td>
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<td><strong>Applicant Proposed Indication(s)/Population(s)</strong></td>
<td>Replacement of endogenous growth hormone in adults with growth hormone deficiency</td>
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<td><strong>Applicant Proposed Dosing Regimen(s)</strong></td>
<td>Starting dose: 1.5 mg/week; 1.0 mg/week (patients &gt; 18 years old); 2.0 mg/week (women receiving oral estrogen). Maximum dose: 8 mg/week</td>
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<td><strong>Recommendation on Regulatory Action</strong></td>
<td>Approval</td>
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#### Material Reviewed/Consulted

| Medical Officer Review | Geanina Roman-Popoveniuc |
| Statistical Review     | Alexander Cambon, Feng Li |
| Pharmacology Toxicology Review | Huiqing Hao, Federica Basso |
| OPQ Review             | Arulvathani Arudchandran, Vicky Borders-Hemphill, Wayne Seifert, Ziyang Su, Candace Gomez-Broughton, Sharon Kelly, Su (Suong) Tran, Patrick Lynch, Xianghong (Emily) Jing |
| CDRH Review            | Matthew Ondeck, Rumi Young, Alan Stevens |
| Clinical Pharmacology Review | Mohammad (Abir) Absar, Sang Chung, Lian Ma, Jayabharathi Vaidyanathan |
| OPDP                   | Charuni Shah, Melinda McLawhorn |
| OSE/DMEPA              | Melina Fanari, Sevan Kolejian |
| DPMH                   | Jeanine Best, Tamara Johnson |
| DRM                    | Till Olickal, Naomi Boston |

OND=Office of New Drugs  
OPQ=Office of Pharmaceutical Quality  
OPDP=Office of Prescription Drug Promotion  
OSE= Office of Surveillance and Epidemiology  
CDRH= Center for Devices and Radiological Health  
DMEPA=Division of Medication Error Prevention and Analysis  
DPMH=Division of Pediatric and Maternal Health  
DRM=Division of Risk Management

Reference ID: 4652775
1. **Benefit-Risk Assessment**

**Benefit-Risk Assessment Framework**

The Applicant has proposed marketing somapacitan-beco, a long acting recombinant human growth hormone (rhGH) derivative with a single point mutation in the rhGH backbone to which a non-covalent albumin-binding moiety has been attached, for the following indication: *replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD)*.

AGHD is a well-characterized condition that can persist from childhood or be newly acquired secondary to structural lesions within or trauma to the pituitary gland. GH (also known as somatropin) deficiency results in inadequate circulating insulin-like growth factor 1 (IGF-I) levels leading to decrease in lean body mass, increase in fat mass, weakness, reductions in exercise capacity, and diminished quality of life.¹

Over the last decades, professional guidelines have recommended GH replacement therapy in adults with GHD. Exogenous somatropin treatment aims at mimicking the function of inadequate GH secretion (i.e. a replacement therapy) leading to normalization of IGF-1 levels and improvement in symptoms and signs of GHD. As per Endocrine Society Guidelines on treatment of AGHD (2011) ², the demonstrated benefits of GH replacement therapy include improvements in body composition, exercise capacity and quality of life. The Endocrine Society emphasizes that “long-term clinical outcome studies on hard endpoints such as fractures, heart disease, cancer, and mortality are still lacking” and GH has not been shown to improve mortality to date.

Seven rhGH products are currently approved and marketed in the US for the replacement of endogenous GH in AGHD.³ Documentation of a drug-induced improvement in body composition parameters has been used historically as a validated surrogate of benefit to establish the efficacy and support the approval of these rhGH formulations. GH and IGF-1 deficiencies in these patients are associated with various signs and symptoms including altered body composition. Replacement of missing hormones with rhGH leads to the improvement in body composition parameters levels and other hormone-associated abnormalities and establishes the benefit of these drugs for that indication. Registration trials have shown that all approved rhGH products improve various body composition parameters (e.g., decrease in total fat mass, trunk fat percent, increase in lean body mass) at different degrees via drug-induced normalization of IGF-1 levels in patients with AGHD. It must be noted that none of the observed thresholds of the improvement in body composition in patients with GHD have been directly linked to an outcome of morbidity/mortality reduction to date and none of the trials established that use of rhGH in patients with AGHD reduce cardiovascular risk or mortality. Thus, FDA accepted statistically significant changes in body composition without prespecified thresholds as a main source of evidence of effectiveness for pharmacological interventions only in the specific condition of AGHD, where clinical manifestations can be traced to a specific hormone deficiency and these manifestations can be reversed by hormone replacement at physiologically justified doses.

**Benefits**

The Applicant demonstrated, in a single adequate and well-controlled trial carried out in adults with GHD that somapacitan-beco significantly reduced baseline trunk fat percentage (TFP) compared to placebo at the end of 34 weeks. Study 4054 was a Phase 3, 34-week, randomized, placebo-controlled (double blind) and active-controlled (Norditropin Flex Pro, open label) comparing the efficacy and safety of somapacitan-beco with placebo and Norditropin Flex Pro (refer to as Norditropin hereafter) in 301 treatment-naïve subjects with AGHD. In this trial, the estimated mean treatment difference (ETD) in TFP between somapacitan-beco and placebo groups was -1.5% (95% CI -2.7; -0.4), p=0.009. The results of analyses of secondary endpoints demonstrated that somapacitan-beco therapy in subjects with AGHD also increased lean body mass values (mean trunk lean body mass by 804 g and mean total lean body mass by 1394 g) compared to the placebo group where these values decreased by the end of the study. Mean ETD in mean trunk lean body mass between somapacitan-beco and placebo groups was 452 g and in mean total lean body mass 1144 g (95% CI 459; 1829). Mean IGF-1 standard deviation scores (SDS)

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The Applicant included the active controlled arm to provide a comparison to a currently approved therapy. The results of the secondary analyses comparing improvement in body composition parameters achieved at the end of 34 weeks between somapacitan-beco and Norditropin suggest that at doses of somapacitan-beco and Norditropin used in the trial there was a less pronounced effect of somapacitan-beco on TFP compared to Norditropin (-1.1% vs. -2.4%, respectively). Mean IGF-1 SDS normalized at the end of the study in both groups of subjects: -0.22 in somapacitan-beco group and -0.23 in Norditropin group. The reasons for the observed differences are not clear. One possible explanation is the uneven enrollment of females on oral estrogen in the treatment groups with a larger proportion of these subjects enrolled in somapacitan-beco group (32%) compared to the proportion of oral estrogen users in the Norditropin group (19%). In this subgroup the mean serum IGF-1 was lower in both treatment arms and somapacitan-beco was suboptimally titrated to the target IGF-1 level. Oral estrogen suppresses the GH-induced synthesis of IGF-1 and increase body weight; women on oral estrogens, in general, require higher doses of rhGH to achieve the same IGF-1 response. The conclusion regarding the superiority of Norditropin over somapacitan-beco in reducing fat mass is also complicated by the fact that the comparison was not made at the maximum doses; the higher doses/longer titration in the treatment arms may have negated any difference in efficacy between products when choosing a product for treatment of AGHD. Even if there was no inferential comparison between somapacitan-beco and Norditropin, we believe physicians and patients need to be aware of these differences, and they should be summarized in the label. Overall, we believe that since somapacitan-beco will be titrated to target IGF-1 levels without the constraints imposed by the titration procedures in Study 4054, it is likely that treatment with somapacitan-beco will achieve similar reduction in TFP and other body composition parameters as other rhGH products, while offering once weekly dosing.

**Risks**

The risks associated with the use of somapacitan-beco are generally consistent with risks expected for the rhGH class of drugs. Major toxicities associated with the use of rhGH include the risks of headache, edema, intracranial hypertension, adrenal insufficiency, hyperglycemia, lipodystrophy, injection site reactions, increased risk of immunogenicity and development of new tumors.

The most common adverse events (AEs) that occurred in subjects treated with somapacitan-beco in Study 4054 were nasopharyngitis (20% of subjects compared to 14.8% subjects on placebo), back pain secondary to fluid retention and nerve compression (10% of subjects; compared to 3.3% of subjects on placebo), arthralgia (6.7%; compared to 1.6% of subjects on placebo), allergic reactions (non-anaphylactic, 6.7%, compared to 14.8% of subjects on placebo). AEs of adrenal insufficiency were mild and occurred in 3.3% of subjects treated with somapacitan-beco and in 1.6% of subjects treated with placebo. No adrenal crisis was reported in any of the subjects. Lypohypertrophy/lipodystrophy occurred in 3.3% of subjects treated with somapacitan-beco only, injection site reactions occurred in 1.7% of subjects treated with somapacitan-beco and 4.9% of subjects treated with placebo. The frequencies of these AEs were similar or lower when compared to AEs that occurred in Norditropin group of subjects in this study. No intracranial hypertension or pancreatitis was reported during the study. No malignant or benign tumors related to somapacitan-beco use were reported in the clinical program. However, the relatively short duration of the trials in the clinical program does not allow to make the definite conclusion (the longest duration of the treatment was 52 weeks). In study 4054, 16 subjects had at least one IGF-1 value>+2SDS (10 subjects treated with somapacitan-beco and 6 subjects treated with Norditropin). All levels normalized without or with the next dose adjustments. All subjects with excessive IGF-1 (above the pre-specified threshold) were asymptomatic. Lastly, small and intermittent increases in blood phosphate and creatine phosphokinase (CPK) levels of unknown clinical significance were observed in subjects treated with somapacitan-beco (17.5% and 9.2% of subjects, respectively); the events resolved without dose adjustment or treatment. All subjects with these laboratory abnormalities were asymptomatic. The immunogenicity data did not raise any concerns: no anti-drug or anti-rhGH antibodies were detected during somapacitan-beco clinical development program. No new safety signals were identified with use of somapacitan-beco in subjects with AGHD in the clinical program. Product labeling will be used to mitigate the known risks associated with somapacitan-beco in the AGHD population.
In conclusion, safety and efficacy data from the single pivotal, randomized, double-blind (placebo) and open label (Norditropin) phase 3 study conducted to support the approval of somapacitan-beco for the proposed indication have demonstrated that the benefits outweigh the potential risks in this population. Specifically, somapacitan-beco provides a benefit in the improvement in body composition parameters through the normalization of IGF-1 levels in patients with AGHD. Safety issues were consistent with the expected class specific side effects (e.g., headache, edema, hyperglycemia, arthralgia); no new safety issues were identified. Safety issues will be mitigated through labeling. Thus, I recommend approval of somapacitan-beco for the proposed indication.

I also agree that the results observed in Norditropin arm should be included in the label descriptively to better inform a decision on the choice of each drug.
# Benefit-Risk Dimensions

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<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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| **Analysis of**   | - AGHD is a well characterized condition that may occur in childhood and persist through adulthood or be newly acquired in adulthood due to trauma or structural lesions.  
                      - GH deficiency results in inadequate circulating GH and IGF-I levels.  
                      - Low levels of IGF-1 in patients with AGHD adversely affect body composition parameters (increase fat mass, decrease lean body mass), decrease muscle strength and reduce exercise capacity.  
                      - Prospective, controlled, data establishing that interventions that increase IGF-1 levels and improves body composition parameters reduce the risk of cardiovascular complications in this population are not available.  
                      - As per Endocrine Society Guidelines on treatment of AGHD (2011) 4, the demonstrated benefits of GH replacement therapy include improvements in body composition, exercise capacity and quality of life. | - AGHD is associated with low GH/IGF-1 levels leading to altered body composition, exercise capacity, bone density, and decreased quality of life in adults. |
| **Current**        | - Multiple recombinant human growth hormone (rhGH; somatropin) products are FDA approved for the for the replacement of endogenous GH in AGHD and on the U.S. market.  
                      - Replacement treatment of AGHD aims to mimic the action of endogenous GH leading to increase in IGF-1 levels and improvement in body composition and other symptoms of AGHD | - The majority of rhGH products are approved for the replacement of endogenous GH in AGHD  
                      - Replacement treatment with rhGH aims to mimic action of endogenous GH leading to increase in IGF-1 levels and improvement in body composition.  
                      - There is no evidence that these treatments affect mortality or major morbidity. |
| **Treatment**      | - Change from baseline to week 34 in trunk fat percentage (TFP) as assessed by dual-energy X-ray absorptiometry (DXA) was the primary endpoint in the single trial providing substantial evidence of effectiveness. Somapacitan-beco significantly reduced TFP from baseline compared to placebo at the end of 34 weeks: the estimated mean treatment difference in TFP between somapacitan-beco and placebo groups was -1.53% (95% CI-2.68; -0.38), p=0.009.  
                      - Mean trunk lean body mass values increased in somapacitan-beco treated subjects by 804 g and mean total lean body mass by 1394 g, respectively and decreased in subjects on placebo.  
                      - Mean IGF-1 SDS normalized at the end of 34 weeks in subjects treated with somapacitan-beco (baseline: -2.54; week 34: -0.17) and remained low in placebo group (-2.62).  
                      - Secondary comparative analyses against Norditropin reported less pronounced effect of somapacitan on TFP over Norditropin and similar effect on lean body mass parameters in both groups. However, the comparison was confounded by the higher | - Treatment with somapacitan-beco normalizes IGF-1 levels and decreases fat body composition parameters and increases lean body mass.  
                      - A net improvement in body composition parameters is consistent with that found with other recombinant GH products in patients with AGHD.  
                      - The observed difference in the magnitude of the improvement in fat body composition parameters between somapacitan and Norditropin groups may have been confounded by the higher proportion of women on oral estrogen in the former. The comparative TFP lowering efficacy of the two drugs when both are used with the titration algorithm targeting IGF-1 |

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<td>proportion of females on oral estrogen in the somapacitan group and suboptimal doses of somapacitan-beco used by these subjects. In addition, the comparison was not made at the maximum doses.</td>
<td>levels without the constraints of the pivotal study protocol is unknown.</td>
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<tr>
<td>Risk and Risk Management</td>
<td>• The safety profile of somapacitan-beco has been generally well characterized and is consistent with the class&lt;br&gt;• No new safety signals for somapacitan-beco in the AGHD population were identified in the clinical program&lt;br&gt;• The most common AEs in study 4054 were nasopharyngitis (20% of subjects), back pain secondary to fluid retention and nerve compression (10% of subjects), arthralgia (6.7%) and allergic reactions (non-anaphylactic) (6.7%)&lt;br&gt;• AEs of adrenal insufficiency were mild and occurred in 3.3% of subjects treated with somapacitan-beco. No adrenal crisis was reported in any of subjects.&lt;br&gt;• Lymphohypertrophy/lipodystrophy occurred in 3.3% of subjects, injection site reactions occurred in 1.7% of subjects.&lt;br&gt;• No AEs of intracranial hypertension or pancreatitis was reported with somapacitan-beco use.&lt;br&gt;• No increased risk of malignant or benign tumors with somapacitan-beco use was observed in the clinical program.&lt;br&gt;• Chronically elevated IGF-1 levels above the normal range (&gt; +2SDS) are associated with various AEs including headache, intracranial hypertension, edema, tumors, etc. In study 4054, 15 subjects had at least one IGF-1 value &gt;+2SDS. All levels normalized without or with next dose adjustments. All subjects were asymptomatic.&lt;br&gt;• Small and intermittent increase in blood phosphate levels were observed in three subjects only; the events resolved without dose adjustment or treatment. All subjects were asymptomatic.&lt;br&gt;• The immunogenicity data did not raise any particular concerns. All allergic reactions were mild. The pre-marketing clinical safety data did not raise concerns related to severe allergic reactions with this product.&lt;br&gt;• Labeling will be sufficient to mitigate risks associated with use of somapacitan-beco in patients with AGHD</td>
<td>• Treatment with somapacitan-beco is associated with fluid retention, headache, arthralgia, myalgia, lipodystrophy, adrenal insufficiency, injection site reactions and hyperglycemia. All risks are monitorable risks. Monitoring and interventions will be recommended in labeling to address these risks.&lt;br&gt;• Potential risks of tumorogenesis, intracranial hypertension, pancreatitis are expected for rhGH class of drugs and will be mitigated through the labeling. Somapacitan-beco will be contraindicated in patients with active malignancies.&lt;br&gt;• Increase in IGF-1 levels above the normal range is a monitorable risk. The risk is mitigated by individualized dose titration based on IGF-1 levels.&lt;br&gt;• The risk of abnormal laboratory values of phosphate will be communicated through the labeling to help practitioners in making decisions regarding patient selection and use of concomitant medications&lt;br&gt;• No risks identified require risk management beyond labeling (such as Risk Evaluation and Mitigation Strategy (REMS) or postmarketing required studies).</td>
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2. Background

On August 28, 2019 Novo Nordisk submitted a Biologics License Application (BLA) for somapacitan-beco, a long acting recombinant human growth hormone (rhGH) derivative under Section 351(a) of the Public Health Service Act in support of the following indication:

Replacement of endogenous growth hormone in adults with growth hormone deficiency.

Somapacitan-beco is a long acting rhGH derivative with a single point mutation in the rhGH backbone to which a non-covalent albumin-binding moiety has been attached. The albumin binding moiety (side chain) consists of an albumin binder and a hydrophilic spacer attached to position 101 of the protein by chemical conjugation. The albumin binding part, binds non-covalently to endogenous albumin and delays elimination of somapacitan-beco and thereby prolongs the in vivo half-life (t½). The potency, pharmacokinetic (PK) and pharmacodynamic (PD) properties make somapacitan-beco suitable for once weekly subcutaneous (s.c.) administration in humans.

Adult growth hormone deficiency (AGHD) is a well-characterized condition that can persist from childhood or be newly acquired secondary to structural lesions within or trauma to the pituitary gland. Growth hormone (GH) deficiency results in inadequate circulating insulin-like growth factor 1 (IGF-I) levels leading to decreased lean body mass, increased fat mass, weakness, reductions in exercise capacity, muscle mass/strength, cardiac performance, bone density, and diminished quality of life.

Human GH extracted from the cadaveric pituitary gland has been used in GH-deficient children from the early1960’s until 1985 to promote linear growth, when its use was abruptly stopped due to reports related to Creutzfeldt-Jacob Disease in recipients of this treatment. In the same year, however, a rhGH was approved by the FDA for therapy of childhood GHD. Over time, other pediatric indications beyond childhood GHD extended the use of these products.

Over the last decades, physicians and professional societies have recommended rhGH (somatropin) replacement therapy and approved products have been proven both effective and safe in AGHD. Exogenous rhGH treatment aims at mimicking the function of inadequate GH secretion (i.e. a replacement therapy) leading to normalization of IGF-1 levels and improvement in symptoms and signs of GHD. As per Endocrine Society Guidelines on treatment of AGHD (2011), the demonstrated benefits of GH replacement therapy include improvements in body composition, exercise capacity and quality of life. The other benefits include improvements in cardiovascular parameters (lipids, endothelial function, etc.), however, these improvements may be negated by increase in insulin resistance. Lastly, the Endocrine Society emphasizes that long-term clinical outcome studies on hard endpoints such as fractures, heart disease, cancer, and mortality are still lacking”.

Observational studies have shown that patients with hypopituitarism, including growth hormone deficiency, have increased risks of premature mortality. Any attribution of growth hormone deficiency as contributor to this risk is fraught with confounders: the underlying condition and treatment of hypopituitarism, other deficient hormones with inadequate replacement doses, etc. Nonetheless, it is known that growth hormone

is lipolytic and has an effect on decreasing visceral fat and, to a lesser extent, on increasing lean body mass. Thus, reversal of body AGHD-related composition changes with rhGH can, at least in theory, predict increased longevity. However, it is important to note that no study has demonstrated improved survival among patients with AGHD, as it is thought that such studies would necessarily be very large and long to demonstrate such benefit, and thus are not considered practical.

Several rhGH products are approved for the replacement of endogenous GH in AGHD and are on the US market. The clinical development of these products demonstrated that improvement/normalization in IGF-1 levels is associated with various improvements in body composition parameters (refer to Regulatory background section below). The safety profile of these products is well characterized and include hypothyroidism, glucose intolerance, fluid retention, arthralgia, carpal tunnel syndrome, myalgias, risk of neoplasm, intracranial hypertension and immunogenicity.

All approved rhGH products require daily or every other day subcutaneous (s.c.) injections to maintain therapeutic blood levels of GH and IGF-1. Compliance with daily administration of rhGH can be affected by concomitant side effects of injection site discomfort, transient edema, and arthralgia. The therapeutic effect of rhGH is often compromised by missed doses. A long-acting form of rhGH has the potential to reduce discomfort and increase compliance by requiring less frequent injections.

**Regulatory background**

*Precedent Case Example: basis of approval for rhGH products with similar proposed claim, i.e. replacement of endogenous GH in AGHD*

As stated above, several rhGH products are approved for the replacement of endogenous growth hormone in AGHD indication. These products are also approved for the treatment of short stature in pediatric patients with GHD and with other non-GHD states; however, these indications are not relevant to the current application for somapacitan-beco, and thus, will not be discussed in this memo.

The efficacy of rhGH products as a replacement therapy in patients with AGHD was established using improvement in various body composition endpoints (lean body mass, total fat mass) as a surrogate of adequate replacement with missing hormone. AGHD is associated with various metabolic abnormalities including loss of lean body mass and fat accumulation due to inadequate GH, and improvement in body composition values are recommended targets for therapeutic interventions in the published literature. rhGH serves to replace GH in AGHD and aims to raise IGF-1 (biomarker of GH activity) leading to the improvement in signs and symptoms of AGHD. Thus, rhGH dose selection is determined by the normalization of serum IGF-1. For the above reasons, the FDA considered body composition, as one of many disease specific measurements, a clinically relevant endpoint in registration trials in the context of proven GHD only. Therefore, these products have received full approval in the past, and not accelerated approval based on a surrogate endpoint reasonably likely to predict a clinical benefit.

Data from these studies demonstrated the statistically significant changes in various body composition parameters in subjects with AGHD treated with rhGH vs. placebo at the end of the study. However, the degree of these changes varied widely between the studies due to the multiple factors including doses of rhGH used in these studies, methods used to measure body compositions (e.g., dual-energy X-ray absorptiometry (DXA), bioelectric impedance), selection of particular body composition compartment(s) used for the evaluation of treatment benefit (total lean body mass, trunk fat mass, total fat mass, etc.), the units used for the evaluation of body composition parameter changes (% vs. kg), duration of the studies (6

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months vs. 12 months), demographic and disease characteristics of the enrolled population at baseline (e.g., severity of metabolic abnormalities, use of concomitant medications with known effect on rhGH therapy or body composition (e.g., oral estrogens, weight-lowering medications). For example, registration trials demonstrated that replacement therapy with rhGH in patients with AGHD improved lean body mass by 0.9 - 2.8 kg or by 2.8-6.4 %, decreased total body fat mass by 1.3-3.8 kg or by 3.6-6.3%, trunk fat by 4.3-7.6% (at the end of 12-month treatment) or by 1.3 kg, trunk fat percent by 4.3-7.6 % (as measured by body impedance).

Regardless of which body composition endpoint was selected as primary endpoint, for the approval, the pivotal studies had to demonstrate superiority of rhGH versus placebo in terms of improvements in selected body composition parameters, i.e. an increase in lean body mass had to be associated with a reduction in fat mass. Moreover, since rhGH is a replacement therapy in a hormone deficient state, the trials had to demonstrate also that the improvements in body composition were associated with improvement/normalization in IGF-1 levels, a biomarker of GH action.

In conclusion, for the reasons mentioned above, FDA accepts statistically significant changes in body composition (without prespecified thresholds) as sufficient proof and as a evidence of effectiveness for pharmacological interventions in the specific condition of AGHD, whose clinical manifestations can be traced to a specific hormone deficiency and these manifestations can be reversed by hormone replacement at physiologically justified doses. Because of the complexity of the interactions among these various parameters (lean body mass, visceral fat mass, bone density) and the variability in the instruments to measure these parameters, FDA had not required a minimal magnitude of effect on a primary endpoint, to weigh against the product safety. Since the safety profile of these products is similar and considered by FDA as class effects, FDA found it difficult to require a minimal magnitude of effect to consider in the benefit risk assessment.

**Somapacitan-beco Regulatory History**

Somapacitan-beco is being developed for the for the replacement of endogenous GH in AGHD. This memorandum will focus on the product’s development program.

- Pre-IND meeting, 4/19/2013.
  FDA provided recommendations regarding the overall development plan for somapacitan-beco (refer to Pre-IND Meeting Comments in DARRTS). At this interaction discussion on IND content requirements for the product was held.
  FDA agreed with the sponsor’s plan to submit an IND that includes a Phase 3 study protocol evaluating somapacitan-beco in AGHD, with the proposed design of this study (i.e. placebo-controlled) and with the proposed doses. FDA agreed with the proposed duration of the study, 6 months, however, commented that “a final decision will have to wait until the EOP2 meeting”. FDA agreed that the primary endpoint should be a measure of body composition but asked for the additional clarification on what particular body composition to be used, trunk fat mass or trunk fat percentage.
  Lastly, FDA also agreed with the sponsor’s overall proposed analysis strategy for the detection and characterization of anti-drug antibodies in the clinical studies and provided further recommendations on the timing of sample collections for antibody detection.

- On 1/22/2014, FDA provided the further recommendations on aspects of the quality program of the product to be used in the phase 3 trial in AGHD (refer to Pre-IND written responses in DARRTS).

- End-of-Phase 2 (EOP2) meeting, 5/19/2014.
During this teleconference, the sponsor and FDA discussed the design of Novo Nordisk Phase 3 clinical trial to support a license application for the replacement of endogenous GH in AGHD.

FDA agreed with Phase 3 trial duration of 34 weeks for the core period and 52 weeks for the extension period, with the proposed doses and titration schedule. FDA also confirmed that “change from baseline to end of main trial period (Week 34) in trunk fat percentage” assessed by DXA is an acceptable primary endpoint for the proposed Phase 3 study. FDA agreed with the proposed secondary endpoints including other body composition measurements and IGF-1 measurements. With regard to the planned evaluation of health-related quality of life by questionnaires for the labeling purposes, FDA noted that these questionnaires have to meet current validation standards first.

At this meeting, the Sponsor also clarified that the purpose of the second comparison (somapacitan-beco vs. Norditropin) for the Phase 3 trial is to support “clinical judgment of the clinical relevance of the estimated treatment difference between somapacitan-beco and placebo” and the results will be reported without p-values. The sponsor also indicated that this comparison was not intended for a labeling claim, however the intention was to describe the “clinical trial results in the labeling”.

Lastly, FDA disagreed with the proposed completer population for the primary analysis and recommended the primary analysis for efficacy to be based on the intention to treat (ITT) population. FDA also recommend to make all efforts to keep the amount of missing data at a minimum.

FDA also agreed with overall plan for the immunogenicity assessment in the Phase 3 trial and provided further recommendations on timing of sampling for antibodies and PK parameters.

- The use of Patient Reported Outcomes (PRO) tool, i.e. the Treatment Related Impact Measure-AGHD (TRIM-AGHD), for the evaluating of patient well-being as a secondary endpoint associated with somapacitan-beco treatment was discussed with FDA on multiple occasions (refer to FDA’s Advice Letters from 2/22/2013 and 9/16/2014 and FDA’s email from 5/13/2014/). However, no agreement on use of TRIM-AGHD in patients with AGHD was reached between the sponsor and the Clinical Outcome Assessment (COA) Staff in the Office of New Drugs to date.

- IND 116327 for somapacitan-beco was opened on 7/23/2014 with a Phase 3 protocol for study NN8640-4054 (referred to as Study 4054 hereafter) evaluating the efficacy and safety of somapacitan-beco compared to placebo after 34 weeks of treatment in treatment-naïve adults with growth hormone deficiency. The sponsor was allowed to proceed with this study.

The statistical section of the protocol was reviewed by biostatistician, Dr. Shuxian Sinks, who concluded that the revised statistical section is in line with FDA’s recommendations provided during EOP2 meeting and is acceptable. The primary analysis uses a multiple imputation method for missing data, the primary analysis population is in line with ITT scenario (defined by the sponsor as full analysis set (FAS) population and consisting of all randomized subjects who received at least one dose of randomized drug), the primary comparison of somapacitan-beco and placebo is a superiority test, the sensitivity analysis is conducted to verify the assumption of missing at random (MAR) for both primary and secondary analysis of primary endpoint (refer to Dr.’s Sinks review in DARRTS from 7/23/2014).

- On 12/12/2014, FDA notified the sponsor that no additional nonclinical studies were required to define the carcinogenic risk related to somapacitan-beco treatment. FDA’s reasons for not requiring carcinogenicity studies were: 1) existing epidemiologic data in humans does not indicate a correlation between GH treatment and increased risk of de-novo development of tumors, 2) GH therapy aims to achieve physiologic levels of IGF-1, 3) animal studies at clinically relevant doses of IGF-1 do not demonstrate an increased risk of tumor development, the carcinogenicity studies in rodents will not provide information regarding risk in humans due to the difference in GH receptor binding between rodents and non-rodents, 4) the incidence or frequency of neoplastic and pre-neoplastic lesions did not
increase during the toxicology program, 5) other components of somapacitan-beco, albumin binder and linker, do not present carcinogenic risk (refer to Dr.’s Quinn review in DARRTS from 10/1/2014).

- On 4/23/2015, FDA notified the sponsor via email that no thorough QT (TQT) study was required for their product and that the proposed plan to assess ECG at close to the expected Cmax in the Phase 3 trial was acceptable (refer to Clinical Pharmacology section below).

- On 9/8/2016, FDA notified the sponsor that the plan not to conduct dedicated drug-drug interaction (DDI) studies with somapacitan-beco was reasonable. FDA acknowledge the sponsor’s plan to address the DDI potential of possible metabolites when the results of Absorption, Metabolism and Excretion (AME) study will be available. FDA also agreed that renal and hepatic impairment studies will be conducted in subjects without GHD.

- On 11/15/2017, the Office of Biologic Products and the sponsor discussed the planned transfer of manufacturing of somapacitan-beco drug substance from the pilot facility to the commercial manufacturing site in the US and overall acceptability of the sponsor’s plan to demonstrate the comparability between drug substances manufactured at the pilot facility and the commercial facility.

- On 4/20/2018, FDA and the sponsor discussed and agreed that the sponsor’s anti-drug antibody assay as presently validated appeared to be sufficient to detect anti-drug antibodies (ADA) in the clinical program. However, FDA indicated that the complete review of the assay will occur at time of BLA submission.

- On 8/30/2018, FDA and the sponsor discussed Human Factors Engineering Plan that included a bridging strategy for the somapacitan-beco pen-injector and the human factors engineering/usability engineering validation data for handling of the FDA approved and marketed pen- injector for Norditropin (Norditropin FlexPro 30 mg/3 ml). FDA agreed that the approach to bridge the sponsor’s human factors data from the Norditropin FlexPro 30 mg pen-injector is acceptable and that a human factors differentiation validation study would not be needed. However, any changes to the product user-interface would warrant further review. FDA also revised the sponsor’s Instructions for Use and provided comments.

- Pre-BLA meeting, 4/25/2019
  During this meeting, the Division and the sponsor discussed and agreed on BLA’s content and format and the completeness of the different BLA modules. FDA and the sponsor agreed that only 10mg/1.5 ml strength will be submitted in the original BLA. Lastly, FDA disagreed with the sponsor’s strategy to pool safety data from three Phase 3 studies in subjects with AGHD due to the different study design and duration, population studied (treatment-naïve vs previously treated with GH). The sponsor agreed to include individual datasets for each study in the BLA submission.

### 3. Product Quality

The review team from Office of Pharmaceutical Quality (OPQ)/ Office of Biotechnology Products (OBP) recommend approval of this application (refer to OPQ executive summary from 6/16/206). The Office of Pharmaceutical Quality and Office of Compliance has determined the manufacturing facilities are acceptable.

Somapacitan-beco is a long-acting rhGH derivative. The sequence of this recombinant protein differs from endogenous GH by a single substitution in the amino acid backbone (leucine at position 101 substituted with cysteine). After injection, endogenous albumin binds non-covalently to the side chain, which is
Somapacitan-beco is a 191 amino acid protein with an average molecular weight of 23290.56 Da. The drug substance is produced. The manufacturing process consists of

Biological activity of somapacitan-beco is measured by the induction of cell growth that is tested by a quantitative cell-based assay using a BA/F3 murine pro-B cell line that depends on growth hormone for growth and survival. Cell proliferation is measured using a redox indicator reagent that detects metabolic activity. Bioactivity values are determined relative to the reference standard. The cell-based bioassay is appropriately validated.

Based on the stability data that has been submitted, OBP reviewer recommends a shelf-life of [number] months for the drug substance when stored at [temperature].

The final drug product is a clear and colorless sterile solution for the subcutaneous injection, which is provided in 1.5 mL glass cartridges assembled into prefilled pen-injectors. Each 10 mg prefilled pen of somapacitan-beco is formulated in L-histidine, poloxamer 188, phenol, mannitol, and water for injection (WFI) up to 1.5 mL at pH 6.8. The product is designed to allow for administration of multiple once-weekly doses from the prefilled pen. The excipients are histidine, hydrochloric acid, mannitol, poloxamer 188, phenol, sodium hydroxide, and WFI.

The container closure system consists of a 1.5 mL Type I colorless glass cartridge, rubber plunger, and rubber disk. The cartridges are assembled into pen-injectors, which shield the product from light.

Overall, no issues with regard to the manufacture of the drug substance, drug product, excipients, impurities, extractables, or leachables that would preclude approval were identified.
The OPQ reviewer indicated that aggregates have no biological activity; however, aggregates may increase risk of immunogenicity. Thus, agreement between OPQ and the Applicant was reached to further mitigate this risk by tightening temperature control limits during the transportation and storage of the drug product.

A shelf-life of 24 months was granted for the drug product when stored at the recommended storage condition of 2-8°C and protected from light. Stability data in this BLA also support an in-use period of 6 weeks at 2-8°C, including unrefrigerated storage period for no more than 72 hours at or below 30°C. In addition, OPQ recommends the label to include clear instructions to no freeze the product and to discard the product if exposed to temperature > 30°C.

**Device**

Dr. Mathew Ondeck from the Center for Devices and Radiological Health (CDRH) reviewed the proposed device and recommended approval (refer to the review from 5/14/2020). The somapacitan-beco 10 mg pen-injector is a drug-device combination product containing 1.5 ml glass cartridge with the drug product somapacitan-beco at a concentration of 10 mg/1.5 ml (Figure 1).

The drug product is enclosed within the cartridge and not in contact with the device. The device is intended to connect to a standard needle thread or a needle with a bayonet coupling prior to drug product administration. The needle is not provided with the device. The injection depth is controlled by the needle size. The reviewer confirmed that all of the component materials are identical to existing marketed devices, such as the Norditropin FlexPro. All materials that form the user interface have been evaluated for biocompatibility and do not pose a risk of cytotoxicity, skin irritation and skin sensitization, or any other biological hazard as defined in ISO 10993-1:2018 [2] when used as intended. The user interface is the same as that of the approved Norditropin FlexPro during dose setting and resetting. The only design difference between the Norditropin Flex Pro (1.5 ml) and the to be marketed somapacitan-beco 10 mg pen injector are the colors of the cap, cartridge holder and dose button.

The to-be-marketed device was used in the pivotal clinical trial.

Dr. Ondeck reviewed the essential performance requirements of this device, i.e. dose accuracy, activation force, injection force (i.e. dose button hold force) and injection time.

Dr. Ondeck identified the following concerns with injection force and injection time. The pen does not have any audible feedback when the injection is complete, only when the injection button is activated. However, there is a visual feedback, i.e. the dial reaching 0 and the user has to wait for 6 seconds after the dial reaches 0. There were two concerns with the proposed instruction to wait for 6 seconds after the dial reaches zero.

First, there was a concern with the risk of underdosing if the user cannot hold the device for 6 seconds. The Applicant provided additional data demonstrating that the user will receive 98% of the intended dose even...
if the needle removed once the dial reaches 0. The reviewer found the data acceptable to mitigate the risk of underdosing.

Second, the originally proposed device specification of injection time (b) did not fit within the above the instruction for use (i.e. 6 seconds). While the reviewer found the lower specification time for injection to be acceptable, he indicated that the upper limit of the injection time specification (b) is not appropriate since it is much higher than the 6 seconds that is recommending in the labeling. The reviewer stated that “it is unreasonable to expect user to hold the device with needle injected for nearly”. In addition, a human factor study was completed with production units of the somapacitan-beco pen injector and demonstrated injection time results of 8 seconds at a maximum based on the design verification testing. Thus, the reviewer concluded that the upper specification of (b) was not adequately validated and should be lowered to a value that more accurately reflects the delivery of somapacitan-beco. The Applicant provided additional information on 5/5/2020 that included the projected injection time of (b). Additionally, the Applicant indicated that in Norditropin human factor studies participants were able to hold the dose button for up to 7 seconds to inject the drug. For this reason, the Applicant proposed to set an injection time specification of (b). The Applicant also provided the results of all required testings of the new proposed injection time. The reviewer found the new proposed injection time to deliver the maximum dose to be acceptable.

During the review of the application, Dr. Ondeck noted that Novo Nordisk A/S, which is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part, has never been inspected. He indicates that the drug is not an emergency use product, the device is a typical pen injector, and it does not include vulnerable population, thus, the inspection is necessary. In addition, the Applicant already manufactures the identically designed device in other sites. However, the reviewer states the inspection can be done post-approval based “on given the risk of the product/user and lack of complexity of the device manufacturing processes”. This issue should not affect approvability.

**Human Factors**

Dr. Melina Fanari from the Division of Medical Errors Prevention and Analysis (DMEPA) previously reviewed the Human Factors Engineering Plan that included bridging strategy for the somapacitan-beco pen-injector to the currently marketed Norditropin FlexPro 30 and the human factors engineering/usability engineering validation data for handling of the FDA approved and marketed pen-injector for Norditropin (refer to Meeting Minutes in DARRTS from 8/30/2018). DMEPA confirmed that somapacitan-beco pen-injector shares the same device user interface, intended use, users and use environment as the currently marketed Norditropin pen. Based on that review, DMEPA concluded that a human factor study was not needed and the approach to bridge the human factor data to Norditropin pen was acceptable. FDA also revised the Applicant’s Instructions for Use (IFU) and provided comments to improve readability and visibility for the patients (refer to the review in DARRTS from 8/30/2018). The Applicant accepted DMEPA’s recommendations and included updated IFU in the current submission. The updated IFU was reviewed by DMPA during the current review cycle. DMEPA had two additional comments to improve readability of IFU; these comments were sent and accepted by the Applicant (refer to DMEPA review in DARRTS from 2/11/2020).

Based on these reviews, there do not appear to be any human factor issues that would preclude approval.
4. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues, and the pharmacology/toxicology reviewers, Drs.’ Huiqing Hao and Federica Basso recommend approval without additional studies (refer to the review in DARRTS from 4/17/2020).

The sponsor conducted all the required non-clinical studies, including pharmacokinetic and toxicokinetic studies to support the chronic use of sompacitan in patients with AGHD. All studies were conducted using subcutaneous route of administration.

In-vitro studies have demonstrated that somapacitan-beco binds to human GH receptor with approximately 3-fold lower potency than native hGH. Once a week administration of somapacitan-beco to hypophysectomised rats resulted in sustained increases in body weight gain and increase in IGF-1 levels.

The toxicity of somapacitan-beco was assessed in series of repeat-dose toxicity studies in rats and monkeys. The reviewers concluded that the toxicology profile observed with somapacitan-beco was related to the pharmacological effects of growth hormone. Somapacitan-beco did not have any effect on hERG current.

In monkeys, treatment related effects were thymic atrophy and mammary gland hypertrophy observed at significantly higher exposure than at Maximum Recommended Human Dose (> 100-fold MRHD). The reviewers indicated that somapacitan-beco did not cause any effects on the central nervous, respiratory, or cardiovascular systems in monkeys.

In rats, administration of somapacitan-beco was associated with growth promoting effects of the drug, including increases in body weight and food consumption, increases in organ weights and histopathology findings of hypertrophy/hyperplasia in a wide range of tissues. Treatment with somapacitan-beco also increased the incidence of brain ventricle dilatations, diabetes, and chronic progressive nephropathy (CPN). The brain finding was observed at the high dose and was consistent with the known adverse reaction of intracranial hypertension in patients treated with recombinant growth hormone. The findings associated with diabetes/hyperglycemia (increased water consumption and urine volume, elevated blood glucose and insulin levels, glycosuria, cataracts, bilateral lenticular degeneration, along with islet cell hypertrophy/ hyperplasia and islet cell vacuolation) were mainly observed in the high dose group of animals. CPN was observed in the mid dose and high dose groups (at approximately >20-fold MRHD).

Lastly, all toxicological effects were observed more prominently in rats despite the presence of anti-drug antibodies resulting in reduced somapacitan-beco exposure following repeated dosing. Monkeys showed minimal antidrug antibody development and no reduction in exposure after repeat dosing. IGF-1 levels were increased throughout dosing in both species.

To explore effects of somapacitan-beco on the liver, liver sections from the 13- and 26-week monkey studies were immunohistochemically stained for Ki67 (nuclear protein associated with cellular proliferation). The study demonstrated that there was no increase in liver cell proliferation.

Local tolerance studies in rabbits showed no adverse injection site reactions.

Fertility studies performed in rats demonstrated no evidence of impaired fertility. Embryofetal development studies in rats revealed increased incidence of skeletal variations (short/bent/thickened long bones) at very high exposures (> 260-fold the exposure at the MRHD; the findings were transient and did not affect postnatal development. In rabbits, decreased fetal, placenta and
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litter weights, and increased incidence of incompletely ossified/unossified metacarpals phalanges were observed (> 130-fold the exposure at MRHD). In a pre-and post-natal developmental study in rats, somapacitan-beco increased the incidence of dilated renal pelvis in high dose offspring at postnatal day 21 (630-fold the exposure at MRHD MRHD). Lastly, in lactating rats, somapacitan-beco-related material was secreted into milk at a concentration 1% lower than observed in maternal plasma. Pharmacology/toxicology reviewers recommend including the above animal findings in 8.1 (Pregnancy) and 8.2 (Lactation) sections of the label.

No carcinogenicity studies with somapacitan-beco were conducted for the reasons described in the Regulatory History section above.

Lastly, the reviewers indicated that there were no novel excipients and no impurities of concerns in the drug substance and drug product. Leachables and extractables from the container closure system are acceptable; all detected leachables were below the 1.5 mcg/day threshold for human exposure.

In conclusion, there are no nonclinical issues that would preclude approval. No new safety signals were identified in the nonclinical program and observed toxicities (hyperglycemia, diabetes, intracranial hypertension, etc.) are consistent with risks expected for the rhGH class of drugs. These risks can be mitigated through product labeling, monitoring, and timely introduction of treatment and/or discontinuation of the drug.

5. Clinical Pharmacology

The Clinical Pharmacology review was completed by Dr. Sang Chung, and Pharmacometrics review was completed by Dr. Liam Ma. There are no outstanding clinical pharmacology issues and both reviewers recommended approval of somapacitan-beco without additional post-approval studies. For a detailed discussion, please refer to their Clinical Pharmacology review in DARRTS dated 5/4/2020.

The clinical pharmacology review concluded that PK of somapacitan-beco has been adequately characterized in the sponsor’s studies in healthy volunteers and in subjects with AGHD. The single dose PK of somapacitan-beco following s.c. administration was evaluated in healthy subjects (Study 3915) at doses 0.01-0.32 mg/kg. The steady state PK was evaluated in subjects with GHD (Study 3947) and in healthy volunteers (Study 3915). Reviewers confirmed that steady-state PK of somapacitan-beco was comparable between subjects with AGHD and healthy volunteers.

Somapacitan-beco is extensively bound to plasma protein (>99%). Based on population PK analyses, the estimated volume of distribution (V/F) of somapacitan-beco in patients with AGHD is approximately 14.6 L. Somapacitan-beco is metabolized via proteolytic cleavage of the linker sequence between the peptide backbone and albumin binder sidechain.

The t1/2 of somapacitan-beco in subjects with AGHD is 2 – 3 days. The primary excretion routes of somapacitan-beco related material were urine (80.9%) and feces (12.9%). No intact somapacitan-beco is excreted, indicating full breakdown of somapacitan-beco prior to excretion.

Following administration of s.c. somapacitan-beco in subjects with AGHD at doses ranging from 0.02 mg/kg/week to 0.12 mg/kg/week, T_{max} was 4 to 24 hours: 8-24 hours after the first dose and 4-12 hours at steady state.
Steady state is achieved following 1–2 weekly doses, and the accumulation ratio is low (ranging from 1 to 2).

Somapacitan-beco displayed approximately linear pharmacokinetics at the clinically relevant dose range (0.02-0.12 mg/kg/week); the PK is non-linear at higher doses. In subjects with AGHD, a 6-fold increase in somapacitan-beco dose resulted in approximately 8-fold increase in both AUC\textsubscript{0-168h} and C\textsubscript{max} of somapacitan-beco (Table 1). The total variability (CV) for AUC\textsubscript{0-168h} ranged from 61.7% to 102.2% and for C\textsubscript{max} from 113.3% to 201.2% across doses (0.02 to 0.12 mg/kg) at steady state in subjects with AGHD. The reviewers also confirmed that “the power model indicates that the nominal somapacitan-beco dose was linear for both AUC\textsubscript{0-168h} and C\textsubscript{max} at steady-state within a dose range of 0.02 to 0.12 mg/kg/week or 1.5 to 11.6 mg/week “. These dose ranges (0.02-0.12 mg/kg/week or 1.5 to 11.6 mg/week) include the proposed therapeutic doses (1 mg/week- 8 mg/week).

Table 1. Steady state PK properties of somapacitan-beco in subjects with AGHD (Study 3947)

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>AUC\textsubscript{0-168h} (ng.hr/mL) (CV)</th>
<th>C\textsubscript{max} (ng/mL) (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02 mg/kg/wk</td>
<td>7</td>
<td>666 (70.9)</td>
<td>14.4 (193.2)</td>
</tr>
<tr>
<td>0.04 mg/kg/wk</td>
<td>6</td>
<td>986 (93.3)</td>
<td>20.6 (201.2)</td>
</tr>
<tr>
<td>0.08 mg/kg/wk</td>
<td>6</td>
<td>2085 (102.2)</td>
<td>45.4 (127.6)</td>
</tr>
<tr>
<td>0.12 mg/kg/wk</td>
<td>7</td>
<td>5431 (61.7)</td>
<td>114.8 (113.3)</td>
</tr>
</tbody>
</table>

Source: clinical Pharmacology review, table 1.

Data from study 3947 demonstrated dose-dependent increase in IGF- levels in subjects with AGHD (Figure 2).

Figure 2. Mean IGF-1 SDS levels by dose over time in subjects with AGHD (Study 3947).

Intrinsic factors (e.g. weight, age, sex) that could influence exposure and activity were evaluated using the results from Phase 1 and 2 studies and Population PK/PD analyses of data from Phase 3 studies. Of all investigated covariates, body weight, age and concomitant oral estrogen intake by females were the major covariates (Table 2).
Table 2. Population pharmacokinetic covariate analysis of somapacitan-beco exposure in patients with AGHD (Studies 4054, 4244 and 4043)

Source: Clinical Pharmacology review, table 4.

The somapacitan-beco exposure was approximately 3-fold higher in subjects with lower body weight (45 kg) as compared to subjects with high body weight (85 kg).

The somapacitan-beco exposure and IGF-1 response was lower in female subjects receiving oral estrogen. The predicted dose-response relationship supported higher doses for females on oral estrogen to reach similar response compared to that of females not using oral estrogens (Figure 3).
Figure 3. Exposure versus dose (A, D, G,), IGF-1 response versus somapacitan-beco exposure (B, E, H,) and IGF-1 response versus somapacitan-beco dose (C, F, I) across body weights, females on oral estrogen group and age groups

Based on the results of these analyses, a lower starting dose and smaller increments are recommended for patients > 60 years old, and a higher starting dose is recommended for females on oral estrogen. These

Source: Clinical Pharmacology review, figure 22, modified.
recommendations (lower doses in older patients and higher doses in females on oral estrogen) are also consistent with dosing recommendations for all other rhGH formulations and with the Endocrine Society Guideline on treatment of AGHD. The reviewers did not recommend dose adjustments based on body weight indicating that “the dose-response is expected to be similar across body weight due to difference in baseline IGF-1 level”. Therefore, since the dose will be titrated based on clinical response, no dose adjustment is recommended based on body weight.

Results from a study conducted in subjects with normal, mild, moderate and severe renal impairment (Study 4297) and subjects requiring hemodialysis showed no significant change in the PK of somapacitan-beco. The reviewers concluded that no specific dosing recommendations in this population is needed.

No PK changes were reported in subjects with mild hepatic impairment (Study 4298). Subjects with moderate hepatic impairment demonstrated a 4.7-fold higher AUC0-168h and 3.5-fold higher Cmax and also 25% lower IGF-1 response compared to the exposure in subjects with normal liver function. Of note, subjects with hepatic impairment also had lower baseline IGF-1 values compared to healthy subjects. It should be noted that the lower IGF-1 levels are not unexpected findings in patients with hepatic impairment, since IGF-1 is synthesized in the liver. The lower IGF-1 levels despite increased somapacitan-beco exposure indicate the higher somapacitan-beco dose may be needed in patients with moderate hepatic impairment to achieve normal IGF-1 levels. However, the use of higher doses may result in higher exposure compared to patients without impairment, for example, AUC0-168h following dose of 0.02 mg/kg/week is 666 ng.hr/ml in subjects without liver impairment and in 3130 ng.hr/ml in subjects with moderate hepatic impairment. Based on the observed exposure-response, the reviewers recommend somapacitan-beco starting dose of 1 mg/week, and maximum dose of 4 mg/week in patients with moderate hepatic impairment.

Somapacitan-beco was not evaluated in subjects with severe hepatic impairment. Thus, the reviewers recommend not using the drug in this subgroup of patients.

Drug-drug interactions studies were not conducted in the somapacitan-beco development program (refer to Regulatory background section above). Dr. Chung concludes that the class drug-drug interactions effects for currently marketed daily rhGH formulations can be applied for somapacitan-beco. Somapacitan-beco effect on CYP450 enzyme activity expression was evaluated in vitro and in vivo in rats and monkeys. No in vitro effects were observed. In vivo observed findings were of unknown clinical relevance: CYP450 activity increased in rats and decreased in monkeys. However, the Clinical Pharmacology reviewers recommended to address concomitant treatment with CYP450 substrates in the label based on the published literature and on class label of all rhGH formulations.

QT assessment

A dedicated QTc study for somapacitan-beco was not required (refer to the Regulatory background section). The interdisciplinary review team (IRT) consultant indicated that a thorough QT study is not required (DARRTS 9/3/19) based on the known rhGH product class safety information (no QT prolongation). According to ICH E14 Guidance on QT/QTc evaluation, large targeted proteins (e.g., rhGH) “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”. There were no QT-related safety signals in nonclinical studies and somapacitan-beco was negative in hERG assay (refer to Nonclinical Pharmacology/Toxicology section above). The IRT also reviewed ECG data obtained from study 4054 in adults with AGHD and concluded that there were no large

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8 Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, 2005
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increases in the QTc interval and none of the subjects in the somapacitan-beco group had QTc > 480 ms or a change from baseline >60 ms. No additional labeling was recommended.

Lastly, the to-be-marketed drug product formulation was used in the pivotal and supportive Phase 3 studies.

Dosing

Based on the results of PK studies and Phase 3 studies, the recommended starting dose for somapacitan-beco is 1.5 mg/week in patients < 60 years old, 1.0 mg in patients > 60 years old and 2 mg in females on oral estrogen. The dose should be increased every 2–4 weeks by increments of approximately 0.5 to 1.5 mg, based on clinical response and serum IGF-1 concentrations. Maintenance dose should not exceed 8 mg/week; the doses up to 8 mg/week were well tolerated in Phases 1 through 3 studies. Starting dose in subjects with moderate hepatic impairment is 1 mg/week, and maximum dose 4 mg/week.

The impact of a missing dose on somapacitan-beco concentrations was evaluated by simulations of data from phase 3 studies. The results of this analysis demonstrated that if one dose is missed, the concentration of somapacitan-beco will decrease, but is expected to be completely restored 2 weeks (i.e., Week 3) after the missed dose. The IGF-1 levels follow the same pattern, i.e. are expected to decrease, but regular steady state profiles are expected to be restored 2 weeks after the missed dose. However, if the dose delayed by 3 days only, “slightly decreased in peak concentrations are expected, while trough concentrations will be higher compared to regular steady state dosing”. IGF-1 values will also decrease to a lower trough value compared to steady state dosing and the two subsequent peak values will be slightly lower and higher, respectively, compared to regular steady state values. Somapacitan-beco concentrations and IGF-1 values are expected to restore two weeks after the delayed dose. Based on the results of these analyses, the missing dose should be administered as soon as possible and not more than 3 days after the missed dose (within 72 hour). If more than 3 days have passed, the dose should be skipped, and the next dose should be administered on the regular dosing day.

6. Clinical Microbiology

Quality microbiology data were reviewed, and then posted by Dr. Wayne Seifert (drug product) on 4/22/2020 and posted by Dr. Ziyang Su (drug substance) on 6/5/2020. Both reviewers recommended approval from a sterility assurance and a microbial control perspective. No additional post-marketing commitments are recommended.

7. Clinical/Statistical- Efficacy

Drs. Roman-Popoveniuc (Clinical) and Cambon (Biostatistical) have reviewed the efficacy data and recommend approval (refer to Clinical Review in DARRTS from 7/23/2020) and Statistical Review in DARRTS from 4/27/2020). The statistical and clinical reviewers concluded that the results of the clinical program provided sufficient evidence to support the efficacy claim proposed in this BLA, i.e. for the replacement of endogenous GH in AGHD.

The somapacitan-beco clinical program for AGHD includes three Phase 3 clinical studies. The primary objective of two Phase 3 studies (Study 4043 and study 4244) was to evaluate safety of somapacitan-beco in subjects with AGHD previously treated with rhGH, thus the results of these will not be discussed in detail here. The primary study to support efficacy of somapacitan-beco is Study 4054, 34-week, randomized, placebo-controlled (double blind) and active controlled (open label) comparing the efficacy and safety of somapacitan-beco with placebo and Norditropin Flex Pro (refer to as Norditropin hereafter). This study was
the largest in the intended population, included treatment-naïve subjects. The results of this study will be briefly summarized below. All other studies will be referenced as needed. For the full list of studies refer to the clinical review in DARRTS.

Study 4054 was a Phase 3, multi-center (92 centers across 16 countries), randomized, placebo-controlled (double blind) and active controlled (Norditropin; open label) 34-week study that investigated the use of somapacitan-beco as a replacement therapy in 301 subjects with AGHD who were treatment-naïve to rhGH.

As per the Applicant, the inclusion of the active controlled arm intended “to assist the clinical judgement of the clinical relevance of the estimated treatment difference between somapacitan-beco and placebo” only; this comparison was not included in the primary analysis and the Applicant did not intend to include any claims in the label based on this comparison. Otherwise, this trial design (randomized, placebo-controlled, superiority trial) and the duration (8 months) were similar to the design of the studies that were used for FDA’s approval of rhGH in past.

The primary objective of the trial was to demonstrate the efficacy of once-weekly dosing of somapacitan-beco compared to placebo after 34 weeks of treatment in subjects with AGHD.

Study population

Consistent with the indication sought in this application (replacement of endogenous GH in AGHD) the study enrolled only subjects with AGHD. All subjects were rhGH-treatment naïve or were not on any rhGH medications for the 3 months prior to screening to eliminate a potential carry over effect of previous medications. The study had clear inclusion criteria to confirm the diagnosis of AGHD by the provocative tests or by deficiencies in three or more pituitary axes. Low IGF-1 levels were not an inclusion criterion, since IGF-1 levels are not required, in general, for the establishment of AGHD diagnosis and normal IGF-1 levels do not exclude AGHD. These inclusion criteria are consistent with current Endocrine Society Guideline on the diagnosis of AGHD. The Applicant appropriately excluded subjects who might be at increased risk of adverse events associated with rhGH treatment, including known active malignancy, intracranial tumors and acute severe illness. The Applicant also prohibited use of weight loss medication within the last 12 months and use of glucocorticoids in supraphysiologic doses within 90 days, since the effect of these treatments may confound overall efficacy (change in body composition) of somapacitan-beco.

Dr. Roman-Popoveniuc’s review of protocol violators did not identify any significant deviations in the way the inclusion/exclusion criteria were applied in the clinical trial.

Study design

Study 4054 included a 34-week randomized, placebo-controlled (double blind) and active-controlled (open label) main period, followed by a 53-week open label period. The main period included the titration period for 8 weeks followed by 26 weeks fixed dose treatment period, followed by 1 week washout period.

Dose titration period (8 weeks).
Eligible subjects were randomized in a 2:2:1 ratio to receive somapacitan-beco, Norditropin or placebo, respectively. The randomization was stratified according to region (Japan and all other countries), sex and diabetic status.
The starting dose for somapacitan-beco was 1.0 mg/week in subjects > 60 years old, 2 mg/week in females on oral estrogen and 1.5 mg/week in all other subjects. The starting doses of Norditropin were: 0.1 mg/day in subjects > 60 years old and 0.3 mg/day in females on estrogen, while all other subjects received 0.2 mg/day. Throughout the 8-week dosing period, doses were allowed to be up-titrated every 2 weeks in all randomized groups based on IGF-1 levels to achieve normal IGF-1 levels defined as IGF-1 levels in range of -0.5 SDS to +1.75 SDS (Table 3. Dose titration algorithm for study drugs).

Table 3. Dose titration algorithm for study drugs

<table>
<thead>
<tr>
<th>IGF-I SDS Interval (1 week and 3 days after last dose adjustment)</th>
<th>somapacitan® or placebo Increment/reduction of weekly dose</th>
<th>Norditropin® FlexPro® Increment/reduction of daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I SDS ≥ 3</td>
<td>-1 mg</td>
<td>-0.1 mg/day</td>
</tr>
<tr>
<td>1.75 &lt; IGF-I SDS ≤ 3</td>
<td>-0.5 mg</td>
<td>-0.05 mg/day</td>
</tr>
<tr>
<td>-0.5 &lt; IGF-I SDS ≤ 1.75</td>
<td>+0.5 mg</td>
<td>+0.05 mg/day</td>
</tr>
<tr>
<td>-2 &lt; IGF-I SDS ≤ -0.5</td>
<td>+0.5 mg</td>
<td>+0.05 mg/day</td>
</tr>
<tr>
<td>IGF-I SDS ≤ -2</td>
<td>+1 mg</td>
<td>+0.1 mg/day</td>
</tr>
</tbody>
</table>

Δ: Change in IGF-I SDS from screening.
Source: Clinical Review, table 7

The maximum dose of somapacitan-beco was 8 mg/week, and of Norditropin was 1.1 mg/day. The Norditropin doses used during the trial are approved Norditropin doses for the replacement of endogenous GH in AGHD.

Overall, the somapacitan-beco starting doses and titration schedule are generally consistent with Endocrine Society Guidelines and with labeled dosing regimens for other rhGH formulations, i.e., taking estrogen administration status and age into considerations and to base the titration on clinical response, side effects and IGF-1 levels.

However, it should be noted, that short duration of the titration period (8 weeks) most likely did not allow for the dose of somapacitan-beco or Norditropin to achieve target IGF-1 levels in most subjects who had IGF-1 SDS > -2 at baseline. Although many subjects achieved predefined normalization of IGF-1 levels at the end of titration period and end of the main period, there were subjects who had subnormal IGF-1 levels at the end of 8-week and, thus, at 34-week treatment period and were on suboptimal doses (Figure 4). Thus, longer titration period might be required in these patients to achieve higher dose and ultimately normalize IGF-1 levels and body composition.
Cross Discipline Team Leader Review
BLA 761156

Figure 4. Box plot of IGF-I SDS by visit

![Box plot of IGF-I SDS by visit](image)

Source: Clinical Study Report (CSR) 4054, Figure 11-2

**Fixed dose period (26 weeks)**

All subjects regardless of whether IGF-1 levels normalized at the end of titration period entered the fixed dose period. The duration of fixed dose treatment period of 26 week was appropriately selected to allow sufficient time to detect changes in body composition parameters associated with hormone replacement and is in line with Endocrine society guideline recommendations to treat for at least 6 months to detect clinical meaningful changes. The primary endpoint, i.e. change in TFP from baseline, was measured at the end of 34-week treatment period.

The dose was not allowed to be increased during the fixed dose treatment period. Dose reduction by 25% was allowed for safety reasons at any time during the trial.

**Extension period (52 weeks)**

After completion the main trial period and 1-week washout period, subjects entered the extension period. The extension period also consisted of titration period (8 weeks), fixed treatment period for 52 weeks and a 2-week washout period. Subjects who were treated with placebo in the main period were switched to
somapacitan-beco treatment in the extension period, those who were treated with somapacitan-beco in the main period were started again on somapacitan-beco treatment in the extension period, and those treated with Norditropin in the main period were re-randomized in 1:1 ratio to receive Norditropin or somapacitan-beco in the extension period. The starting doses and 8-week titration schedule were the same as in the main period of the trial, i.e. the starting doses for somapacitan-beco in the extension period were 1 mg/week (subjects > 60 years old), 1.5 mg/week or 2 mg/week (females on oral estrogen) and for Norditropin- 0.1 mg/day (subjects > 60 years old), 0.2 mg/day or 0.3 mg/day (females on oral estrogen) (refer to Table 3, above).

Primary efficacy outcome

The primary endpoint was the change in TFP from baseline at week 34 as measured by DXA in FAS population (all randomized subjects who received at least one dose of randomized drug). FDA found the use of this population for the primary analysis purposes to be acceptable and is in “line with ITT scenario” (refer to the Regulatory background section above). Trunk fat percentage was defined as 100 times trunk fat mass (kg) divided by the sum of trunk fat mass (kg) and trunk lean body mass (kg).

The selection of change in trunk fat percentage as an endpoint to establish clinical benefit of replacement therapy with somapacitan-beco in patients with AGHD is briefly discussed below:

- As summarized in Regulatory Section above, all currently marketed rhGH were approved for the replacement of endogenous GH in AGHD based on their effects on various body composition values, as measured by different imaging devices and methods. These body composition parameters included total fat mass, lean body mass, etc.; changes in trunk fat percentage were used as efficacy endpoint in Nutropin registration trial(s).

- AGHD is associated with loss of lean body mass and fat accumulation due to inadequate GH. rhGH therapy in adult GHD is a replacement therapy to supply GH to normalize IGF-1, leading to the improvement in signs and symptoms of AGHD. Thus, the normalization of GH and IGF-1 levels improve body composition values that may ultimately translate in the improvement of metabolic and other complications of the disease.

- Improvement in body composition values are the most recommended targets for therapeutic interventions in patients with AGHD published literature. Current treatment guidelines for AGHD (Endocrine Society, 2011) recommend “that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity”. Thus, the FDA’s approach is consistent with expert opinions described in the current treatment guidelines for AGHD management.

- However, none of the observed thresholds in the improvement in body composition values in patients with GHD have been directly linked to reduced morbidity/mortality. In the absence of clinical trial data directly informing the question of clinical benefits gained by replacement with rhGH, FDA continues to accept rhGH-induced, placebo-adjusted statistically significant changes in the selected body composition parameters (without prespecified thresholds) as evidence of effective rhGH replacement in patients with deficient state only. However, the trials evaluating efficacy of rhGH in patients with AGHD also have to demonstrate that the improvement in a body composition parameter selected as primary efficacy endpoint are also associated with beneficial changes in other body composition parameters affected by GHD along with normalization of IGF-1 levels.

- Lastly, the selection of TFP as the primary endpoint to be used in Phase 3 pivotal trial was discussed on multiple occasions (refer to Meeting Minutes from 4/19/2013 and EOP2 Meeting Minutes). During these
meetings, FDA agreed that the proposed primary endpoint is acceptable to demonstrate the efficacy of somapacitan-beco for the replacement of endogenous GH in AGHD. Since the denominator in TFP includes changes in lean body mass, and this is expected to increase with rhGH treatment, the resulting number is expected to be more sensitive to changes than assessing simply changes in trunk fat mass.

Secondary endpoints

- Changes in trunk fat mass (kg), trunk lean body mass, total fat mass, lean body mass, appendicular skeletal muscle mass from baseline at Week 34 assessed by DXA in FAS population
- Changes in visceral adipose tissue (VAT), android fat mass, gynoid fat mass from baseline at the end of 34-week treatment period (only if the DXA scanner permits)
- Changes in IGF-1 SDS, IGFBP-3 SDS from baseline to the end of main trial period
- Changes from baseline in patient’s well-being and treatment satisfaction scores as assessed by various PRO questionnaires (TRIM-AGHD, SF-36v2)
- Changes in lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides), cardiovascular parameters (hsCRP and IL-6), body weight and waist circumference at the end of the main period of the trial

All body composition compartments were measured by DXA. Dr. Roman-Popoveniuc reviewed the Study Imaging Charter and confirmed that all quality control measures and procedures were appropriate. All DXA images were read centrally. No adjustments for multiple comparisons to control the overall type 1 error or hierarchical testing were proposed. The Applicant indicated that DXA scans were provided to the imaging laboratory for reading in a blinded manner.

Efficacy results

Subject disposition and completion rate

A total of 301 subjects with AGHD were enrolled in the study and were randomized to one of three treatment arms: 121 subjects were randomized to somapacitan-beco group, 61 subjects to the placebo group, and 119 subjects to the Norditropin group. Of 301 subjects, 300 were included in FAS population and one subject randomized to somapacitan-beco group did not receive any treatment.

Completion rate of the main period of the study (34 weeks) was approximately 92% (277/300 subjects); the highest completion rate was in the somapacitan-beco group (95%, 115/120 subjects). The completion rate in placebo and Norditropin groups was 90%, each. The most common reasons for discontinuation were lost to follow up and subject’s decision (Table 4). A total of 5 subjects discontinued study preliminary due to adverse events (AE): 1-in the placebo group and 4 - in the Norditropin group; no subjects in the somapacitan-beco group discontinued study treatment due to adverse events.

Table 4. Subjects disposition
Baseline demographic and disease characteristics

The randomized groups were relatively well balanced at baseline with respect to main demographic and
disease characteristics. The mean age at baseline was 44.6 years (range 23 to 75 years) in the somapacitan-beco
group subjects, 45.7 years (range 23 to 77 years) in Norditropin group subjects and 45 years (range
23 to 76 years) in subjects on placebo; approximately 50% of all subjects were female. Approximately a
third of the enrolled subjects in each group had childhood onset of AGHD. Mean baseline body mass
index (BMI) was 26-28 kg/m². Mean TFP values at baseline were similar in the somapacitan-beco and
Norditropin groups (39.1% and 38.1%, respectively) and slightly lower in placebo group (36.9%). The
mean (SD) baseline IGF-1 SDS were similar across treatment groups: -2.54 (1.26) (somapacitan-beco), ­
2.64 (1.28) (placebo), -2.53 (1.27) (Norditropin).  Approximately, 25% of all subjects enrolled in the study
were from the US.  Although most subjects were from outside of US, the diagnostic criteria for AGHD are
the same and patients with AGHD generally have similar disease etiology worldwide (including the US).
The disease characteristics and comorbidities are also similar in these patients and are due to GH
deficiency as well as to other pituitary hormonal deficiencies (i.e. hypothyroidism, hypocortisolism,
hypogonadism) and include abnormal body compositions, hyperlipidemia, hypertension, etc.
Consequently, common medications include hormonal replacement therapies (i.e. levothyroxine,
hydrocortisone, estrogen/testosterone), antihypertensive, lipid lowering medications, etc. Thus, the
efficacy and safety data on somapacitan-beco use obtained in subjects from other countries is applicable to
US subjects.
Dr. Roman-Popoveniuc also indicated that the groups were well balanced at baseline with respect to other
baseline comorbidities and concomitant medication, with exception of use of oral estrogens. Twice as many
females in somapacitan-beco group compared to other two groups used oral estrogen (61.3% in
somapacitan-beco group vs. 37.3% in placebo group and 31.3% in Norditropin group, respectively).

Primary analysis: Treatment difference in TFP between somapacitan-beco and placebo at the end of 34-
week treatment
Dr. Alexander Cambon reviewed the primary statistical analysis methods used to support the establishment of efficacy. Efficacy findings are also reviewed and discussed in Dr. Roman-Popoveniuc’s review. For detailed discussions of the efficacy findings, see these reviews. My memorandum provides a summary of the main efficacy findings.

The Applicant conducted the primary efficacy analysis in 300 subjects who were randomized and received at least one dose of study drug (FAS). As stated above, FDA agreed that use of FAS population is “in line with ITT scenario” and accepted the use of FAS population for the primary analysis. The estimated mean treatment difference in TFP between somapacitan-beco and placebo groups was -1.53% (95% CI-2.68; -0.38), p=0.009 (Table 5). Dr. Cambon independently verified the Applicant’s results for the primary analysis and confirmed that pivotal study establishes the superiority of somapacitan-beco over placebo in terms of reduction in TFP from baseline. The primary efficacy analysis was repeated by Dr. Cambon under different scenarios and imputations including ANCOVA analysis wherein only subjects with at least one TFP value during the study were included or only subjects who had final assessment within 34± 4 weeks were included (the Applicant used only Week 34 assessment). The difference between treatment arms remained statistically significant. Due to the unequal randomization ratio between somapacitan-beco 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 other analyses. Dr. Cambon also indicated that no method was used to address missing data since the missing data and discontinuation rates were very low (Table 6).

### Table 5. Primary and Secondary Endpoints – Applicant’s Analysis Results

<table>
<thead>
<tr>
<th>Endpoint*</th>
<th>Exp.</th>
<th>Ctrl.</th>
<th>Diff.</th>
<th>LCL</th>
<th>UCL</th>
<th>P-Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in % Trunk Fat</td>
<td>-1.06</td>
<td>0.47</td>
<td>-1.53</td>
<td>-2.68</td>
<td>-0.38</td>
<td>0.009</td>
</tr>
<tr>
<td>Change in Trunk fat mass (g)</td>
<td>-123</td>
<td>373</td>
<td>-496</td>
<td>-1049</td>
<td>57</td>
<td>0.075</td>
</tr>
<tr>
<td>Change in Trunk lean body mass (g)</td>
<td>804</td>
<td>352</td>
<td>452</td>
<td>25</td>
<td>880</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*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 (somapacitan-beco); Ctr.-Control Arm (placebo); Diff.-Treatment Difference; LCL- Lower Confidence Limit; UCL -Upper Confidence Limit; P-Val-P-Value. Source: Biostatistician’s review, table 4.

### Table 6. Primary and Secondary Endpoints – FDA Results

<table>
<thead>
<tr>
<th>Endpoint*</th>
<th>Exp.</th>
<th>Ctrl.</th>
<th>Diff.</th>
<th>LCL</th>
<th>UCL</th>
<th>P-Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in % Trunk Fat *</td>
<td>-1.10</td>
<td>0.31</td>
<td>-1.41*</td>
<td>-2.61</td>
<td>-0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in Trunk fat mass (g)</td>
<td>-145</td>
<td>343</td>
<td>-488</td>
<td>-1015</td>
<td>39</td>
<td>0.069</td>
</tr>
<tr>
<td>Change in Trunk lean body mass (g)</td>
<td>811</td>
<td>381</td>
<td>430</td>
<td>-0.4</td>
<td>860</td>
<td>0.050</td>
</tr>
</tbody>
</table>

*All endpoints are assessed at Week 34. No multiple testing procedure was used to control Type 1 error over primary and secondary endpoints; Results of primary analysis are in red font.
Dr. Cambon also confirmed that improvement were also observed in two secondary endpoints that were components of the primary endpoint calculation, decrease in trunk fat mass and increase in trunk lean body mass (refer to “Analyses of secondary endpoints (somapacitan-beco vs. placebo)” section below), and concluded that the observed changes in these body composition compartments were supportive of the primary endpoint and correlated with changes in TFP.

The estimated treatment difference between somapacitan-beco and placebo in reduction of TFP was not affected by age and GHD onset (childhood vs. adult). However, the estimated treatment difference in reduction of TFP was higher in males (-2.52) compared to females (-0.9). As per Dr. Roman-Popoveniuc, it can be explained by higher estrogen levels in females; estrogens have a known effect on the GH binding in other tissues.

The estimated treatment difference was also consistent between subgroups from Asia and Europe and was consistent with overall effect of somapacitan-beco on TFP reduction. However, the subgroup from North America (NA) demonstrated positive treatment difference of 1.41 between somapacitan-beco and placebo in favor of placebo (Table 7). The estimated treatment difference for Norditropin vs. placebo was also less pronounced in US subpopulation vs. other regions: -0.31.

Table 7. Changes from baseline to week 34 in TFP by region (trial 4054) – FDA requested analysis
Thus, FDA requested the Applicant to evaluate factors that may account for the observed difference in efficacy between regions (refer to the FDA’s Information Request from 4/16/2020). The Applicant provided the results of the requested additional post-hoc analyses to FDA on 4/22/2020; these results were further confirmed by Dr. Cambon. Based on the results of these analyses, it appeared that there was a positive placebo effect (-1.7% vs. negative placebo effect for Asia and Europe regions, 0.26% and 1.85%, respectively) observed in NA subgroup. The positive placebo effect in NA subgroup was most likely influenced by data from 3 subjects on placebo who had reduction in TFP by > 5% due to use of concomitant weight reduction medications and underlying medical conditions (lung fibrosis). After the exclusion of these 3 subjects from the analyses, the reduction in TFP in NA group was consistent with TFP reduction seen in subjects from other regions (Table 8).
The additional analyses also revealed that subjects in the NA subgroup had higher baseline BMI compared to subjects from the other regions and higher baseline TFP (Table 9), and the results of the analysis including BMI as a covariate demonstrated that the treatment effect for somapacitan-beco and Norditropin increased (refer to Dr. Cambon’s review for details).

Table 9. Mean (SD) Body weight and BMI characteristics by region

<table>
<thead>
<tr>
<th>Region</th>
<th>Placebo</th>
<th>Norditropin</th>
<th>Somapacitan-beco</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77.6 (18.6)</td>
<td>90.1 (21.1)</td>
<td>92.0 (23.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.0 (7.9)</td>
<td>31.8 (6.5)</td>
<td>31.3 (7.1)</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>69.8 (19.9)</td>
<td>76.1 (22.6)</td>
<td>70.2 (14.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 (6.3)</td>
<td>27.1 (5.5)</td>
<td>26.8 (5.6)</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>65.0 (19.9)</td>
<td>65.6 (18.9)</td>
<td>70.6 (17.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 (4.8)</td>
<td>25.3 (5.1)</td>
<td>26.4 (4.7)</td>
</tr>
</tbody>
</table>

Lastly, to explore whether BMI could be a treatment effect modifier, Dr. Cambon 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. Results of this analysis using the same covariates for the primary analysis for the primary endpoint, but only including subjects with BMI > 27 kg/m² demonstrated that the treatment difference between somapacitan-beco and placebo in reduction of TFP decreased to -0.97% from -1.41% (refer to Table 6 above, Primary and Secondary Endpoints – FDA Results).

Based on the results of these analyses, Dr. Cambon concluded that the observed regional difference in the estimated treatment difference was most likely due to the overall NA small sample size (44 subjects: 30 subjects on somapacitan-beco and 14 on placebo), and smaller treatment effect on TFP for somapacitan-beco and Norditropin may be explained by higher baseline BMI and TFP in subjects from NA. Dr. Cambon also concluded that somapacitan-beco may be less effective treatment in obese patients. These conclusions are supported by Clinical Pharmacology findings that BMI is one of the intrinsic factors that
affects the efficacy of somapacitan-beco (refer to Clinical Pharmacology section above) and that subjects with higher BMI may require higher doses to achieve IGF-1 normalization leading to the improvement in body composition. However, Clinical Pharmacology reviewers also confirmed (using PK/PD model evaluating impact of weight on exposure response and dose response) that normalization of IGF-1 levels can be achieved within the proposed dose range (refer to Clinical Pharmacology section, Figure 3, above).

**Analyses of secondary endpoints (somapacitan-beco vs. placebo)**

- **Changes in various body composition parameters from baseline at the end of Week 34 (Table 10).**

The results of these secondary analyses demonstrated that somapacitan-beco replacement therapy in subjects with AGHD induced a reduction in the majority of other body fat compartment values (android fat mass, trunk fat mass, total body fat mass) and an increase in lean body mass values (trunk lean body mass, appendicular skeletal muscle mass (ASMM), total lean body mass).

Overall, the results of these analyses are supportive for the conclusion drawn from the trial’s primary endpoint. The observed improvements in body composition are also overall consistent with improvements in body composition values observed with other rhGH treatments in AGHD (refer to Regulatory background section). However, as Dr. Roman-Popoveniuc noted, direct comparison between effects on body compositions induced by somapacitan-beco or other rhGH formulations is complicated due to the differences in study designs, baseline patient characteristics, statistical methods used to evaluate efficacy endpoints, methods to measure body composition, etc. Statistical significance of the observed changes should also be interpreted with caution, since there were no pre-specified hierarchical testing procedure and multiple testing procedure for secondary endpoints. Thus, the secondary endpoints should not be included in the label.

Table 10. Changes from baseline to week 34 in body composition parameters for somapacitan-beco vs. placebo

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>Somapacitan (N = 120)</th>
<th>Placebo (N = 61)</th>
<th>ETD</th>
<th>[95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral adipose tissue (cm²)</td>
<td>-10</td>
<td>3</td>
<td>-14</td>
<td>[-21, -7]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Truncal fat mass (g)</td>
<td>-123</td>
<td>373</td>
<td>-496</td>
<td>[-1049, 57]</td>
<td>0.0786</td>
</tr>
<tr>
<td>Android fat mass (g)</td>
<td>-68</td>
<td>48</td>
<td>-116</td>
<td>[-223, -10]</td>
<td>0.0326</td>
</tr>
<tr>
<td>Gynoid fat mass (g)</td>
<td>26</td>
<td>11</td>
<td>15</td>
<td>[-144, 175]</td>
<td>0.8511</td>
</tr>
<tr>
<td>Total fat mass (g)</td>
<td>-31</td>
<td>236</td>
<td>-266</td>
<td>[-1197, 664]</td>
<td>0.5746</td>
</tr>
<tr>
<td>Truncal lean body mass (g)</td>
<td>804</td>
<td>352</td>
<td>452</td>
<td>[25; 880]</td>
<td>0.0380</td>
</tr>
<tr>
<td>ASMM (g)</td>
<td>558</td>
<td>-121</td>
<td>679</td>
<td>[340; 1019]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total lean body mass (g)</td>
<td>1394</td>
<td>250</td>
<td>1144</td>
<td>[459; 1829]</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

**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.

Changes in visceral adipose tissue should be interpreted with caution, since it was measured by CT scan that is not preferred and validated method for VAT measurement.

Source: Clinical Review, table 18.
Mean IGF-1 SDS were low at baseline in both groups of subjects: -2.54 in somapacitan-beco group and -2.64 in placebo group, respectively. At the end of 34-week treatment, mean (SD) IGF-1 SDS normalized in somapacitan-beco group (-0.17 (SD 1.25)) and remained low in placebo group (-2.62 (SD 1.33)). The estimated treatment difference between somapacitan-beco and placebo was 2.40 (95% CI 2.09; 2.72). These results are overall supportive of the primary endpoint and the proposed indication for somapacitan-beco as a replacement therapy in patients with AGHD. Please refer to our discussion of changes in IGF-1 among subgroups, in the “Secondary Comparisons of the efficacy endpoints: somapacitan-beco vs. Norditropin”.

Other endpoints that were examined included changes in weight, waist circumference, lipid parameters, and subject well-being and satisfaction assessed by various questionnaires. Dr. Roman-Popoveniuc reviewed other endpoints and concluded that there were no meaningful changes in any of these parameters. Lastly, although some improvement in subject well-being scores was noted in those treated with somapacitan-beco, none of PRO instruments have been validated for patients with AGHD to date, which limits interpretability of these data and does not allow for any labeling claims based on the PRO data. I agree with her conclusions and do not recommend including any of these analyses results in the labeling.

**Secondary Comparisons of the efficacy endpoints: somapacitan-beco vs. Norditropin**

The study was not designed to inferentially compare the efficacy of somapacitan-beco to Norditropin. The titration algorithm for Norditropin was the same as the algorithm used for somapacitan-beco, however, no statistical non-inferiority was pre-specified or required. The Applicant states that the only purpose of this comparison was “to assist the clinical judgement of the clinic relevance of the estimated treatment difference between somapacitan-beco and placebo”. Therefore, the results of these analyses should be interpreted with caution.

**Changes in TFP**

Based on the Applicant’s and Dr. Cambon’s analyses comparing somapacitan-beco induced changes in TFP vs. Norditropin-induced changes in TFP, somapacitan-beco was inferior to Norditropin in terms of reduction of TFP (Table 5). At the end of 34-week treatment, reduction in TFP from baseline in somapacitan group was smaller compared to Norditropin group (-1.10% vs. -2.38%, respectively) and the treatment difference in reduction of TFP between Norditropin and somapacitan-beco was 1.28% (95% CI 0.29%; 2.26%). When the TFP changes at the end of the treatment were compared between Norditropin and placebo groups (posthoc analysis), the estimated treatment difference between Norditropin and placebo was -2.82% (95% CI -4.0%; -1.63%); larger than observed estimated treatment difference in TFP reduction between somapacitan-beco and placebo (-1.53%).

**Changes in other body compositions measurements**

The changes in the other body fat measurements from baseline were also larger in the Norditropin group compared to the somapacitan-beco group at the end of 34-week treatment. However, changes in lean body mass were similar between Norditropin and somapacitan-beco groups (Table 11).
Overall, it seems that Norditropin might have a better effect on reduction in fat body composition parameters but have similar effect on the improvement in lean body mass. The less pronounced effect on the fat compartment only observed with somapacitan-beco is unclear. This issue was discussed during the Late-Cycle meeting between FDA and the Applicant on 4/23/2020. The Applicant noted that one of possible factors that may explain the observed treatment difference between somapacitan-beco and Norditropin is uneven enrollment of females on oral estrogen among treatment groups (refer to the Applicant’s response to FDA’s IR from 4/23/2020 and see discussion below). Indeed, the reviewers confirmed that more subjects on oral estrogen were enrolled in somapacitan-beco group (31.7% (38/120 subjects) vs. 19% (23/119 subjects) in Norditropin group and 16.4% (10/61 subjects) in placebo group). The results of the Applicant’s pot-hoc analyses evaluating the effect of study drugs on TFP in females on oral estrogen and in the entire study population excluding subjects on oral estrogen demonstrated that the estimated mean treatment difference in TFP reduction between somapacitan-beco and Norditropin decreased from 1.28% to 0.84% in enrolled population after subjects on oral estrogens were excluded from the analyses.

The results of these analyses also demonstrated that the effect of somapacitan-beco on TFP was small in subjects on oral estrogen (reduction in TFP by 0.15%) at the average dose used during the study (3.45 mg/week). Oral estrogen suppresses the GH-induced synthesis of IGF-1, and women, in general, require higher doses of rhGH to achieve the same IGF-1 response. IGF-1 SDS in the post-titration period were also lower in this group of subjects compared to other groups and 42% of estrogen-treated females in somapacitan-beco group had IGF-1 SDS < 0.5 (only 17% of females not on estrogen in somapacitan-beco group had IGF-1 SDS < 0.5). The low somapacitan-beco exposure in estrogen-treated females was also confirmed by Applicant’s population-based modeling analysis evaluating impact of sex and oral estrogen on the dose exposure, exposure response and dose-response. Based on the results of this analysis, the somapacitan-beco exposure is lower in females on oral estrogen, and the starting dose of 2 mg is predicted to reach similar response compared to other patients (refer to Clinical Pharmacology section above and 9 Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Shalet SM, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96(6): 1587-609

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Figure 3). Lastly, the results of this analysis also demonstrated that normalization of IGF-1 can be achieved with use of higher, but still within the proposed range doses.

In conclusion, the suboptimal effect of somapacitan-beco on the reduction in TFP compared to Norditropin may be due, at least in part, to uneven enrollment of estrogen-treated female in the treatment groups and use of the suboptimal doses in these females. Use of higher doses (but still within the proposed dose range) in these subjects is expected to normalize IGF-1 levels and decrease TFP. This was not possible under the constraints of the titration guidelines in the protocol directing Study 4054. Lastly, the conclusion regarding the superiority of Norditropin over somapacitan-beco in reducing fat mass is further complicated by the fact that the comparison was not made at the maximum doses due to the trial design and a longer titration time in the treatment arms may have negated any difference in efficacy between products.

However, I agree with reviewers’ recommendations to include the changes in TFP observed in Norditropin group in the label to provide useful information to health care providers and patients regarding expected changes in body composition with each drug. These results should be presented descriptively only; no superiority claim for Norditropin should be made. Such results may better inform the preference for either a product with possibly greater effect on the reduction of fat body composition parameters (Norditropin) or for a product with greater convenience due to less frequent injections (somapacitan).

**Extension Data**

During open-label single-arm extension period of Study 4054, the treatment effect observed with somapacitan-beco in 34-week treatment period was maintained up to 86 weeks (TFP, lean body mass, IGF-1 SDS, etc.). Although data from extension trial provide some evidence of persistence of the somapacitan-beco effect for almost 2 years, the quantitative efficacy data obtained from such open-label, uncontrolled trials should not be used for labeling because by the very nature of its design, the trial selected a study population likely to have benefited from the drug, and a control group is lacking.

**Supportive evidence of effectiveness of somapacitan-beco in patients with AGHD from studies 4244 and 4043.**

As stated above, both studies were designed primarily as safety studies comparing safety profile of somapacitan-beco to Norditropin in subjects previously treated with rhGH. The starting doses were the same as in Study 4054. The doses were allowed to be titrated every 4 weeks during the first 20 weeks in study 4244 and every 2 weeks during first 8 weeks in study 4043 (Table 12).
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Table 12. Dose titration algorithm for somapacitan-beco and Norditropin in trials 4244 and 4043

<table>
<thead>
<tr>
<th>IGF-I SDS interval</th>
<th>Somapacitan</th>
<th>Norditropin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I SDS $&gt;3$</td>
<td>Decrease by 1 mg/week</td>
<td>Decrease by 0.1 mg/day</td>
</tr>
<tr>
<td>$2 &lt; IGF-I SDS \leq 3$</td>
<td>Decrease by 0.5 mg/week</td>
<td>Decrease by 0.05 mg/day</td>
</tr>
<tr>
<td>$0 &lt; IGF-I SDS \leq 2$</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>$-2 &lt; IGF-I SDS \leq 0$</td>
<td>Increase by 0.7 mg/week</td>
<td>Increase by 0.1 mg/day</td>
</tr>
<tr>
<td>IGF-I SDS $\leq -2$</td>
<td>Increase by 1.5 mg/week</td>
<td>Increase by 0.2 mg/day</td>
</tr>
</tbody>
</table>

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

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

Source: Summary of Clinical Efficacy, Table 1-6, p. 24.

Improvements in adipose tissue parameters were evaluated as secondary endpoint in study 4244 at the end of 32-week treatment. Both studies evaluated IGF-1 SDS at the end of treatment. Results from both studies demonstrated that IGF-1 levels were maintained within normal range from baseline to the end of the treatment in subjects treated with somapacitan-beco. Maintenance in adipose tissue parameters was also observed in study 4244 at the end of 32-week treatment. Overall these findings consistent with results observed in Study 4054 and provide additional evidence that somapacitan-beco is effective as a replacement therapy in patients with AGHD. However, these results should be interpreted with caution due to the multiple factors including that the studies were not designed to evaluate efficacy, were small, and did not have a placebo arm, body composition was assessed by CT method (as oppose to DXA scan in Study 4054), all subjects had been exposed to other rhGH therapies prior to the enrollment, etc.

**Conclusion**

I agree with both the statistical and clinical recommendations for the approval of the drug for the proposed indication. The results of the trial provided substantial evidence of efficacy of somapacitan-beco as a replacement therapy in patients with AGHD and demonstrated that somapacitan-beco significantly reduced TFP compared to placebo at the end of 34-week treatment and that untreated subjects on placebo had increase in TFP at the end of the trial: the estimated mean treatment difference in TFP between somapacitan-beco and placebo groups was -1.53% (95% CI -2.68%; -0.38%), p=0.009. Directional changes in other body compartments values (lean body mass, total fat, trunk fat mass) were consistent with expectations and suggest that somapacitan-beco use is associated with a net improvement in body composition. The most important that the improvement in the body composition parameters positively correlated with normalization in IGF-1 SDS indicating that somapacitan-beco effectively replaces the missing hormone leading to the improvement in signs and symptoms associated with deficient sate in these patients. The observed difference in the improvement in TFP between US and non-US regions was most likely due to small subgroup, the disproportional enrollment of subjects with high BMI in the US group of subjects, use of suboptimal doses in subjects with high BMI and by positive placebo effect in 3 subjects who were treated with weight-controlled medication/had underlying medical condition associated with weight loss. The difference was less prominent when the data was reanalyzed excluding these subjects. The additional biostatistician’s analyses and clinical pharmacology data also confirmed that body weight is one of major covariates that affect exposure and the activity of the drug and that patients with higher BMI may require higher doses (but still within the proposed dose range) to achieve IGF-1 normalization leading to the improvement in body composition. Since the dose will be titrated based on clinical response, no dose adjustment is recommended based on body weight.
The lower effect of somapacitan-beco on TFP was also observed in females on oral estrogen (-0.15%) at the average dose used during the study (3.45 mg/week) compared to the other subgroup of subjects. Estrogen has known inhibitory effect on IGF-1 secretion by the liver and also has negative effect on body weight. Clinical Pharmacology also confirmed that oral estrogen is one of the intrinsic factors that affect exposure and action of somapacitan-beco. Thus, the lower effect on TFP in this subgroup is most likely due to the suboptimal doses of somapacitan-beco used, as demonstrated by the fact that 40% of females on estrogen did not achieve normalization of IGF-1 levels at the end of the titration period at doses used. Use of higher doses (but still within the proposed dose range) in these patients is expected to normalize IGF-1 levels and decrease TFP and is supported by the results of the population-based modeling analysis.

The secondary analyses comparing efficacy of somapacitan-beco with Norditropin suggest that at doses of somapacitan-beco and Norditropin achieved in the trial there was a less pronounced effect of somapacitan-beco on fat body compartments compared to Norditropin; however, a similar effect of both drugs on lean body mass was observed at the end of the treatment. The observed differences are unclear and may be due by uneven enrollment of females on oral estrogen in treatment groups with the largest proportion of these subjects randomized to the somapacitan-beco group and suboptimal doses of somapacitan-beco used in this subgroup. The conclusion regarding the superiority of Norditropin over somapacitan-beco in reducing fat mass is further complicated by the fact that the comparison was not made at the maximum doses; the higher doses/ longer titration in the treatment arms may have negated any difference in efficacy between products. However, I agree that the results observed in Norditropin arm, i.e. effect of Norditropin on TFP, should be included in the label descriptively to make health care providers aware of the body composition changes that are expected with the use of each drug.

Lastly, additional evidence of somapacitan-beco effect as replacement therapy in GHD states comes from published studies using somapacitan-beco in children with GHD to accelerate linear growth associated with GHD. The data from this publication have not yet been reviewed by FDA. Adult and pediatric GHD are well understood entities and share several important features in common; the most important fact is that both conditions are states of GH deficiency and exogenous somatropin treatment aims at mimicking the function of inadequate GH secretion (i.e. a replacement therapy). The published results from Phase 2, randomized, controlled, double-blind (somapacitan-beco doses) study with a 26-week main and 26-week extension phase demonstrated comparable effects on annualized growth velocity (AGV) between somapacitan-beco and daily rhGH at week 26 of treatment: mean (SD) AGV for the somapacitan-beco groups was 8.0 (2.0) (dose 0.04 mg/kg/week), 10.9 (1.9) (dose 0.08 mg/kg/week), and 12.9 (3.5) (dose 0.16 mg/kg/week) cm/year, respectively, vs 11.4 (3.3) cm/year for daily GH (dose 0.034 mg/kg/day); estimated treatment difference (somapacitan-beco 0.16 mg/kg/week-daily GH): 1.7 [95% CI -0.2 to 3.6] cm/year. Although these results do not support effectiveness of the drug in the proposed indication, they provide reassuring insight that this product replaces GH and improves signs and symptoms of GHD similarly to other rhGH formulations.

Based on the result of Study 4054, I recommend starting dose for somapacitan-beco 1.5 mg/week in patients < 60 years old, 1.0 mg in patients > 60 years old and 2 mg in females on oral estrogen (due to the lower exposure as discussed above). Doses should be titrated every 2–4 weeks by 0.5 -1.5 mg based on

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clinical response and serum IGF-1 concentrations. Lastly, I also agree with the reviewers that since the
dose will be titrated based on clinical response, no dose adjustment is required based on body weight.

8. Safety

The primary safety data in support of the proposed indication of somapacitan-beco in patients with AGHD
is derived from the pivotal Study 4054. Supportive safety data in subjects with AGHD come from two Phase
3 study in subjects with AGHD (Study 4244 and 4043). The Applicant also included the results of pooled
analyses of safety data from all three Phase 3 studies. However, as were discussed during Pre-BLA meeting,
FDA disagreed with the pooling strategy, since it is not informative and may be misleading due to the
different study designs, different study populations (treatment naïve vs previously treated), different
duration of the study, etc. In addition, the data from studies 4244 and 4043 provide only limited data on the
safety of the product itself since these studies were conducted in subjects who were on rhGH formulations
prior to the enrollment in the studies, thus, the results are confounded by the previous exposure to rhGH and
should be interpreted with caution. Lastly, the Applicant included the results of five Phase 1 studies: four
studies were conducted in healthy volunteers and in subjects with renal and hepatic impairment and one
study of short duration (4 weeks) was conducted in 26 subjects with AGHD. The results from these studies
will not be discussed in this memorandum, since the majority of these studies have been conducted in the
different populations and were of short duration. Thus, they provide only limited information on the safety
of the drug in the intended population. Refer to Dr.’s Roman-Popoveniuc review for the details.

Overall, 561 subjects received at least 1 dose of somapacitan-beco; of these, 333 subjects with AGHD were
exposed to somapacitan-beco in three Phase 3 studies and 26 subjects with AGHD in Phase 1 study. Based
on data obtained to date (cutoff date 3/31/2019) from three Phase 3 studies in 333 subjects with AGHD, 319
subjects received drug for > 6 months, and 109 subjects for > 18 months. This level of exposure is acceptable
for this drug to support chronic dosing.

This CDTL review will further focus on the safety observations made in the main period of pivotal Study
4054. This period provides the most informative data on common product related safety issues because the
study allows side by side comparison of somapacitan-beco to placebo, were obtained in randomized groups
in blinded fashion with frequent assessment and had an approximately 8-month duration of controlled
observation. The individual safety data from the studies 4244 and 4043 will be summarized only briefly
and as needed. The additional sources will be mentioned only when relevant.

In the controlled period of Study 4054, 116 subjects were treated with somapacitan-beco for > 6 months,
and 4 subjects for < 3 months. The mean somapacitan-beco dose in all subjects in study 4054 was 2.59
mg/week. The mean somapacitan-beco dose was 1.4 mg/week for subjects > 60 years old, 2.1 mg/week for
subjects < 60 years old and 3.8 mg/week for females on oral estrogen. The mean doses used in all subjects
in trials 4244 and 4043 were lower, 2 mg/kg and 1.78 mg/kg, respectively.

Death

Dr. Roman-Popoveniuc reviewed all death cases and concluded that none were not related to the study
drugs.

There were five deaths in Study 4054: four deaths occurred in the extension phase (two subjects were
treated with somapacitan-beco and two subjects were treated with Norditropin) and one death - in the main
phase in a subject treated with placebo. There was no imbalance in fatal events between treatment groups
and no specific cause of death occurred in more than one subject.
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In the extension phase, two subjects were switched to somapacitan-beco from placebo or Norditropin and died. The cause of death was ventricular fibrillation, cardiogenic shock and aspiration pneumonia in one subject who received placebo in main period; the death occurred in 2 weeks after the drug was discontinued. The cause was not reported in the other subject; however, this subject had been off the drug for 5 months. The causes of death in Norditropin group were pneumonia and influenza.

In conclusion, I agree that no deaths were related to the study drugs. There study drugs were discontinued for 16 days - 9 months in 3/4 subjects treated with active drugs and all subjects were > 60 years old with underlying serious medical conditions. The reported deaths were more likely due to the complications of underlying serious medical conditions (e.g., angina, adrenal insufficiency, panhypopituitarism) or caused by acute illness in elderly patient population (pneumonia, influenza).

There were no deaths in studies 4043 and 4244.

**AEs that led to the study discontinuation**

No subjects treated with somapacitan-beco in main period of Study 4054 discontinued the study due to the AEs. Four subjects treated with Norditropin and one subject treated with placebo discontinued the study due to the AEs. The AEs that led to the study discontinuation were: hepatic enzymes increased in a subject treated with placebo and diabetes, gastroenteritis, hemoconcentration and dermatitis atopic in subjects treated with Norditropin.

In study 4043, only one subject who was treated with somapacitan-beco discontinued the study due to non-serious AEs of asthenia.

No subjects on somapacitan-beco discontinued study 4244.

**Serious Adverse Events (SAE)**

A total of 32 SAEs were reported in 23 subjects in the main period of Study 4054. The number of subjects who developed SAEs and the number of SAEs were similar across all treatment groups: 11 subjects in Norditropin group (13 events), seven subjects in somapacitan-beco group (12 events) and five subjects in the placebo group (seven events), respectively.

In the somapacitan-beco group gastroenteritis was reported in three subjects (gastroenteritis in two subjects and viral gastroenteritis in one subject). All other SAEs in the somapacitan-beco group were reported in one subject each: adrenal insufficiency, inguinal hernia, stomatitis, vomiting, pyrexia, appendicitis, herpes, sepsis, viral upper respiratory tract infection.

No increase in frequency of SAEs and no new safety signals were identified with longer exposure to the study drugs.

All SAEs that occurred in studies 4043 and 4244 were considered as unrelated to the study drugs.

**Common Adverse Events**

A total of 72% (87/120) of subjects treated with somapacitan-beco, 75% (46/61) of subjects treated with placebo, and 80% (95/119) of subjects treated with Norditropin experienced at least one AE during the controlled period of the Study 4054.

Overall, the AE profile observed in Study 4054 was consistent with the known AE profile of rhGH in patients with AGHD.
The review team conducted a separate analysis of the treatment emergent adverse reactions (ARs) using FDA Medical Queries (FMQ). FMQs were developed by FDA to improve the capture of synonymous adverse event terms and to improve overall safety signal detection. The results of this analysis revealed additional ARs that occurred more frequently in somapacitan-beco arm compared to placebo arm or rendered different results than reported and included in Section 6 of the label by the Applicant (Table 13). The ARs that are new or rendered different results than the original table in Section 6 of the label are marked in bold in Table 13. The RR and % difference to presented in the table below highlighting FDA’s rationale and are not meant to be displayed in the prescribing information.

Table 13. Adverse reactions with > 2% overall incidence in subjects with AGHD treated with somapacitan-beco compared to placebo and Norditropin during main phase of Study 4054.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SOGROYA (N = 120)</th>
<th>Placebo (N = 61)</th>
<th>Relative risk</th>
<th>Absolute % difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>24</td>
<td>20</td>
<td>9</td>
<td>14.8</td>
</tr>
<tr>
<td>Back pain</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>8</td>
<td>6.7</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>5</td>
<td>4.2</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>4.2</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Tonsilritis</td>
<td>4</td>
<td>3.3</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increase</td>
<td>4</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>4</td>
<td>3.3</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>4</td>
<td>3.3</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>4</td>
<td>3.3</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>3.3</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>2.5</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
<td>5.8</td>
<td>3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

N= number of subjects having the event, (%) = proportion of subjects having the event
Nasopharyngitis includes Preferred terms (PT): viral upper respiratory infection and pharyngitis
Back pain includes preferred terms (PT): back pain and sciatica
Dyspepsia includes PT: dyspepsia, abdominal discomfort, abdominal pain upper and abdominal pain
Urinary tract infection (UTI) includes PT: cystitis and UTI
Sleep disorder includes PT: sleep disorder and hypersomnia
Dizziness includes PT: dizziness and vertigo
Anemia includes PT: anemia and iron deficiency anemia
Pyrexia includes PT: pyrexia and body temperature increased
Abdominal pain includes PT: abdominal discomfort, abdominal pain and abdominal pain upper

Overall, since the use of grouped terms (FMQ) captures synonymous adverse event terms and improves the overall safety information in the label, the reporting of ARs in Section 6 of the label should be based on the results of FDA analysis. The criteria used for the selection of the ARs to be included in Section 6 Adverse Reaction table of the Prescribing Information, include event rate for SOGROYA > 2%, relative risk (RR) > 1.3, and absolute incidence (%) difference > 1%, compared to placebo.

Dr. Roman-Popoveniuc analyzed further all AEs that have not been reported with previous use of rhGH but
were observed more frequently with somapacitan-beco use compared to placebo in Study 4054. As per her analyses, there was a higher rate of the events of back pain and blood creatine phosphokinase (CPK) increase reported with somapacitan-beco use. The AEs of back pain are briefly summarized below, the AEs of elevated CPK levels are discussed in Laboratory Parameters section.

There were 12 subjects who developed back pain during the treatment with somapacitan-beco compared to 2 subjects treated with placebo and 4 subjects treated with Norditropin. All events of back pain were non-serious, mild and resolved in all but one case, without dose reduction. No fractures were reported. Back pain can be explained by fluid accumulation (known risk associated with rhGH) and subsequent nerve compression. The risk of this event can be mitigated through the proper labeling.

Adverse events of special interest (AESI)

The Applicant analyzed a total of 21 AESI. They were intended to capture class-specific adverse reactions included in the other rhGH labels or described in published literature. These AEs are summarized in Table 14, below.

Table 14. Medical Events of Special Interest that occurred in study 4054, Main Period.

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Somapacitan-beco</th>
<th>Norditropin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>E</td>
<td>N (%)</td>
<td>E</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>10 8.3</td>
<td>10 8.4</td>
<td>10 16.4</td>
</tr>
<tr>
<td><strong>Allergic reactions (non-anaphylactic)</strong></td>
<td>8 6.7 9</td>
<td>11 9.2 13</td>
<td>9 14.8 10</td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>8 6.7 8</td>
<td>10 8.4 10</td>
<td>1 1.6 1</td>
</tr>
<tr>
<td><strong>Fatigue/Asthenia</strong></td>
<td>5 4.2 5</td>
<td>9 5.8 9</td>
<td>4 6.6 4</td>
</tr>
<tr>
<td><strong>Adrenal Insufficiency</strong></td>
<td>4 3.3 4</td>
<td>2 1.7 2</td>
<td>1 1.6 1</td>
</tr>
<tr>
<td><strong>Peripheral edema</strong></td>
<td>4 3.3 6</td>
<td>9 5.8 11</td>
<td>1 1.6 1</td>
</tr>
<tr>
<td><strong>Weight increased</strong></td>
<td>4 3.3 4</td>
<td>1 0.8 1</td>
<td>0 0 0</td>
</tr>
<tr>
<td><strong>Lipohypertrophy/lipodystrophy</strong></td>
<td>4 3.3 4</td>
<td>0 0</td>
<td>0 0 0</td>
</tr>
<tr>
<td><strong>Paresthesia</strong></td>
<td>3 2.5 4</td>
<td>1 0.8 1</td>
<td>2 3.3 2</td>
</tr>
<tr>
<td><strong>Injection site reactions</strong></td>
<td>2 1.6 5</td>
<td>8 6.7 8</td>
<td>3 4.9 5</td>
</tr>
<tr>
<td><strong>Myalgia</strong></td>
<td>2 1.6 4</td>
<td>4 3.4 4</td>
<td>3 4.9 3</td>
</tr>
<tr>
<td><strong>Hyperglycemia/Type 2 DM</strong></td>
<td>4 1.8 7</td>
<td>4 3.4 8</td>
<td></td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>1 0.8 1</td>
<td>3 2.5 1</td>
<td>1 1.6 1</td>
</tr>
<tr>
<td><strong>Carpal tunnel syndrome</strong></td>
<td>0 0 0</td>
<td>0 0 0</td>
<td>0 0 0</td>
</tr>
<tr>
<td><strong>Neoplasms benign, malignant and unspecified.</strong></td>
<td>0 0 0</td>
<td>2 1.7 2</td>
<td>0 0 0</td>
</tr>
<tr>
<td><strong>Intracranial hypertension</strong></td>
<td>0 0 0</td>
<td>0 0 0</td>
<td>0 0 0</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>0 0 0</td>
<td>0 0 0</td>
<td>1 1.6 1</td>
</tr>
<tr>
<td><strong>Severe hypersensitivity</strong></td>
<td>0 0 0</td>
<td>0 0 0</td>
<td>0 0 0</td>
</tr>
</tbody>
</table>

Source: Clinical Review, Table 48, modified.

Several AESI (e.g., headache, allergic reactions, fatigue, paresthesia, injection site reactions, myalgia, hypothyroidism) were observed with lower frequency in the somapacitan-beco group compared to the placebo group. No increase in incidence of AESIs including arthralgia and peripheral edema (due to the known effect of rhGH on fluid retention), hyperglycemia, lipoatrophy was observed during the treatment with somapacitan-beco compared to Norditropin. No AEs of intracranial hypertension, pancreatitis, were
reported in somapacitan-beco-treated subjects. Lastly, the frequency of the injection site reactions was similar between somapacitan and Norditropin groups, and lower than in the placebo group.

Adrenal insufficiency

GH increases cortisol metabolism via the enhanced conversion of cortisol to inactive cortisone. Thus, treatment with rhGH formulations may unmask adrenal insufficiency (AI) in hypopituitary patients who have decreased ACTH reserve. Patients treated with glucocorticoid replacement therapy may also require increase in doses of glucocorticoids during the treatment with somapacitan-beco. Therefore, risk of hypoadrenalism is included in Warnings and Precautions section of all rhGH labels.

The incidence of AI associated with somapacitan-beco was low. In the main phase of Study 4054, four subjects in somapacitan-beco group developed adrenal insufficiency compared to three subjects in the Norditropin group and one subject in the placebo group. Overall, there was no imbalance in observed number of cases, since 1/4 patient in somapacitan-beco group developed AI in washout period, thus, the event was unrelated to the study drug. All events were mild and resolved with appropriate treatment. No adrenal crisis was reported in any patient.

Neoplasms benign/malignant

IGF-1 is growth promoting factor, and thus, chronically elevated IGF-1 levels may play a role in tumorogenesis. There is no evidence regarding increased risk of neoplasms in patients with GHD treated with rhGH to date, however, based on the putative biological mechanism, all rhGH formulations are contraindicated in patients with active malignancies and risk of neoplasm is included in the Warnings and Precautions section of all rhGH labels.

The overall incidence of neoplasms associated with use of somapacitan-beco reported was low in clinical program and there was no imbalance in number of subjects with neoplasms reported in somapacitan-beco-treated subjects vs. Norditropin-treated subjects (2.1% vs. 2.4%, respectively).

No tumors in subjects treated with somapacitan-beco were reported in the main period of Study 4054. In the extension period of Study 4054, three subjects treated with somapacitan-beco were reported to have malignant tumors (basal cell carcinoma, bladder carcinoma and multiple myeloma). However, all these subjects were treated with Norditropin in the main phase of the trial, thus, the causality assessment between the events and somapacitan-beco is confounded by the previous exposure to Norditropin. In addition, absence of placebo comparator group in the extension study complicates the assessment further. A total of four subjects treated with somapacitan-beco (three subjects in the extension period of Study 4054 and one subject in Study 4244) had AEs of benign tumors (one lipoma and three pituitary tumors). Overall, pituitary tumors are most likely unrelated to the study drug; pituitary tumors are common in patients with GHD and one of the major causes of the disease. In addition, of three subjects with pituitary tumors, two were previously exposed to the other rhGH, thus causality assessment is complicated.

In conclusion, no increased risk of malignant or benign tumors with somapacitan-beco use was observed in the clinical program. The proposed labeling for somapacitan-beco appropriately contraindicate the drug in patients with active malignancies and includes this SAEs in Warnings and Precautions of the label. In addition, the risk of tumorogenesis is mitigated by the proper titration of the drug based on IGF-1 levels and avoiding chronically elevated IGF-1 levels above normal range.

Laboratory parameters

Parameters of glucose control (fasting blood glucose, HbA1C and insulin levels)
There is a known risk of hyperglycemia associated with use of rhGH due to direct insulin antagonistic effects of GH. The risk of hyperglycemia is included in all rhGH labels. Thus, the Clinical Reviewer paid special attention to the occurrence of out-of-range values and adverse events related to these biochemical changes.

The mean fasting glucose ranged from 88.2-93.6 mg/dL (4.9 - 5.2 mmol/L) across all treatment groups during the trial. Mean HbA1C ranged from 5.4 % to 5.5 %. The mean insulin levels were within reference range in all groups up to week 86. Nine subjects treated with somapacitan-beco and six subjects treated with Norditropin had at least one fasting glucose value > 126 mg/dL (7 mmol/L) and/or HbA1C > 6.5%. All subjects were asymptomatic and no SAEs were reported; the events resolved with or without appropriate treatment.

No subjects treated with somapacitan-beco in the main period of the Study 4054 had a new diagnosis of diabetes mellitus (DM). One subject treated with somapacitan-beco in the extension period of the study was diagnosed with DM (non-serious AE) and discontinued the study preliminary.

No clinically meaningful changes in glucose parameters were observed in trials 4043 and 4244.

**IGF-1**

There is a concern with all rhGH formulations that chronically elevated IGF-1 levels above the normal range may be associated with various AEs characteristic of acromegaly, including headache, intracranial hypertension, edema, tumors, etc. Thus, treatment with rhGH is individualized and dose titration is based on IGF-1 levels with goal to normalize IGF-1 levels but not to exceed +2 SDS - +3 SDS.

In Study 4054, 15 subjects had at least one IGF-1 value > +2SDS, but < +4SDS. All levels normalized without or with next dose adjustments. All subjects were asymptomatic. No adverse reactions were reported at time of the recorded IGF-1 elevation.

No subject treated with somapacitan-beco in study 4043 had elevated IGF-1 > +2SDS. Two subjects in study 4244 had elevated IGF-1 > +2SDS. They were asymptomatic, and IGF-1 levels decreased at the next visit.

**Elevated serum phosphate levels**

Mean serum phosphate level at the end of 34-week treatment increased in subjects treated with somapacitan-beco or Norditropin compared to baseline levels but remained within normal range (Figure 5). This is an expected action of growth hormone on renal tubular reabsorption of phosphate and risk of elevated serum inorganic phosphorus levels is included in Warnings and Precautions section of all rhGH labels.

In somapacitan-beco group more subjects had a shift in phosphate levels from normal at baseline to elevated above upper reference range at the end of the trial (17.5%; 21 subjects) at the end of 34-week treatment, compared to three subjects in the Norditropin group and three subjects in the placebo group. The number of subjects with at least one elevated phosphate value above upper reference range during main phase of Study 4054 was higher in somapacitan-beco group (35%), compared to Norditropin (27%), and placebo (8.2%), respectively. All elevations in phosphate levels were intermittent. Phosphate levels returned to the baseline levels in all subjects without treatment or dose adjustment. All subjects were asymptomatic, and calcium levels were normal. No phosphate-related AEs were reported in any of subjects.
A similar trend in phosphate levels was noted in studies 4043 and 4244.

**Elevated blood CPK levels**

More subjects with normal baseline CPK levels in the somapacitan-beco group (11 subjects, 9.2%) compared to Norditropin (six subjects; 5%) or placebo (four subjects; 6.6%) had elevated CPK levels at the end of 34-week treatment. However, no changes in mean CPK levels from baseline at the end of 34-week treatment were observed across all treatment groups.

AEs of CPK increased were reported only in the somapacitan-beco group (four subjects), all events were mild and of short duration, and resolved in all subjects without treatment. All subjects were asymptomatic (no myalgia, renal parameters changes, etc.).

The results from study 4043 were inconsistent with findings from the pivotal study and demonstrated opposite changes, i.e. more subjects in Norditropin group compared to somapacitan-beco group had shift in CPK values from normal at baseline to high at the end of the treatment (6.6% vs. 9.7%, respectively).

**Other laboratory parameters**

Analyses of other laboratory values do not identify any new safety signals.

**Vital signs**

There were no significant changes in vital signs between the treatment groups.

**Immunogenicity**

The immunogenicity data were reviewed by Dr. Arulvathani Arudchandran from the Division of Biotechnology Research and Review II, Office of Biotechnology Products (OBP) (refer to the review from 6/16/2020). The OBP reviewer concludes that the immunogenicity assay is properly validated and suitable for the evaluation of the presence of anti-drug antibodies. No anti-drug or anti-rhGH antibodies were detected during somapacitan-beco clinical development program.
Cross Discipline Team Leader Review
BLA 761156

Conclusion

The safety observations made during somapacitan-beco clinical program in subjects with AGHD are consistent with the known rhGH class specific side effects (e.g., AEs associated with fluid retention including weight gain, arthralgia, edema, AI, hyperglycemia, lipodystrophy, injection site reactions). Somapacitan-beco was not associated with increased tumorogenesis and no severe hypersensitivity reactions was reported in the trial. No new safety issues were identified in subjects with AGHD treated with somapacitan-beco. All safety issues will be mitigated through labeling. However, I recommend to include ARs in Section 6 of the label based on the results of FDA safety analysis using FMQ. Use of grouped terms captures synonymous adverse event terms and improves the overall safety information in the label. Based on the results of FDA’s analysis, I recommend including ARs that occurred in > 2% of patients with AGHD treated with somapacitan-beco and occurred with a relative risk > 1.3 and with at least 1% greater incidence in somapacitan-beco group compared to placebo group. Lastly, small and intermittent elevations in CPK and phosphate levels were observed more frequently in somapacitan-beco-treated subjects compared to Norditropin- or placebo--treated subjects during the trials. The abnormal laboratory parameters were observed in few subjects only and resolved without dose adjustment or treatment. All subjects were asymptomatic. No safety signals associated with these abnormalities were identified in non-clinical studies. Overall, I agree that changes in phosphate levels and CPK levels should be added to the label to make practitioners aware of the existence of these abnormal laboratory values and to help practitioners in making decisions regarding patient selection and use of concomitant medications.

9. Advisory Committee Meeting

No AC meeting was held, as this was not the first drug in class, the application did not raise significant public health questions on the role if the biologic, and there were no controversial issues that would benefit from advisory committee discussion.

10. 
11. Other Relevant Regulatory Issues

Division of Scientific Investigation
A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on 4/3/2020. Four clinical sites were investigated. Dr. Kleppinger concluded that the inspectional findings and the study data generated from four clinical sites were considered acceptable and may be used in support of this BLA. No sites were issued a Form FDA-483.

Financial Disclosure and compliance with Good Clinical Practice standards
Dr. Roman-Popoveniuc’s review indicates that the Applicant has submitted FDA Form 3455 and that all investigators were certified to have no conflict of interest that could influence the outcome of the trial(s). She also confirms that all studies were conducted in accordance with the principles of Good Clinical Practice governing clinical study conduct.

Proprietary name
The proposed proprietary name, SOGROYA, was found to be acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on 9/20/2019.

Nonproprietary name
The proposed nonproprietary name that includes four-letter suffix -beco, i.e. somapacitan-beco, was found to be acceptable by the Office of Medication Error Prevention and Risk Management on 7/2/2020.

Division of Pediatric and Maternal Health (DPMH) Consult
DGE had consulted DPMH to provide an input on the proper format and content of the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of Somapacitan-beco labeling to follow the Pregnancy and Lactation Labeling Rule (PLLR). DPMH
revised relevant sections of labeling for compliance with the PLLR and recommended to describe the lack of available human data with somapacitan and lack of adverse developmental effects in animals. The reviewers also recommend to include the clinical rhGH product class information in section 8.1 and 8.2. Lastly, DPMH also concluded that published data with short acting rhGH over several decades of use in pregnant and lactating women were useful in evaluating safety of somapacitan-beco in these specific populations. Therefore, DPMH agreed that postmarketing pregnancy safety and lactation studies are not required at this time for somapacitan-beco. Refer to the DPMH review from 4/17/2020 in DARRTS.

12. Labeling

Prescribing Information

Agreement on the final labeling language has not been reached at the time that this memorandum was completed. Refer to the complete labeling in the approval letter. The following sections should be addressed in the label:

- INDICATIONS AND USAGE:
  - The Applicant’s proposed indication, i.e. replacement of endogenous GH in AGHD, is appropriate.
  - The drug should not be used in patients with severe hepatic impairment. Patients with hepatic impairment have higher drug exposure and lower IGF-1 levels due to the impaired synthesis of IGF-1 by liver and higher doses may result in higher exposure compared to patients without impairment. Somapacitan-beco was not evaluated in patients with severe hepatic impairment; thus, safe and effective doses in this subgroup of patients remain unknown.

- DOSAGE AND ADMINISTRATION:
  - The starting doses should be 1.5 mg/week in patients < 60 years old, 1.0 mg in patients > 60 years old and 2 mg in females on oral estrogen. Maintenance dose should not exceed 8 mg/week. The efficacy and safety of these doses are provided from well-controlled trial in patients with AGHD.
  - Dose should be increased every 2–4 weeks by 0.5 to 1.5 mg based on clinical response and serum IGF-1 concentrations.
  - If the dose is missed, the missing dose should be administered as soon as possible and not more than 3 days after the missed dose (within 72 hours). If more than 3 days have passed, the dose should be skipped, and the next dose should be administered on the regular dosing day.
  - Starting dose in patients with moderate hepatic impairment should be 1 mg/week and maximum dose 4 mg/week based on the results of the exposure-response analysis.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - Consistent with class rhGH contraindications, somapacitan-beco is contraindicated in patients with acute critical illness, active malignancies and with hypersensitivity to the drug.
  - WARNINGS AND PRECAUTIONS section appropriately describes class specific adverse reactions associated with rhGH use including increased risk of mortality in patients with acute critical illness, increased risk of malignancy progression, impaired glucose tolerance, intracranial hypertension, hypersensitivity, fluid retention, hypoadrenalism and hypothyroidism, pancreatitis and lipoatrophy/lipohypertrophy.
Somapcitan-beco is not indicated for the treatment of pediatric patients.

**WARNING AND PRECAUTION** section also appropriately describes risk of laboratory abnormalities associated with all rhGH formulations including increase in alkaline phosphatase, and parathyroid hormone. Risk of elevated blood phosphorus should be added to this section. should be removed from this section.

### ADVERSE REACTIONS section:
- I recommend reporting ARs in this section based on the results of FDA analysis using FMQ, since the use of grouped terms (FMQ) captures synonymous adverse event terms and improves the overall safety information in the label. The ARs that occurred with rate for somapcitan-beco > 2%, relative risk (RR) > 1.3, and absolute incidence (%) difference > 1%, compared to placebo should be included in Table 1.

### CLINICAL STUDIES section:
- I recommend including the efficacy results from main period of Study 4054 only in this section. These results from this study provided substantial evidence of effectiveness of the drug for the proposed indication.
- I agree with clinical and statistical recommendations to include descriptively observed changes in TFP in Norditropin group of patients to make health care providers aware of the changes that are expected with the use of each drug. However, no superiority claim should be made due to the limitations of the analyses described above.

### 13. Postmarketing Recommendations

**Risk Evaluation and Management Strategies (REMS)**

A Risk Evaluation and Management Strategy (REMS) is not needed for somapcitan-beco for the proposed indication. All risks are appropriately labeled in the label to inform patients and prescribers and mitigate risks associated with use of this drug (refer to the Division of Risk Management review in DARRTS from 7/14/2020).

**Postmarketing Requirements (PMRs) and Commitments (PMCs)**

The following pediatric post marketing studies are required to be conducted/completed by the Applicant:
- Study NN8640-4172, a 1-year phase 2, randomized, open-label, active-control, dose finding trial, to investigate efficacy and safety of once-weekly somapcitan-beco versus daily Norditropin (somatropin) in pre-pubertal children with Growth Hormone Deficiency (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.
- Study NN8640-4263, a 1-year phase 3 randomized, parallel group, open-label trial, to evaluate the efficacy and safety of once weekly somapcitan-beco versus daily Norditropin (somatropin) 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.

In addition, a post-approval inspection is required for Novo Nordisk which is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part.

14. **Recommended Comments to the Applicant**

The above listed clinical PMRs and requirement for the post-approval inspection should be added to the Action Letter.
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/

MARINA ZEMSKOVA
08/06/2020 12:17:46 PM

THERESA E KEHOE
08/06/2020 12:24:30 PM
I concur with the scientific and regulatory conclusions outlined in this memo.

ILAN IRONY
08/06/2020 12:29:41 PM
I concur with the CDTL Memorandum.