NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy supplement
Application Number(s)	BLA 761156/S-012, S-014, and S-015
Priority or Standard	Standard
Submit Date(s)	May 06, 2025
Received Date(s)	May 06, 2025
PDUFA Goal Date	March 06, 2026
Division/Office	Division of General Endocrinology (DGE) / Office of New Drugs (OND)
Review Completion Date	See DARRTS stamped date
Established/Proper Name	Somapacitan-beco
(Proposed) Trade Name	Sogroya
Pharmacologic Class	Recombinant human growth hormone analog
Code Name	NNC0195-0092
Applicant	Novo Nordisk, Inc.
Dosage form	Liquid solution available in a single-patient-use prefilled pen in concentrations of 3.3 mg/mL, 6.7 mg/mL, or 10 mg/mL.
Applicant Proposed Dosing Regimen	Starting dose of 0.24 mg/kg per body weight per week; individualize dosage for each patient based on growth response.
Applicant Proposed Indication(s)/Population(s)	S-012: Treatment of pediatric patients with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age. S-014: Treatment of pediatric patients with growth failure associated with Noonan syndrome (NS). S-015: Treatment of pediatric patients with idiopathic short stature (ISS).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	S-012: Treatment of pediatric patients aged 2.5 years and older with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age. S-014: Treatment of pediatric patients aged 2.5 years and older with growth failure associated with Noonan syndrome (NS). S-015: Treatment of pediatric patients aged 2.5 years and older with idiopathic short stature (ISS).
Recommended Dosing Regimen	0.24 mg/kg/week somapacitan via subcutaneous injection.

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Reviewers of Multi-Disciplinary Review and Evaluation

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

BLA 761156/S-012, S-014, S-015
Sogroya (somapacitan-beco) injection
Multidisciplinary Review

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Satyajit Ghosh, PhD	OB/DB II	Sections:8.1.1.4, 8.1.1.7, 8.1.1.8	**Select one:** _X_ Authored ___ Approved
	Signature:	SATYAJIT GHOSH -S (Affiliate)	Digitally signed by SATYAJIT GHOSH -S (Affiliate) Date: 2026.02.19 11:31:40 -05'00'	
Statistical Team Leader	Feng Li, PhD	OB/DB II	Sections:8.1.1.4, 8.1.1.7, 8.1.1.8	**Select one:** ___ Authored _X_ Approved
	Signature:	Feng Li -S	Digitally signed by Feng Li -S Date: 2026.02.19 11:38:17 -05'00'	
Pharmacometrics Team Leader	Justin Earp, PhD	OCP/DPM	Sections: 6.2, 6.3, 15.3.1	**Select one:** _X_ Authored ___ Approved
	Signature:	JUSTIN C. EARP -S	Digitally signed by JUSTIN C. EARP -S Date: 2026.02.19 11:46:06 -05'00'	
Clinical Pharmacology Reviewer	Yaning Sun, PhD	OCP/DCEP	Sections: 6, 8.3.4.9, 15.3.2	**Select one:** _X_ Authored ___ Approved
	Signature:	Yaning Sun -S	Digitally signed by Yaning Sun -S Date: 2026.02.19 12:11:41 -05'00'	
Clinical Pharmacology Team Leader	Li Li, PhD	OCP/DCEP	Section: 6, 8.3.4.9, 15.3.2	**Select one:** ___ Authored _X_ Approved
	Signature:	Li Li -S	Digitally signed by Li Li -S Date: 2026.02.19 12:26:12 -05'00'	
Clinical Reviewer	Nicholas Heiniger, MD	OCHEN/DGE	Sections: 1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 15	**Select one:** _X_ Authored ___ Approved
	Signature: (See appended electronic signature page)			

BLA 761156/S-012, S-014, S-015
Sogroya (somapacitan-beco) injection
Multidisciplinary Review

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Nicholas Heiniger, MD	OCHEN/DGE	Section: 1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 15	**Select one:** ___ Authored _X_ Approved
	Signature: (See appended electronic signature page)			
Associate Director for Labeling	LaiMing Lee, PhD	OCHEN/DGE	Section: 11	**Select one:** _X_ Authored ___ Approved
	Signature: Lai M. Lee -S Digitally signed by Lai M. Lee -S Date: 2026.02.19 12:30:20 -05'00'			
Deputy Division Director (Clinical)	Marina Zemskova, MD	OCHEN/DGE	Section: All	**Select one:** ___ Authored _X_ Approved
	Signature: (See appended electronic signature page)			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AGHD	adult growth hormone deficiency
AHV	annualized height velocity
ALP	alkaline phosphatase
AO	adult onset
aPTT	activated partial thromboplastin time
AR	adverse reaction
BA	bone age
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CO	childhood onset
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GH	growth hormone
GHD	growth hormone deficiency

GHR	growth hormone receptor
GRMP	good review management practice
HbA1c	Hemoglobin A1c
hGH	human growth hormone
ICH	International Conference on Harmonisation
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IH	Intracranial hypertension
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	idiopathic short stature
ITT	intent to treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MAED	Medical Dictionary for Regulatory Activities-Based Adverse Events Diagnostics
mITT	modified intent to treat
mPEG	methyl polyethylene glycol
NAbs	Neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NS	Noonan syndrome
OCMQ	Office of New Drugs Custom Medical Queries
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamic
PEG	polyethylene glycol
PGHD	pediatric growth hormone deficiency
PI	prescribing information
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RD	risk difference
REMS	risk evaluation and mitigation strategy

rhGH	recombinant human growth hormone
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SC	subcutaneous
SCFE	slipped capital femoral epiphysis
SGA	Small for gestational age
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TS	Turner syndrome
ULN	upper limit of normal

1 Executive Summary

1.1. Product Introduction

The Applicant (Novo Nordisk, Inc.) submitted three Prior Approval Supplement Biological License Applications (sBLA; BLA 761156, S-012, S-014, and S-015) on May 06, 2025, for somapacitan-beco, and hereafter also referred to as somapacitan) injection under Section 351 of the Public Service Health (PHS) Act, for the following indications:

- S-012: Treatment of pediatric patients with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age.
- S-014: Treatment of pediatric patients with growth failure associated with Noonan syndrome (NS).
- S-015: Treatment of pediatric patients with idiopathic short stature (ISS).

Sogroya (somapacitan; BLA 761156) was approved on August 28, 2020, for the replacement of endogenous growth hormone (GH) in adult growth hormone deficiency (GHD). On April 28, 2023, Sogroya (BLA 761156/S-005) was approved for the additional indication of treatment of pediatric patients aged 2.5 years and older with growth failure due to inadequate secretion of endogenous GH.

Somapacitan is a long-acting recombinant human growth hormone (rhGH; somatropin) derivative, with a single amino acid substitution in the peptide backbone (leucine [L] at position 101 is substituted with cysteine [C]) to which a non-covalent albumin moiety has been attached. The albumin binding moiety (side chain) consists of a C16 fatty acid moiety and a hydrophilic spacer. After injection, endogenous albumin binds non-covalently to the albumin binding moiety. The reversible binding of albumin to this side chain increases the *in vivo* half-life of the molecule by decreasing renal clearance and metabolic degradation. Somatropin is a protein manufacture to be nearly identical to naturally occurring, endogenous human growth hormone somatotropin.

Somapacitan is a drug-device combination product. The drug product is supplied as a sterile solution for subcutaneous (SC) use as a 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL ready-to-use, single-patient-use prefilled pen for once weekly administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The current submissions provide substantial evidence of effectiveness of somapacitan for the treatment of pediatric patients aged 2.5 years and older with:

- Short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age (S-012)
- Growth failure associated with Noonan syndrome (NS) (S-014)
- Idiopathic short stature (ISS) (S-015)

Each of the proposed indications are for the treatment of growth failure associated with a non-GHD syndrome. For each of the proposed indications, substantial evidence of effectiveness was provided by the 3 adequate and well-controlled clinical sub-trials within the pivotal phase 3 basket trial NN8640-4467 conducted in the SGA, NS, and ISS populations. Each sub-trial was randomized, used the same primary endpoint (annualized height velocity at Week 52), and included independent primary efficacy analyses conducted for each population.

The sub-trials provide evidence that is more generalizable as they were conducted in distinct but related patient populations within the same proposed indication category (non-GHD syndrome associated with short stature). While each condition results in short stature as a result of different etiologies, there is a mechanistic understanding of how hGH exerts its effect in children with short stature born SGA, associated with NS, or with ISS. Exogenous hGH therapy improve growth by acting along a similar mechanism of action in all three conditions. The wide variety of GH biological effects are mediated through a single mechanism of action: GH binding to and activating GH receptors with subsequent transcription of genes encoding various proteins, including insulin-like growth factor 1 (IGF-1), which stimulates proliferation of chondrocytes and results in bone growth. No alternative receptors mediating GH activity have been identified. The active moiety of somapacitan has the same primary amino acid sequence as endogenous growth hormone and is expected to have the same action at the target receptor.

Primary efficacy results demonstrated non-inferiority of somapacitan to Norditropin on improvement in AHV in all three populations:

- SGA population: Somapacitan (11.0 cm/year) was non-inferior to both 0.035 mg/kg/day Norditropin (9.4 cm/year) and 0.067 mg/kg/day Norditropin (11.1 cm/year), with treatment differences of 1.6 cm/year (95% CI: 0.91, 2.23) and -0.1 cm/year (95% CI: -0.75, 0.60), respectively.
- NS population: Somapacitan (10.4 cm/year) was non-inferior to 0.05 mg/kg/day Norditropin (9.2 cm/year), with a treatment difference of 1.2 cm/year (95% CI: 0.32, 2.03).
- ISS population: Somapacitan (10.2 cm/year) was non-inferior to 0.05 mg/kg/day Norditropin (10.5 cm/year), with a treatment difference of -0.3 cm/year (95% CI: -1.00, 0.42).

All lower limits of the 95% confidence intervals were above the prespecified non-inferiority margin of -1.6 cm/year.

Supportive evidence from the phase 2 dose-finding trial NN8640-4245 in the SGA population and the phase 3 trial NN8640-4469 in adolescents born SGA, or with NS or ISS, further strengthen the conclusion that substantial evidence of effectiveness had been provided.

The clinical team recommends approval of somapacitan for pediatric patients aged 2.5 years and older for all three proposed indications, as no subjects younger than 2.5 years were included in the clinical program and the safety and pharmacokinetic/pharmacodynamic profile in this younger population remains unknown. In addition, ISS and short stature associated with being born SGA is not typically diagnosed in subjects much younger than 2.5 years of age. For children with NS, treatment of short stature with GH therapy during early childhood, including < 2.5 years of age, is controversial, in part due to safety concerns such as cardiac comorbidity and an increased risk of certain malignancies.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant proposes somapacitan, a long-acting recombinant human growth hormone (hGH) that reversibly binds to endogenous albumin via a non-covalent albumin-binding moiety for the treatment of pediatric patients with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age; pediatric patients with growth failure associated with Noonan syndrome (NS); and pediatric patients with idiopathic short stature (ISS). The proposed dose is 0.24 mg/kg/week, as a weekly subcutaneous (SC) injection.

Somapacitan is currently approved for the replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) and for the treatment of pediatric patients aged 2.5 years and older who have growth failure due to inadequate secretion of endogenous growth hormone (GH). The drug is currently supplied as a drug-device combination product. The drug product is supplied as a sterile solution for subcutaneous use as a 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL ready-to-use, single-patient-use PDS290 prefilled pen for once weekly administration.

There are multiple non-GHD conditions that are associated with the proportional short stature in pediatric patients, including SGA, ISS and NS.

SGA is defined as a weight and/or length < -2 SDS at birth. These infants are at an increased risk for perinatal morbidity, neurodevelopmental disorders, persistent short stature, and metabolic alterations later in life. Children born SGA are shorter during childhood and, as adults, can reach heights that are on average lower than the mean. Children born SGA should have diagnostic work up if they have not had sufficient catch-up growth in the first 6 months or those who remain short at 2 years of age, as these children may continue to have growth failure and should be evaluated for other conditions that may limit growth.

NS is a clinically and genetically heterogeneous autosomal dominant condition with characteristic findings including short stature, distinctive facial features, chest deformity, scoliosis, congenital heart disease, and electrocardiogram abnormalities. Approximately 50% to 70% of individuals with NS have short stature; birth weight and length are typically normal, but there is subsequent growth failure and deceleration of height and weight to ≤ 3rd percentile. Mean height then follows the 3rd percentile until puberty, when below average annualized height velocity (AHV) and attenuated adolescent growth spurt tend to occur.

ISS is defined by a height SDS < -2 or < -2.25 in patients for whom a complete diagnostic evaluation has excluded other causes of short stature, ruling out evidence of systemic, endocrine, nutritional, or chromosomal abnormalities.

Multiple hGH products are approved by FDA ("Agency") to treat short stature in children born SGA without catch-up growth, growth failure associated with NS, and ISS. Most are administered via daily or every other day SC injection. These have been approved based on the improvement in AHV and/or height SDS. Clinical data from trials of short acting hGH formulations demonstrated that hGH-induced changes in short-term AHV ultimately translate into increased final adult height. The hGH-induced increase in growth in these populations is clearly understood. GH-induced increases in growth via GH binding to and activating GH receptors with subsequent transcription of genes encoding a variety of proteins, including insulin-like growth factor 1 [IGF-1], which stimulates the proliferation of chondrocytes and results in bone growth). Clinical data from earlier trials of short acting hGH formulations (e.g., data from Humatrope [BLA 019640] or Nutropin AQ [BLA 020522] treatment in subjects with ISS, and Norditropin [BLA 021148] treatment in subjects born SGA or NS) where some subjects had been treated to final adult height and demonstrated that improvement in short-term growth was associated with improvement in final adult height. Therefore, FDA accepted short term changes in AHV that are non-inferior to an active comparator (approved hGH with known effect on AHV) as a surrogate endpoint to evaluate the benefit of products with a native GH sequence for the treatment of pediatric patients with short stature associated with non-GHD conditions including born SGA and with no catch-up growth by 2 years of age; NS; and ISS. In this context, requirement of longer trials would be an unnecessary burden.

The clinical development program of somapacitan for children born SGA, NS, and ISS consisted of one phase 3 basket trial individually evaluating children 2.5 to 11 years of age of each of the proposed populations (trial NN8640-4467; hereafter also referred to as trial 4467), one phase 2 trial in children aged 2.5 to 11 years of age born SGA (trial NN8640-4245; hereafter also referred to as trial 4245), and one phase 3 basket trial in children 10 to 18 years of age of each of the proposed populations (trial NN8640-4469; hereafter also referred to as trial 4469). The 52-week Main Period of the phase 3 trial 4467 was the primary source of efficacy and safety of somapacitan in each of the proposed populations.

Trial 4467 was a randomized, open-labeled, active controlled (Norditropin; somatropin) phase 3 basket trial to compare the efficacy and safety of once-weekly somapacitan to daily somatropin after 52 weeks in GH-treatment naïve pre-pubertal children with short stature associated with being born SGA, with NS, or ISS. Based on the results of the trial, somapacitan was non-inferior to Norditropin in the improvement of AHV in all populations.

Benefits

In the SGA cohort (142 subjects), somapacitan was found to be non-inferior to the effect of 0.035 and 0.067 mg/kg/day Norditropin:

- The estimated treatment difference in mean AHV at 52 weeks between somapacitan (11 cm/year) and 0.035 (9.4 cm/year) and 0.067 mg/kg/day (11.1 cm/year) Norditropin was 1.6 cm/year (95% CI 0.91, 2.23; p-value < 0.001) and -0.1 cm/year (95% CI -0.75, 0.6; p-value = 0.823), respectively, and the lower limits of the 95% CI (0.91 and -0.75, respectively), were above the prespecified non-inferiority margin of -1.6 cm/year.
- The lower limit of the 95% CI (0.91) for the estimated treatment was > 0 in mean AHV at 52 weeks between somapacitan and 0.035 mg/kg/day Norditropin.

In the NS cohort, somapacitan was found to be non-inferior to the effect of 0.05 mg/kg/day Norditropin:

- The estimated treatment difference in mean AHV at 52 weeks between somapacitan (10.4 cm/year) and 0.05 mg/kg/day Norditropin (9.2 cm/year) was 1.2 cm/year (95% CI 0.32, 2.03; p-value = 0.0071), and the lower limit of the 95% CI (0.32), was above the prespecified non-inferiority margin of -1.6 cm/year.
- The lower limit of the 95% CI (0.32) for the estimated treatment was > 0 in mean AHV at 52 weeks between somapacitan and 0.05 mg/kg/day Norditropin.

In the ISS cohort, somapacitan was found to be non-inferior to the effect of 0.05 mg/kg/day Norditropin:

- The estimated treatment difference in mean AHV at 52 weeks between somapacitan (10.2 cm/year) and 0.05 mg/kg/day Norditropin (10.5 cm/year) was -0.3 cm/year (95% CI -1, 0.42; p-value=0.4107), and the lower limit of the 95% CI (-1), was above the prespecified non-inferiority margin of -1.6 cm/year.

In addition, a test for superiority was prespecified and controlled for type 1 error using a hierarchical testing approach. Somapacitan was found to be superior in the SGA population to the effect of 0.035 mg/kg/day Norditropin and in the NS cohort to the effect of 0.05 mg/kg/day Norditropin in the improvement of AHV at 52 weeks.

The results of secondary analyses, including height SDS, support the primary efficacy endpoint. Short stature in pediatric patients is defined as height below -2.0 SDS for age, sex, and race. Height SDS is widely used in clinical practice to evaluate the appropriate growth of children at various stages of development. Thus, change in height SDS is traditionally accepted and used as a supportive growth endpoint in trials evaluating the effect of hGH on growth in pediatric patients with short stature associated with these conditions. Both somapacitan and Norditropin therapy resulted in an improved height SDS at Week 52 compared to baseline:

1) SGA population: the change in mean height SDS from baseline was 1.17 in the somapacitan group and 0.85 and 1.22 in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively.
2) NS population: the change in mean height SDS from baseline was 1.07 in the somapacitan group and 0.75 in the 0.05 mg/kg/day Norditropin group.
3) ISS population: the change in mean height SDS from baseline was 0.99 in the somapacitan group and 1.09 in the 0.05 mg/kg/day Norditropin group.

The overall data in this trial establish the benefit of somapacitan therapy in the treatment of short stature in pediatric patients associated with being born SGA, with NS, or ISS. However, it should be noted that the Applicant did not use the maximum approved doses of the comparator for ISS and NS in the trial, therefore non-inferiority was not established at maximum doses of Norditropin. Further, the relevance of the superiority of somapacitan-induced 52-week AHV to less than maximal dosing of Norditropin (i.e., 0.035 and 0.05 mg/kg/day Norditropin for children born SGA or with NS, respectively), is not clear. Therefore, Section 14 should indicate that the comparison was made to sub-maximum dosing of Norditropin for prescribers' awareness when selecting the GH for the treatment. In addition, (b) (4). The superiority findings are based on a single sub-trial comparing the effect of two drugs on a surrogate endpoint, AHV, and the observed difference of 1.2 cm/year in the NS population and 1.6 cm/year in the SGA population in AHV at 52-weeks, at less than maximum dosing of the comparator, is small and of unclear clinical significance. It remains unknown whether this difference will ultimately translate to a difference in final adult height. Lastly, statistical significance was not consistent between all subgroups, e.g., compared to the SGA population treated with the maximum dosing of Norditropin, and in subjects with ISS, somapacitan was not superior to Norditropin.

The open label extension period of the pivotal phase 3 trial 4467, the phase 2 trial 4245 in subjects born SGA, and the phase 3 trial 4469 in children older than 10 years of age provided additional evidence of effectiveness. The results demonstrated long-term improvement in growth parameters in children 2.5 years of age and older with short stature born SGA and no catch-up growth by 2 years of age, with growth failure associated with NS, or with ISS, and open epiphyses.

Risks

The risks associated with somapacitan are expected to be consistent with the risks expected for the hGH and analog class of drugs, including the risks already observed with somapacitan use in the adults with GHD and children with short stature due to GHD. The current label already includes the following: the risk of hyperglycemia, development of new tumors, intracranial hypertension, slipped capital femoral epiphysis (SCFE), pancreatitis, adrenal insufficiency, hypothyroidism, progression of preexisting scoliosis, severe hypersensitivity, injection site reactions (including lipoatrophy/lipohypertrophy), edema, and elevations in alkaline phosphatase and phosphate.

The most commonly reported AEs by subjects in the Main Period of the pivotal phase 3 trial 4467 across the SGA, NS, and ISS populations (≥ 10% of subjects and more frequently in the somapacitan group compared to either Norditropin group (RD ≥ 1%) included cough, respiratory tract infection, diarrhea, pyrexia, nasopharyngitis, headache, ear infection, vomiting, and injection site reactions. The pattern of the most commonly reported AEs did not raise concerns for new safety signals, and these AEs are not uncommon in general pediatric population.

Small and intermittent increases in glucose levels were observed in subjects treated with somapacitan and Norditropin. During the main period of the phase 3 trial 4467, AEs of hyperglycemia were reported in only a few subjects treated with somapacitan in each population (0%, 4.1%, and 0%, in the SGA, NS, and ISS populations, respectively). The other class AEs were also reported infrequently in the SGA, NS, and ISS populations exposed to somapacitan in the main period of trial 4467: hypothyroidism (1.4%, 2%, and 1.7%, respectively), injection site reactions (5.8%, 8.2%, and 10.2%, respectively), edema (0, 2%, and 0%, respectively), hyperphosphatemia (1.4%, 4.1%, and 0%, respectively). The proportion of subjects with AEs related to injection site reactions and lipoatrophy demonstrated no imbalance in the rate of these reactions across the treatment groups or subject populations, and the majority were not severe, non-serious, and did not require any changes or interruption in somapacitan therapy. No other class AEs associated with hGH or analog therapy (i.e., AEs related to scoliosis, SCFE, pancreatitis, intracranial hypertension, or adrenal insufficiency) were reported in subjects treated with somapacitan in the Main Period of trial 4467. There was a low incidence of neoplasm reported with somapacitan therapy in the clinical development program, with no imbalance seen between treatment groups or populations. Mean alkaline phosphatase and phosphate values increased in subjects of all populations, but was comparable between treatment groups (i.e., Norditropin or somapacitan) within populations (i.e., SGA, NS, or ISS). Only few subjects had AEs related to increased alkaline phosphatase or phosphate values and all were asymptomatic, and did not require dose adjustment.

The GH Research Society recommend that "during treatment of non-GHD states, in order to achieve an acceptable growth response [with hGH therapy] IGF-1 may transiently be above the normal range [i.e., IGF-1 > 2 SDS]; however, the safety implications are unknown."[1] Therefore, in pediatric patients treated with hGH for ISS or short stature associated with NS or SGA at birth, goal IGF-1 levels are typically below 2 or 3 SDS. During 52 weeks of treatment with somapacitan and Norditropin, mean IGF-1 levels remained within these ranges. The mean 52-week IGF-1 SDS for children 1) born SGA was 1.9, 1.1, and 2 in the somapacitan and 0.035 and 0.067 mg/kg/day Norditropin groups, respectively; 2) with NS was 1 and 0.2 in the somapacitan and 0.05 mg/kg/day Norditropin groups respectively; and 3) with ISS was 1.6 and 1.3 in the somapacitan and 0.05 mg/kg/day Norditropin groups respectively. In the SGA and ISS populations of the phase 3 trial

[1] Johannsson G, et al. Growth Hormone Research Society. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. *Endocr Connect*. 2018 Mar;7(3):R126-R134.

4467, the number of subjects treated with somapacitan who had IGF-1 > 2 or 3 SDS on at least two consecutive visits was small and either comparable to, or lower than, the proportion of subjects treated with Norditropin who had IGF-1 > 2 or 3 SDS on at least two consecutive visits. Only one subject, in the ISS population, treated with somapacitan had the dose of somapacitan reduced in response to elevated IGF-1 >3 SDS during the Main Period of trial 4467, and the most recently documented IGF-1 for this subject remained elevated 6 weeks after this reduction in dose. A higher percentage of subjects with NS treated with somapacitan (10.2%), compared to subjects treated with Norditropin (0), had IGF-1 > 2 SDS on at least two consecutive visits; no subject with NS had IGF-1 > 3 SDS on at least two consecutive visits. Subjects with prespecified elevated IGF-1 SDS were asymptomatic, and no IGF-1 related AEs were reported in any of the subjects with elevated IGF-1 levels. IGF-1 related AEs can be monitored if concerns of IGF-1 related adverse reactions in response to treatment are noted in clinical practice.

As with all therapeutic proteins, there is potential for immunogenicity that could decrease efficacy of the drug and/or induce various hypersensitivity reactions. The submitted immunogenicity data do not raise particular concerns. There was an increased proportion of subjects in the SGA and ISS populations (14.5% and 11.9%) treated with somapacitan who generated anti-drug antibodies (ADAs), compared to 0 and 3.6% of subjects treated with Norditropin in the SGA and ISS populations, respectively, who generated anti-hGH antibodies in the Main Period of the pivotal phase 3 trial, but was within the range of observed ADA with use of somapacitan in pediatric patients with GHD (approved indication; 12.1%). In the NS population, only a few subjects treated with somapacitan generated ADAs, and at a comparable rate to subjects treated with Norditropin who generated anti-hGH antibodies (4.1% vs. 3.6%, respectively). In all subjects who generated ADA following initiation of somapacitan therapy in the pivotal phase 3 trial, there were no neutralizing antibodies, the titers were overall low, and the presence of ADAs did not appear to have a significant impact on safety or efficacy of somapacitan. There were no somapacitan-related anaphylactic or hypersensitivity reactions.

Overall, the safety profile of somapacitan seen in the clinical trials in children in the SGA, ISS, and NS populations are consistent with the known safety profile of approved hGH products and analogs. There were no unexpected safety signals; reporting of adverse events in the current clinical programs was consistent with the reported findings in the approved somapacitan label.

Lastly, the Applicant proposes to indicate this drug for all pediatric patients with open epiphyses in the proposed populations. However, the development program provided no safety data on the use of somapacitan for subjects younger than 2.5 years of age for any of these populations. The PK and PD profile of this long-acting drug is different from other approved rhGH formulations and the PK/PD

profile, and the safety of this drug, in this younger population is unknown at this time. Further, for children born SGA, initiation of GH therapy is not recommended before 2 years of age as many of these children have appropriate catch-up growth by this time, and to allow for evaluation of underlying growth-limiting conditions if they do not have appropriate growth by this time. For children with ISS, this is a

diagnosis of exclusion and an appropriate duration of time to evaluate for growth failure and evaluation of underlying growth-limiting conditions must also be conducted. For children with NS, treatment of short stature with GH therapy during early childhood, including < 2.5 years of age, is controversial, in part due to safety concerns such as cardiac comorbidity and increased risk of certain malignancies. Because of these concerns, somapacitan should not be indicated for patients born SGA, or with NS or ISS, who are < 2.5 years of age.

Summary

In conclusion, the Applicant has provided substantial evidence of efficacy that somapacitan is an effective treatment of pediatric patients with short stature born small for SGA and with no catch-up growth by 2 years of age; pediatric patients with growth failure associated with NS; and pediatric patients with ISS at the proposed dose and the benefits outweigh the risks in children over 2.5 years of age. Risks can be monitored and mitigated through patient labeling.

I recommend the approval of somapacitan for the treatment of pediatric patients 2.5 years of age and older with short stature born small for SGA and with no catch-up growth by 2 years of age; pediatric patients with growth failure associated with NS; and pediatric patients with ISS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Short stature in pediatric patients may be associated with various non-GHD syndromes including NS and ISS, and in those born SGA. • SGA is defined as a weight and/or length < -2 SDS. These infants are also at an increased risk for perinatal morbidity, neurodevelopmental disorders, persistent short stature, and metabolic alterations later in life. Children born SGA typically have diagnostic work up if they have not had sufficient catch-up growth in the first 6 months or those who remain short at 2 years of age. • NS is a clinically and genetically heterogeneous autosomal dominant condition with characteristic findings including short stature, distinctive	• Short stature in children born SGA without catch up growth by 2 years of age, growth failure in children associated with NS, and children with ISS are all associated with poor growth velocity and ultimately decreased final adult height.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	facial features, chest deformity, scoliosis, congenital heart disease, and electrocardiogram abnormalities. • ISS is defined by a height SDS < -2 or < -2.25 in patients for whom a complete diagnostic evaluation has excluded other causes of short stature, ruling out evidence of systemic, endocrine, nutritional, or chromosomal abnormalities.	
Current Treatment Options	• There are multiple approved daily or every other day human growth hormone (hGH) product formulations available for the treatment of short stature associated with being born SGA, with NS, or ISS in children. • Treatment with hGH results in increases in growth via GH binding to and activating GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, which stimulates the proliferation of chondrocytes and results in bone growth and ultimately final adult height. • hGH formulations with a native GH sequence have generally been approved by FDA for these indications based on improvements in height velocity and clinical data from earlier trials of short acting hGH products where some subjects had been treated to final adult height and demonstrated that improvement in short-term growth was associated with improvement in final adult height.	• Currently, there are multiple hGH products available for the treatment of short stature associated with being born SGA, with NS, or ISS in children, most of which require daily or every other day administration via subcutaneous injection. • Treatment with exogenous hGH aims to act on GH receptors to increase IGF-1 levels that act on growth plates to increase growth. • In these populations, there is evidence that hGH-induced improvements in AHV sustained over years of treatment leads to improvement in final adult height. • A long-acting formulation of hGH has the potential to be less burdensome by requiring less frequent injections in these pediatric populations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant demonstrated that somapacitan increases AHV at the end of 52 weeks of treatment in patients born SGA, with ISS, or with NS in the adequate and well controlled phase 3 trial 4467. The evidence of efficacy for each population was provided from the individual sub-trials conducted in each population included in the phase 3 trial. Each sub-trial was adequate and well controlled, randomized, used the same primary endpoint, i.e., AHV at week 52, used individual Norditropin control group(s) and independent primary and secondary analyses. Somapacitan-induced improvement in AHV was non-inferior to Norditropin-induced improvement in AHV (with a predefined non-inferiority margin of -1.6 cm/year). • In the SGA cohort: – The estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.035 and 0.067 mg/kg/day Norditropin was 1.6 cm/year (95% CI 0.91, 2.23; p-value < 0.001) and -0.1 cm/year (95% CI -0.75, 0.6; p-value = 0.823), respectively. • In the NS cohort: – The estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.05 mg/kg/day Norditropin was 1.2 cm/year (95% CI 0.32, 2.03; p-value = 0.0071). • In the ISS cohort: – The estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.05 mg/kg/day Norditropin was -0.3 cm/year (95% CI -1, 0.42; p-value = 0.4107).	• FDA accepts one-year AHV that is non-inferior to the active comparator (an approved hGH product with a known effect on AHV) to support benefit of products with a native GH sequence for the treatment of short stature associated with being born SGA, with NS, or ISS in pediatric patients. • The evidence of efficacy in each of the intended populations was established in each of the sub-trials included in the basket phase 3 trial 4467. Each sub-trial was adequate and well controlled, randomized, used the same primary and secondary endpoints, but was conducted in the different proposed populations, i.e., SGA, NS, or ISS. • Treatment with somapacitan increases AHV at Week 52 in the intended populations. The improvement in AHV was within prespecified non-inferiority margins compared to Norditropin in each population. The observed improvement in somapacitan-induced AHV at 52 weeks was also consistent with 52-week AHV seen with other hGH products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The results of secondary analyses were supportive of the primary analyses for all three populations: – At Week 52, for children 1) born SGA, the change in mean height SDS from baseline was 1.17 in the somapacitan group and 0.85 and 1.22 in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively; 2) with NS, the change in mean height SDS from baseline was 1.07 in the somapacitan group and 0.75 in the 0.05 mg/kg/day Norditropin group; and 3) with ISS, the change in mean height SDS from baseline was 0.99 in the somapacitan group and 1.09 in the 0.05 mg/kg/day Norditropin group.	• The improvement in other growth parameters, i.e., height SDS, after 52 weeks of therapy are supportive of the primary analysis and are consistent with that found with other hGH products in pediatric patients born SGA, or with NS or ISS. • However, subjects in the SGA cohort treated with 0.035 mg/kg/day Norditropin, and subjects in the NS and ISS cohorts treated with Norditropin were treated with sub-maximum approved doses of Norditropin for these indications, and the efficacy of somapacitan compared to efficacy of Norditropin at maximum approved dose remains unknown. Therefore, the label should include the statement that Norditropin used not at maximum approved dose for the prescribers to decide regarding the selection of hGH products.
Risk and Risk Management	• The safety profile of somapacitan was well characterized in the clinical development program. • No unexpected safety signals for somapacitan were identified in children with ISS or with short stature associated with being born SGA or with NS. • The most commonly reported AEs by subjects in the Main Period of the pivotal phase 3 trial 4467 across the SGA, NS, and ISS populations (≥ 10% of subjects in any treatment arm) included cough, respiratory tract	• Adverse events observed with somapacitan use in children with short stature associated with being born SGA, with NS, or ISS were consistent with those known to the drug class. Such AEs as hyperglycemia, hypothyroidism, injection site reactions (including lipoatrophy /lipohypertrophy),

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infection, diarrhea, pyrexia, vomiting, nasopharyngitis, ear infection, bronchitis, headache, injection site reaction, abdominal pain, and wound. • SAEs of adenoid/tonsillar hypertrophy requiring surgical correction were observed in 2subjects in the Main Period of the phase 3 trial 4467 (1 subject each in the SGA and ISS cohorts). Although there was no imbalance in the rate of these events, there were other confounding factors (presence of tonsillar/adenoid hypertrophy prior to the onset of treatment) and they are not uncommon in general pediatric population, there is a known tissue grow stimulating risk associated with IGF-1 (mediator of GH action and these events are labeled event with use of hIGF-1 (Increlex)). Therefore, the risk of adenoid/tonsillar hypertrophy in pediatric subjects using somapacitan cannot be ruled out completely. • AEs that are potentially associated with the known adverse reactions of hGH products and analogs were seen with low frequency in subjects with SGA, NS, and ISS treated with somapacitan in the Main Period of the phase 3 trial 4467: hyperglycemia (0%, 4.1%, and 0%, respectively), headache (5.8%, 10.2%, and 10.2%, respectively), hypothyroidism (1.4%, 2%, and 1.7%, respectively), injection site reactions (5.8%, 8.2%, and 10.2%, respectively), edema (0, 2%, and 0%, respectively), and hyperphosphatemia (1.4%, 4.1%, and 0%, respectively). No other AEs associated with hGH or analog therapy (i.e., progression of preexisting scoliosis, severe hypersensitivity, intracranial hypertension, SCFE, pancreatitis, and adrenal insufficiency) were reported in subjects treated with somapacitan in the Main Period of trial 4467. • No increased risk of tumorigenesis with somapacitan use was observed in the clinical program. However, two subjects reported melanocytic nevi.	edema, and elevations in alkaline phosphatase and phosphate were reported at low frequency in all subjects treated with somapacitan. The other class-specific AEs (i.e., progression of preexisting scoliosis, severe hypersensitivity, intracranial hypertension, SCFE, pancreatitis, and adrenal insufficiency) were not reported in these populations. AEs of adenoidal/tonsillar hypertrophy were observed in clinical program with use of somapacitan or Norditropin. The risks are monitorable, included already in the somapacitan label, and can be adequately identified and managed by healthcare providers. Lastly, due to the uncertainties regarding the risk of adenoid/tonsillar hypertrophy, this potential risk will be included in Section 6 of the label. • Increase in IGF-1 levels above the normal range is a monitorable risk. The risk is mitigated by monitoring IGF-1 levels if there are concerns of adverse reactions and by dose adjustment. • No risks were identified that require risk management beyond labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Chronically elevated IGF-1 above 2 or 3 SDS may be associated with a potential risk for various AEs, including headache, intracranial hypertension, edema, and tumors. • The mean 52-week IGF-1 SDS was comparable and within acceptable ranges with treatment across all populations. For children 1) born SGA was 1.9, 1.1, and 2 in the somapacitan and 0.035 and 0.067 mg/kg/day Norditropin groups, respectively; 2) with NS was 1 and 0.2 in the somapacitan and 0.05 mg/kg/day Norditropin groups respectively; and 3) with ISS was 1.6 and 1.3 in the somapacitan and 0.05 mg/kg/day Norditropin groups respectively. • In the main period of the pivotal phase 3 trial, 10.2% of subjects with NS treated with somapacitan had IGF-1 > 2 SDS but ≤ 3 SDS on at least two consecutive visits. • In the SGA and ISS populations, the proportion of subjects treated with somapacitan, compared to those treated with Norditropin, who had IGF-1 > 2 or 3 SDS on at least two consecutive visits was either comparable, or lower. – All but one subject in ISS population did not require dose adjustments and IGF-1 levels normalized on the majority of subjects. – There were no consistent patterns of AEs in subjects with prespecified elevated IGF-1 values during the clinical development program. • Immunogenicity data do not raise particular concerns. • The proportion of subjects in the SGA and ISS populations with positive ADA (14.5% and 11.9%, respectively) treated with somapacitan were higher compared to Norditropin groups with positive ADAs (0 and 3.6%, respectively).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The proportion of subjects with NS treated with somapacitan who generated ADAs was comparable to subjects treated with Norditropin who generated ADA (4.1% vs. 3.6%, respectively). • The proportion of subjects with ADA was also comparable to the rate of ADA observed in pediatric patients with GHD treated with somapacitan and within the rate observed with treatment with other hGHs. • No neutralizing antibodies were reported. • ADAs did not impact safety or efficacy of somapacitan.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Sections 8.1.1.19, 8.1.2.22, and 8.1.3.18
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Conditions

2.1.1. SGA With No Catch-Up Growth by 2 Years of Age

Professional society guidelines recommend that SGA be defined as a weight and/or length < -2 SDS at birth and note that these infants are at an increased risk for perinatal morbidity, neurodevelopmental disorders, persistent short stature, and metabolic alterations later in life.[2, 3, 4] Individuals born SGA may have low lean mass and may have increased central adiposity; cognitive impairment is independently associated with low birth weight, short birth length, and small head circumference for gestational age, and those without catch-up in height or head circumference have worse outcomes. Children born SGA are shorter during childhood and, as adults, can reach heights that are on average approximately 1 SD lower than the mean.[5] Levels of GH, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor binding protein 3 (IGFBP-3) are typically within normal ranges, and have not been shown to be predictive of subsequent growth. In general, children born SGA experience catch up growth during the first year of life that nears completion by the second year of life; they undergo a period of accelerated linear growth during the first 12 months of life that results in stature > -2 SDS in 90% of these individuals.[6] However, children born SGA should have diagnostic work up if they have not had sufficient catch-up growth in the first 6 months or those who remain short at age 2 years, as these children may continue to have growth failure and should be evaluated for other conditions that may limit growth.[7]

[2] Hokken-Koelega ACS, et al. International Consensus Guideline on Small for Gestational Age: Etiology and Management From Infancy to Early Adulthood. *Endocr Rev*. 2023 May 8;44(3):539-565.

[3] Clayton PE, et al. Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocinol Metab.* 2007;92(3):804-10.

[4] Hokken-Koelega ACS, et al. International Consensus Guideline on Small for Gestational Age: Etiology and Management From Infancy to Early Adulthood. *Endocr Rev*. 2023 May 8;44(3):539-565.

[5] Clayton PE, et al. Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocinol Metab.* 2007;92(3):804-10.

[6] Clayton PE, et al. Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocinol Metab.* 2007;92(3):804-10.

[7] Clayton PE, et al. Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocinol Metab.* 2007;92(3):804-10.

2.1.2. Growth Failure Associated With NS

NS is a clinically and genetically heterogeneous autosomal dominant (AD) condition. Heterozygous mutations in multiple genes (e.g., PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1, and CBL) have been documented in this disorder or clinically related phenotypes, allowing diagnosis to be confirmed genetically in about 75% of affected individuals.[8]

The characteristic findings of NS include short stature, distinctive facial features, chest deformity (such as pectus carinatum superiorly and pectus excavatum inferiorly), scoliosis, congenital heart disease (including pulmonary valve stenosis, secundum atrial septal defect, hypertrophic cardiomyopathy, and partial atrioventricular canal defect), and electrocardiogram (ECG) abnormalities (wide QRS intervals and left axis deviation).[9,10] Additionally, a heterogeneous group of abnormalities of blood coagulation has been reported in up to 60% of patients with NS.[11] Individuals with NS may have normal or delayed puberty, and, in males, deficient spermatogenesis may be present and possibly related to cryptorchidism, which is present in 60% to 80% of individuals.[12]

According to clinical practice guidelines, approximately 50% to 70% of individuals with NS have short stature; birth weight and length are typically normal, but there is subsequent growth failure and deceleration of height and weight to ≤ 3rd percentile.[13] Mean height then follows the 3rd percentile until puberty, when below average annualized height velocity (AHV) and attenuated adolescent growth spurt tend to occur.[14] These guidelines also note that these individuals may have either GHD, neurosecretory dysfunction, or normal GH secretion, which is likely a reflection of the genotypic heterogeneity of NS. In many individuals with NS, decreased IGF-1 and IGFBP-3 may suggest impaired GH release or disturbance and a mild GH

[8] Tartaglia M, et al. Noonan syndrome and clinically related disorders. *Best Pract Res Clin Endocrinol Metab*. 2011 Feb;25(1):161-79.

[9] Romano AA, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010 Oct;126(4):746-59.

[10] Carcavilla A, et al. Síndrome de Noonan: actualización genética, clínica y de opciones terapéuticas [Noonan syndrome: genetic and clinical update and treatment options]. *An Pediatr* (Engl Ed). 2020 Jul;93(1):61.e1-61.e14.

[11] Artoni A, et al. Hemostatic abnormalities in Noonan syndrome. *Pediatrics*. 2014 May;133(5):e1299-304.

[12] Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2025 Jun 5]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/

[13] Romano AA, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010 Oct;126(4):746-59.

[14] Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2025 Jun 5]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/

resistance related to post-receptor signaling defects has been reported in individuals with NS and a PTPN11 pathogenic variant.[15]

2.1.3. ISS

ISS is defined by a height SDS < -2 or < -2.25 in patients for whom a complete diagnostic evaluation has excluded other causes of short stature. According to clinical practice guidelines, ISS describes a heterogenous group of children consistent with many presently unidentified causes of short stature; approximately 60% to 80% of all children with a height SDS < -2 fit the definition of ISS.[16] To establish the diagnosis of ISS, systemic (e.g., celiac disease, inflammatory bowel disease, juvenile chronic arthritis), endocrine (GHD or GH resistance, hypothyroidism, or Cushing syndrome), nutritional, or chromosomal abnormalities (e.g., Turner syndrome) should be excluded and subjects should be GH sufficient (stimulated GH levels should be > 10 ng/mL).[17,18]

2.2. Analysis of Current Treatment Options

Multiple hGH products are FDA-approved to treat short stature in children born SGA without catch-up growth, short stature associated with NS, and ISS. All available U.S. market hGH formulations have a native GH sequence.

rhGH products approved by FDA for the treatment of children with ISS, growth failure associated with NS, or growth failure associated with being born SGA, were approved based on improvement in AHV, height SDS, and/or final adult height (Humatrope [BLA 019640] for ISS and Norditropin [BLA 021148] for SGA and NS). The target/receptor of rhGH is well characterized in published literature and there are no other known molecular target/receptors by which hGH may affect its physiologic activity on the efficacy endpoint of interest for the non-GH deficient short stature syndromes. The interaction between rhGH and GH receptor (GHR) is well-understood with a well-defined dose-response with respect to the efficacy endpoint of interest for pediatric patients with the non-GH deficient short stature

[15] Seo GH, Yoo HW. Growth hormone therapy in patients with Noonan syndrome. Ann Pediatr Endocrinol Metab. 2018 Dec;23(4):176-181.

[16] Cohen P, et al. 2007 ISS Consensus Workshop participants. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab*. 2008 Nov;93(11):4210-7.

[17] Cohen P, et al. 2007 ISS Consensus Workshop participants. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab*. 2008 Nov;93(11):4210-7.

[18] Yau M, Lu J, Rapaport R. Idiopathic Short Stature and Growth Failure of Unknown Etiology. [Updated 2023 Oct 24]. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK596800/

syndromes (i.e. improvement in linear growth and final height). Therefore, FDA accepted AHV as an objective primary endpoint in short-term trials evaluating the efficacy of rhGH formulations with a native GH sequence in pediatric patients born SGA with short stature without catch-up growth, with short stature associated with NS, and with ISS.

2.2.1. SGA and With No Catch-Up Growth by 2 Years of Age

Short stature in children born SGA without catch-up growth by two years of age is the second most common indication for hGH therapy, after growth failure due to growth hormone deficiency.[19] Professional society guidelines note that children born SGA are often considered eligible for hGH treatment if by 2 years or 4 years of age they have a height < -2.5 SDS or < -2 SDS, respectively, and treatment initiation at a young age is one of the most important factors predicting favorable growth response. [20,21]

The approved hGH products and guidelines recommend starting doses of 0.035 to 0.07 mg/kg/day (0.25 to 0.49 mg/kg/week). These doses result in mean gains in height of 1.2 SDS to 2 SDS after 3 years of treatment, and most of this height gain is maintained through treatment to adult height.[22]

2.2.2. Growth Failure Associated With NS

Approved hGH products recommend doses up to 0.46 mg/kg/week to treat short stature associated with NS. Clinical practice guidelines also note that dose ranging from 0.23 to 0.46 mg/kg/week, with an estimated mean dose of 0.35 mg/kg/week, are often used.[23] The guidelines also note that improved height outcomes occur with earlier initiation, and longer duration, of GH therapy.

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[19] Hokken-Koelega ACS, et al. International Consensus Guideline on Small for Gestational Age: Etiology and Management From Infancy to Early Adulthood. *Endocr Rev*. 2023 May 8;44(3):539-565.

[20] Clayton PE, et al. Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocinol Metab.* 2007;92(3):804-10.

[21] Hokken-Koelega ACS, et al. International Consensus Guideline on Small for Gestational Age: Etiology and Management From Infancy to Early Adulthood. *Endocr Rev*. 2023 May 8;44(3):539-565.

[22] Clayton PE, et al. Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocinol Metab.* 2007;92(3):804-10.

[23] Romano AA, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010 Oct;126(4):746-59.

It should be noted, that use of hGH in children with NS < 2.5 years of age is concerning, in part due to safety concerns such as cardiac comorbidity and reports that NS may confer an increased risk of certain benign and malignant proliferative conditions.[24]

2.2.3. ISS

Approved hGH doses for ISS are within recommended doses by clinical practice guidelines: starting dose of 0.24 mg/kg/week, with some patients requiring doses as high as 0.47 mg/kg/week. The optimal age for starting GH treatment in these patients is from 5 years of age to early puberty.[25, 26] These guidelines also note that there is considerable inter-patient variability in growth responses without a clear dose-response relationship between change in height SDS and dose of GH administered to patients with ISS, so the lowest dose of GH with demonstrated efficacy should be used.

2.2.4. hGH Therapy in the Proposed Indications

The efficacy of hGH therapy in children born SGA without catch-up growth, short stature associated with NS, and ISS is monitored by growth response. The relationship between IGF-1 and growth rate or final adult height is influenced by many factors, such as bone age, birth length, and nutritional status, and as such, IGF-1 has a limited role as a marker for efficacy.[27] hGH treatment of pediatric patients for short stature of any etiology should not continue at pediatric doses beyond epiphyseal fusion.

The safety profile of all hGH products is generally well-characterized. Adverse reactions include severe hypersensitivity reactions, hypothyroidism, adrenal insufficiency, impaired glucose tolerance and diabetes mellitus, intracranial hypertension, edema, slipped capital femoral epiphysis (SCFE), progression of scoliosis, pancreatitis, arthralgia, and immunogenicity. GH therapy is contraindicated in patients with active malignancy due to the theoretical concern that the potential mitogenic and antiapoptotic effects of GH and IGF-1 may promote neoplasia development.

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[24] Seo GH, Yoo HW. Growth hormone therapy in patients with Noonan syndrome. *Ann Pediatr Endocrinol Metab*. 2018 Dec;23(4):176-181. doi: 10.6065/apem.2018.23.4.176. Epub 2018 Dec 31. PMID: 30599478; PMCID: PMC6312920.

[25] Grimberg A, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: Growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr*. 2016;86(6):361-97.

[26] Cohen P, et al. 2007 ISS Consensus Workshop participants. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab*. 2008 Nov;93(11):4210-7.

[27] Johannsson G, et al. Growth Hormone Research Society. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. *Endocr Connect*. 2018 Mar;7(3):R126-R134.

The use of GH therapy in patients with normal GH levels, such as the proposed populations, may be associated with supraphysiologic IGF-1 and GH levels. There are safety concerns that chronically elevated GH and IGF-1 levels are associated with an increased risk of the above adverse events associated with GH therapy. The GH Research Society recommend that during "treatment of non-GHD states, in order to achieve an acceptable growth response [with hGH therapy], IGF-1 may transiently be above the normal range; however, the safety implications are unknown."[28] Therefore, in pediatric patients treated with hGH for ISS or short stature due to NS or born SGA, goal IGF-1 levels are typically below 2 or 3 SDS. Precise levels that correlate with a potential risk of AEs are unknown.

Most hGH products approved for these non-GHD short stature indications are administered via daily or every other day SC injection. A long-acting formulation of hGH can potentially reduce discomfort by requiring less frequent injections, a particular advantage in the pediatric population.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BLA 761156 for Sogroya (somapacitan), a long-acting recombinant human growth hormone derivative, was approved on August 28, 2020, for the replacement of endogenous GH in adult GHD. On April 28, 2023, Sogroya (BLA 761156/S-005) was approved for the additional indication of treatment of pediatric patients aged 2.5 years and older with growth failure due to inadequate secretion of endogenous GH. It is currently available in 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL ready-to-use, single-patient-use prefilled pens for once weekly SC administration.

3.2. Summary of Presubmission/Submission Regulatory Activity

This section will focus on the product development program for the treatment of short stature associated with SGA, NS, and ISS under IND 116327.

On September 05, 2018, a type B, End-of-Phase 2 (EOP2) meeting was held to discuss phase 3 development plans for somapacitan in pediatric patients with short stature due to GHD. During this meeting, the Sponsor also requested guidance on a phase 3 development plan for

[28] Johannsson G, et al. Growth Hormone Research Society. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. *Endocr Connect*. 2018 Mar;7(3):R126-R134.

somapacitan in pediatric patients with short stature due to SGA, based on phase 2 trial data in children with GHD. For the SGA indication, FDA recommended:

- Conducting a phase 2, dose finding study in subjects with SGA prior to proceeding to phase 3 trials in this patient population, to obtain clear dose-response data from subjects with short stature due to non-GHD disorders.
- Establishing an appropriate dose that is effective in increasing annualized height velocity (AHV), after a minimum of 6 months, and that is safe in subjects with normal insulin-like growth factor (IGF)-1, is essential.

Refer to meeting minutes in DARRTS, dated September 25, 2018.

On February 15, 2019, the Sponsor submitted a phase 2, dose finding protocol (NN8640-4245[29]; hereafter also referred to as trial 4245) in subjects with SGA to evaluate AHV at 3 months of treatment (refer to Clinical Review in DARRTS, dated April 05, 2019). On October 18, 2019, the Sponsor submitted an amendment to Study 4245 that changed the evaluation of the primary endpoint (i.e., AHV) from 13 to 26 weeks, which was acceptable.

On October 06, 2021, a type B, EOP2 meeting was held to discuss the phase 3 development plan for somapacitan in pediatric patients with short stature (b) (4) . The Sponsor provided data from the phase 2 study conducted in subjects with SGA to support a phase 3 trial. Data from the phase 2 trial showed similar somapacitan-induced AHV after 6 months of treatment between two doses, 0.24 mg/kg/week and 0.2 mg/kg/week, both of which were also comparable to the Norditropin-induced 6-month AHV. In their proposed phase 3 program, the Sponsor:

- Proposed to evaluate somapacitan induced 52-week AHV compared to Norditropin (BLA 021148; somatropin), with a non-inferiority margin of 1.6 cm/year for each indication, followed by a single-arm, 104-week open label Extension Period.
- Proposed to use only the highest of the dose of somapacitan (0.24 mg/kg/week) for all proposed indications.
- Proposed to use 2 different doses of Norditropin (0.035 and 0.067 mg/kg/day) as comparators for subjects with SGA, in part because in the European Union (EU), 0.035 mg/kg/day is the approved dosing of Norditropin for the SGA-related indication, while in the US (b) (4) dosing is approved up to 0.067 mg/kg/day.
- Proposed a dose of 0.05 mg/kg/day Norditropin as the comparator for subjects with (b) (4) NS, or ISS, in part, due to the fact that this is the approved dose for (b) (4) . However, in the US, the maximum approved dosing of Norditropin for subjects with ISS is 0.067 mg/kg/day and for subjects with NS is 0.066 mg/kg/day.

[29] Trial NN8640-4245, title: A dose-finding trial evaluating the effect and safety of once-weekly treatment of somapacitan compared to daily Norditropin in children with short stature born small for gestational age with no catch-up growth by 2 yeas of age or older.

FDA agreed that the phase 2 trial in children with short stature due to being born SGA was acceptable to support the design of phase 3 trials in children with short stature associated with SGA, NS, ISS, (b) (4) and, in general, agreed with the design of the proposed 52-week phase 3 trial comparing Norditropin to somapacitan in each proposed indication, with a non-inferiority margin of 1.6 cm/year.

Additionally:

- The Agency recommended that the Sponsor also assess 0.2 mg/kg/week somapacitan in the phase 3 program due to mean IGF-1 levels > 2 SDS with 0.24 mg/kg/week somapacitan (mean [SD] IGF-1 after 6 months: 2.8 [1.6] SDS) in trial 4245, and the safety concerns related to IGF-1 levels persistently elevated > 2 SDS.
- FDA did not have objections to the lower dose of Norditropin as the comparator but noted that using Norditropin at less than maximum dosing as a comparator may affect labeling.
- Because children with short stature associated with SGA who have more severe height deficiency at baseline may respond differently to treatment, FDA recommended that the Applicant also stratify randomization in the SGA population based on baseline height SDS and to pre-specify a subgroup analysis on primary endpoint based on baseline height SDS.

Refer to Meeting Minutes in DARRTS, submitted November 04, 2021.

On April 29, 2022, the Sponsor submitted a protocol for the pivotal phase 3 clinical trial NN8640-4467[30] (hereafter also referred to as trial 4467) that included treatment naïve pediatric patients with short stature (b) (4). In a basket design, subjects with each diagnosis enrolled into separate sub-trial cohorts (refer to Clinical Review submitted to DARRTS June 17, 2022). Trial 4467 only included evaluation of somapacitan at a dose of 0.24 mg/kg/week and included the doses of both 0.035 and 0.067 mg/kg/day Norditropin as the comparator for children with SGA, and the dose of 0.05 mg/kg/day Norditropin as the comparator for children with (b) (4) ISS, and NS. The trial did not include stratification or subgroup analysis based on baseline height SDS and did not evaluate the 0.2 mg/kg/week somapacitan dose. The Sponsor responded to the Division's information request sent on September 06, 2022, that they planned to only assess 0.24 mg/kg/week somapacitan.

On September 21, 2022, in order to include older (b) (4) subjects in their phase 3 program, the Sponsor submitted a protocol (NN8640-4469[31]; hereafter also referred to as trial 4469) for an open label, uncontrolled phase 3 trial to evaluate safety and efficacy of somapacitan in treatment naïve and non-treatment naïve subjects who would otherwise be

[30] Trial NN8640-4467, title: A study comparing the effect and safety of once weekly dosing of somapacitan with daily Norditropin as well as evaluating long-term safety of somapacitan in a basket study design in children with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome, or idiopathic short stature.

[31] Trial NN8640-4469, title: A study evaluating the safety and efficacy of once-weekly dosing of somapacitan in a basket study design in paediatric participants with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome, or idiopathic short stature.

eligible for trial 4467, but who were (b) (4) older than those included in trial 4467 (refer to Clinical Review submitted to DARRTS October 31, 2022).

During review of the Initial Pediatric Study Plan (iPSP), it was determined that children of the proposed populations younger than 2.5 years of age would likely not receive meaningful therapeutic benefit/may not yet receive the proposed diagnoses. Therefore, the Applicant noted the intent to submit a waiver involving children (b) (4) below 2.5 years of age. Trial 4469 (b) (4) include subjects older than those who qualify for trial 4467 (see iPSP, dated October 24, 2022).

On April 17, 2024, the Applicant submitted a type C meeting package to discuss the somapacitan clinical program to support sBLA submissions for the new indications of the treatment of short stature (b) (4). The Applicant proposed:

1. that the other populations of Trial 4467 will fulfill requirements for demonstrating substantial evidence of effectiveness for each individual indications, since each of these indications considered are closely related indications;
2. that trials 4245 and 4469 could provide supportive data for each of these indications;
3. (b) (4);
4. that they would submit (b) (4);
5. that the cutoff date for the inclusion of data from the ongoing Extension Periods of trials 4467 and 4245 would coincide with completion of the NS sub-study of trial 4467;

FDA provided the following comments:

1. FDA agreed that the proposed approach to use individual sub-trials from trial 4467 as a single adequate and well-controlled clinical investigation to provide substantial evidence of effectiveness for each of the individual indications, with the other sub-trials providing confirmatory evidence from a related indication, was reasonable if the Applicant can provide adequate justification.
2. FDA agreed that it was acceptable to provide additional safety and efficacy data from trials 4245 and 4469 as supportive evidence.
3. the Agency requires submissions of separate sBLAs for each proposed indication, though data from one sBLA may be incorporated *via* cross-reference to other sBLAs that rely upon the same data.
4. FDA agreed that the cutoff data for inclusion of data from the ongoing Extension Periods of trials 4467 and 4245, as well as from trial 4469, should allow the inclusion of safety and efficacy data from a sufficient number of subjects treated with somapacitan to evaluate long-term safety and efficacy.

(Refer to Meeting Minutes and clinical review, submitted to DARRTS June 28 and July 25, 2024, respectively).

On May 06, 2025, the Applicant submitted 3 sBLAs for the use of somapacitan for the following proposed indications:

- S-012: Treatment of pediatric patients with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age.
- S-014: Treatment of pediatric patients with growth failure associated with Noonan syndrome (NS).
- S-015: Treatment of pediatric patients with idiopathic short stature (ISS).

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

4.1. Office of Scientific Investigations (OSI)

Clinical data from the phase 3 Trials NN8640-4467 and NN8640-4469 were submitted in these sBLAs for the proposed indications (i.e., treatment of pediatric patients with short stature born SGA and with no catch-up growth by 2 years of age [S-012]; treatment of pediatric patients with growth failure associated with NS [S-014]; and treatment of pediatric patients with ISS [S-015]). Two domestic clinical investigators, Dr. Josha Smith (Site 113) and Dr. Michael Tansey (Site 123), and two foreign clinical investigators, Dr. Violeta Iotova (Site 380) in Bulgaria and Dr. Renata Stawerska (site 451) in Poland, were inspected for Trial NN8640-4467. Based on the overall inspection results of these clinical investigators and the regulatory assessments, the data collected by the clinical investigators and submitted by the Applicant are verifiable. The clinical data submitted by the Applicant appear acceptable in support of the respective indications (see Clinical Inspection Summary submitted to DARRTS on January 23, 2026).

4.2. Product Quality

The Office of Pharmaceutical Quality/Office of Biotechnology recommends approval of these BLA 761156/S-012, S-014, and S-015 from a product quality perspective (refer to the review from 11/24/2025).

The reviewers noted that for the Chemistry, Manufacturing, and Controls (CMC), no new information is provided in these supplements. The reviewers also noted that the assessment of ADA assays is applicable to all three supplements. Anti-drug antibody (ADA) assays were approved in the initial BLA 761156 (anti-somapacitan) and NDA 021148 (anti-somatropin) to analyze the treatment-emergent ADAs in clinical studies. These assays were transferred from the approved (b) (4) laboratory to (b) (4) laboratory to analyze the ADAs in the Chinese patient samples for the clinical studies performed to support the indications reported in supplement #12, #14, and #15. The same ADA assays were used for immunogenicity assessment for supplements 12, 14, and 15.

The reviewers also noted that no safety concern is identified for the dose proposed in these supplements. The Applicant proposes a higher dose (i.e., 0.24 mg/kg/week) somapacitan compared to currently approved dosing to treat children with growth failure due to GHD (i.e., 0.16 mg/kg/week). The review team did not identify any significant concerns for the potential level of contamination of the adventitious agents in the proposed dose of the drug product (DP). For the 0.24 mg/kg/week somapacitan dose, safety assessments confirmed acceptable endotoxin levels ((b) (4) to (b) (4) EU/kg/hour, below the recommended USP <85> limit of 5 EU/kg/hour).

4.3. Clinical Microbiology

The Office of Pharmaceutical Manufacturing Assessment evaluated the changes requested in BLA 761156/S-012, S-014, and S-015, efficacy supplements with no proposed changes to the approved CMC information, and OPQ has concluded that a determination of compliance with CGMP requirements is not necessary to support an action on these supplements. Refer to OPMA memo in DARRTS from December 17, 2025.

4.4. Devices and Companion Diagnostic Issues

No new information included in the current submissions.

Somapacitan is a drug-device combination product. Single-patient-use prefilled pen, with strengths of 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL ready-to-use is already approved for once weekly administration.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There were no new nonclinical data included in the current supplement. Refer to Section 4.4 Nonclinical Pharmacology/Toxicology in the review of the original BLA submission, submitted to DARRTS on July 23, 2020.

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data for somapacitan in children with non-growth hormone deficiency (non-GHD) conditions including small for gestational age (SGA), Noonan syndrome (NS), and idiopathic short stature (ISS). The review is based on population pharmacokinetic/pharmacodynamic (PK/PD) modeling analyses

from phase 2 study 4245 (SGA) and phase 3 studies 4467 and 4469 (basket studies), with supportive single-dose PK data from clinical pharmacology study 4042 in children with GHD.

The clinical pharmacology program demonstrates that somapacitan exhibits suitable PK/PD properties for once-weekly subcutaneous administration across all three non-GHD indications. The population PK/PD models adequately characterized somapacitan exposure and IGF-I response. Exposure-response relationships support the proposed 0.24 mg/kg/week dose, showing increasing height velocity with increasing somapacitan exposure and IGF-I response.

Key findings include consistent pharmacokinetic properties across indications, with terminal half-lives of 36.4-37.1 hours, accumulation ratios (1.06-1.07), and steady-state achievement within 1-2 doses. IGF-I responses were proportional with dose-dependent increase in the range of 0.16 to 0.24 mg/kg/week in SGA patients and suitable time profiles for once-weekly dosing.

Overall, findings from population PK/PD, E-R analyses and immunogenicity analysis support once-weekly administration of 0.24 mg/kg somapacitan for the treatment of children with short stature due to SGA, NS, or ISS. The Office of Clinical Pharmacology recommends approval of the proposed efficacy supplements.

6.2. Summary of Clinical Pharmacology Assessment

The clinical pharmacology of somapacitan was first characterized in adult patients with adult growth hormone deficiency (AGHD) (Clinical Pharmacology Review, 2020, Reference ID: 4602384). The clinical pharmacology characterization was expanded to pediatric populations with non-growth hormone deficiency conditions (SGA, NS, ISS) in the current submission.

The current submission includes:

- Study 4245 (Phase 2): Dose-finding study in 62 GH treatment-naïve children born SGA; somapacitan 0.16, 0.20, 0.24 mg/kg/week vs. Norditropin® 0.035, 0.067 mg/kg/day (ongoing, 208 weeks completed).
- Study 4467 (Phase 3, Pivotal): Basket study in children with short stature - 142 SGA, 77 NS, 88 ISS participants; somapacitan 0.24 mg/kg/week vs. Norditropin® (0.035/0.067 mg/kg/day for SGA, 0.05 mg/kg/day for NS/ISS) (ongoing, 52 weeks completed).
- Study 4469 (Phase 3, Supportive): Basket study in children and adolescents with short stature - 12 SGA, 13 NS, 11 ISS participants; somapacitan 0.24 mg/kg/week only (ongoing, 26 weeks completed).

All studies evaluated children born small for gestational age (SGA), with basket studies also including Noonan syndrome (NS) and idiopathic short stature (ISS) populations.

PK and PD data from studies that enrolled children with non-GHD conditions (216 participants from studies 4245 [SGA], 4467 [SGA/NS/ISS basket study], and 4469 [SGA/NS/ISS basket study]) were used to develop population PK/PD models. The population PK/PD models estimated individual exposures which were then used to characterize exposure-response (E-

R) relationships for height velocity and IGF-I response across the three non-GHD indications. The updated population PK/PD analyses were conducted separately for each indication. The analyses characterized the relationship between somapacitan exposure and IGF-I response, and the efficacy of somapacitan in children born SGA (studies 4245, 4467, 4469), children with NS (studies 4467, 4469), and children with ISS (studies 4467, 4469). Using population modeling frameworks, E-R analyses for height-based efficacy endpoints were conducted using pooled data from studies 4245 and 4467.

In addition, dosing adherence assessments including missed doses and changes to the dosing day frequency, and guidance of switching from daily GH treatment to once weekly somapacitan were provided in the submission.

Based on the submitted data and analyses, the Applicant proposes somapacitan 0.24 mg/kg/week administered subcutaneously once weekly for the treatment of pediatric patients with SGA, NS, and ISS.

Key Review Questions for Clinical Pharmacology:

1. Is the proposed dosing regimen appropriate based on the available pharmacokinetic, pharmacodynamic and efficacy data?
2. Does immunogenicity impact the drug's pharmacokinetics, pharmacodynamics, or clinical efficacy profile?

Overall, findings from population PK/PD, E-R analyses and immunogenicity analyses support once-weekly administration of 0.24 mg/kg somapacitan for the treatment of children with short stature due to SGA, NS, or ISS. No dose adjustment is required based on sex, race, or population differences.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's population PK analysis showed the terminal half-life of somapacitan was estimated to be 36.4-37.1 hours across indications. The volume of distribution (V/F) ranged from 2.97-3.23 L. The accumulation ratio was 1.06-1.07.

The covariate analysis demonstrated body weight was the only consistently significant covariate affecting somapacitan exposure in the participants across the three indications. The Applicant states that only minor differences in exposure were observed across body weight categories due to weight-based dosing (mg/kg/week) approach No clinically relevant impact of other evaluated covariates was observed for somapacitan exposure or IGF-I response (including sex, race, or population differences between SGA, NS, and ISS).

According to the Applicant, the average somapacitan exposures and IGF-I responses over the treatment duration were consistently identified as statistically significant metrics correlated with height velocity and other growth-related efficacy endpoints. Within the exposure range achieved with the 0.24 mg/kg/week dosing regimen, higher exposure values were associated with higher probability of achieving growth-related efficacy endpoints across all three indications.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose for treatment of children with short stature due to SGA, NS, or ISS is somapacitan 0.24 mg/kg administered subcutaneously once weekly. Injections should be administered in the upper legs (thighs), buttocks, upper arms, or stomach area (abdomen) with rotation within these body areas for each injection.

Therapeutic Individualization: Recommendations in Relevant Patient Subsets Based on Various Intrinsic Extrinsic Factors

Body Weight: Body weight was identified as a significant covariate affecting somapacitan exposure. However, due to weight-based dosing (mg/kg/week), only minor differences in exposure were observed across body weight categories.

Sex: Sex did not significantly impact somapacitan exposure or IGF-I response across the three indications.

Race: Race effects were observed but should be interpreted with caution due to relatively low numbers of participants in some racial groups. Asian non-Japanese participants showed slightly higher exposure in some analyses.

Population: Minimal differences were observed between the three indication populations (SGA, NS, ISS) in terms of PK/PD properties.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Mechanism of Action

Somapacitan is a long-acting recombinant human growth hormone (GH) derivative engineered for prolonged action through albumin binding. The molecule contains a single amino acid substitution (leucine at position 101 substituted with cysteine) to which an albumin binding moiety has been covalently attached. This albumin binding moiety consists of a C16 fatty acid moiety and a hydrophilic spacer attached to position 101 of the protein by chemical conjugation. The non-covalent, reversible binding to endogenous albumin delays elimination of somapacitan and thereby prolongs the in vivo half-life and duration of action. This technique is previously used for insulin and GLP-1 molecules such as Levemir®, Victoza®, and Ozempic®.

The pharmacological effects of somapacitan are similar to those of human GH (hGH). GH is essential for normal longitudinal growth in children and acts partly by direct GH-mediated action on growth plates and partly by stimulation of IGF-I release from the liver. In response to GH, IGF-I is produced and secreted from the liver, constituting circulating levels of IGF-I. Additionally, autocrine and paracrine secretion of IGF-I is stimulated by GH. Apart from effects on growth, GH and IGF-I have effects on various organs and tissues and are involved in metabolic processes in both children and adults.

Pharmacokinetics

Absorption: Somapacitan exhibits dual absorption pathways from the subcutaneous depot through first-order absorption and zero-order absorption via a transit compartment.

Steady-state exposures increase with dose in a greater than dose-proportional manner, i.e., C_{avg} values of 46.4, 71.4, and 140.0 ng/mL for the 0.16, 0.20, and 0.24 mg/kg/week doses, respectively.

Distribution: Volume of distribution (V/F) at steady-state ranges from 2.97-3.23 L across indications.

Metabolism: Somapacitan elimination is described by Michaelis-Menten-type elimination

Half-life: Terminal half-life ranges from 36.4-37.1 hours across indications

Accumulation: Low accumulation ratio (1.06-1.07) indicating the drug is largely cleared during the dosing interval.

Pharmacodynamics

IGF-I is used as the primary biomarker for somapacitan activity. Steady-state IGF-I is reached within 1-2 doses with minor accumulation. Time to maximum IGF-I levels ranges from 63.6-68.2 hours across indications. Dose-response relationship exists between somapacitan dose and IGF-I response.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

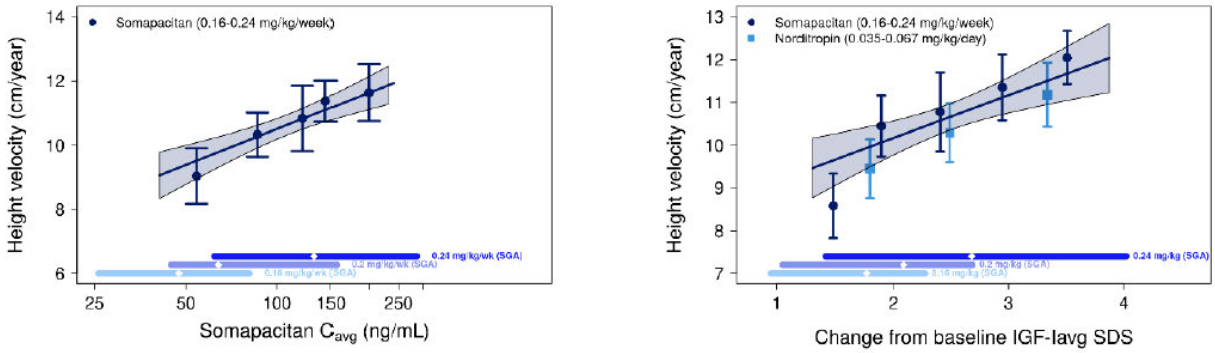
Yes. The population PK/PD modeling analyses demonstrate somapacitan exposure and IGF-I response relationships that support the proposed 0.24 mg/kg/week dose for all three indications. In addition, exposure-response analyses showed increasing height velocity with increasing somapacitan exposure and IGF-I response. Plots of height velocity against somapacitan $C_{average}$ are shown in Figure 1 through Figure 3 for different patient populations (SGA, ISS, NS) from studies 4245 and 4467. These plots illustrate the continual response to the drug across the range of studied exposures and potentially suggest that further response may be achieved. However, despite the clear continuous exposure-response relationship, the

dose selection is mainly supported by the non-inferiority comparison to the active control, Norditropin, in Trial 4467 (See Section 8 for further details of this comparison).

Additionally, the right panel in these figures depicts the correlation between height velocity and IGF-I. This relationship supports that the Applicant's exposure response relationship for IGF-I can be utilized in dose selection considerations, particularly as it pertains to dosing frequency and how to handle missed doses. This relationship is further strengthened by the observation that the relationship for the active control appears to superimpose on the relationship from the somapacitan data.

Figure 1. Height Velocity (Cm/Year) vs. Somapacitan Exposure and vs. Average IGF-I Response in Children Born SGA (Studies 4245 and 4467)

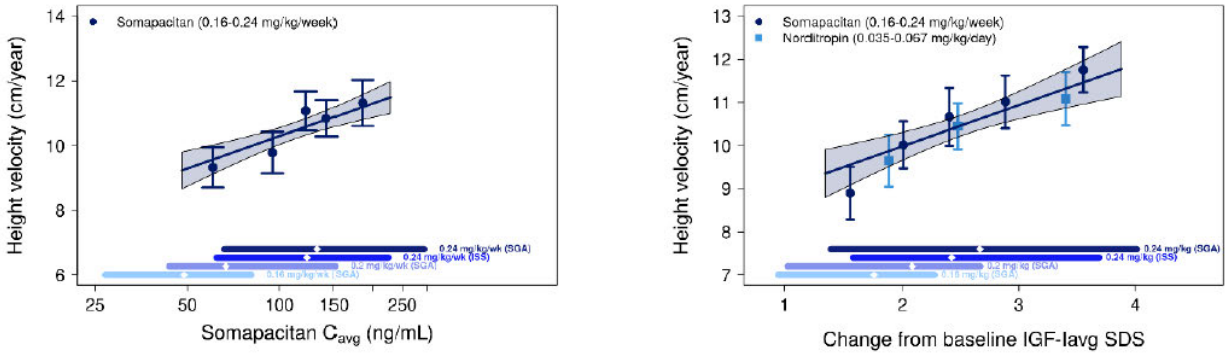
Panel A is the exposure response relationship for height velocity and Panel B is the PD-clinical endpoint relationship between height velocity and change from baseline in IGF-I.



Source: Applicant's Population PK and PK/PD Report, Figure 1-6

Figure 2. Height Velocity vs. Somapacitan Exposure and vs. Average IGF-I Response in Children Born SGA (Studies 4245 and 4467) or With ISS (Study 4467)

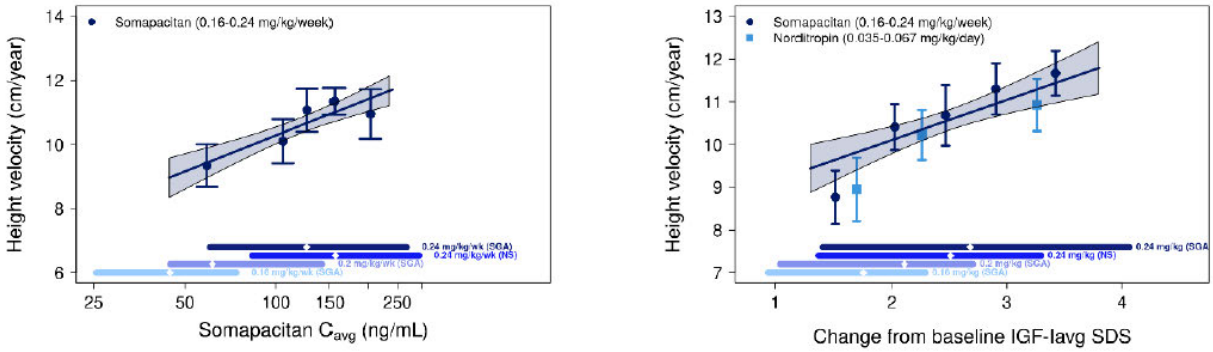
Panel A is the exposure response relationship for height velocity and Panel B is the PD-clinical endpoint relationship between height velocity and change from baseline in IGF-I.



Source: Applicant's Population PK and PK/PD Report, Figure 1-12

Figure 3. Height Velocity (Cm/Year) vs. Somapacitan Exposure and vs. Average IGF-I Response in Children Born SGA (Studies 4245 and 4467) or With NS (Study 4467).

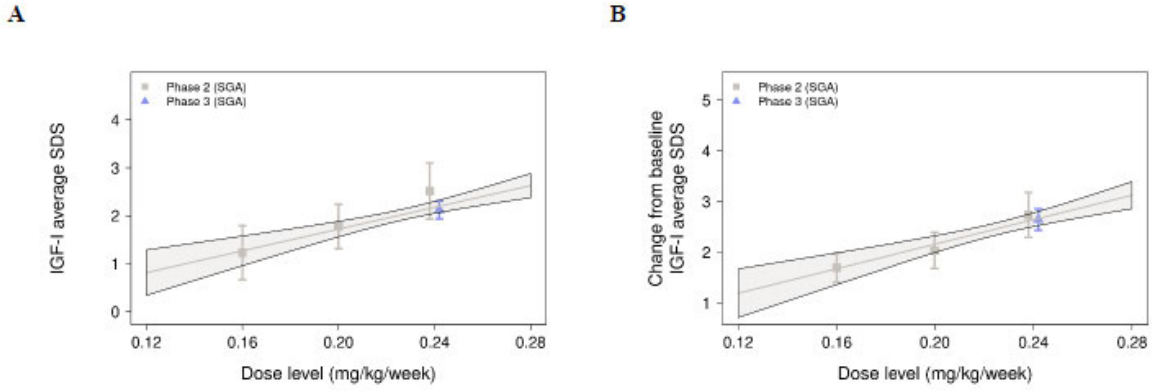
Panel A is the exposure response relationship for height velocity and Panel B is the PD-clinical endpoint relationship between height velocity and change from baseline in IGF-I.



Source: Applicant's Population PK and PK/PD Report, Figure 1-18

Figure 4 through Figure 6 depict the dose-response relationship for somapacitan and IGF-I in studies 4245 and 4467 by each of the subpopulations (SGA, ISS, and NS). While there may be apparent differences in response by subpopulation at the 0.24 mg/kg dose, the dose-response relationship appears to be linear within the studied dose range for the phase 2 SGA data.

Figure 4. Dose-IGF-1 Response for Somapacitan in Children Born SGA

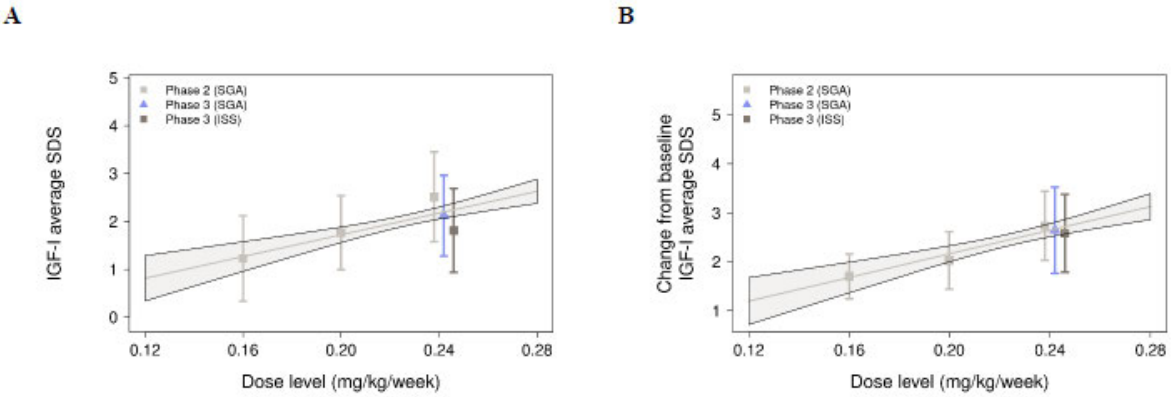


Notes: Symbols and bars indicate means with 95% CIs of individual estimates in studies 4245, 4467 and 4469 (A) and in studies 4245 and 4467 (B). Lines are linear fit to individual estimates with 95% CIs.

Abbreviations: CI: confidence interval, IGF-I average SDS: average IGF-I standard deviation score in a dosing interval.

Source: Applicant's Population PK and PK/PD Report, Figure 6-16

Figure 5. Dose-IGF-1 Response for Somapacitan in Children Born SGA or With ISS

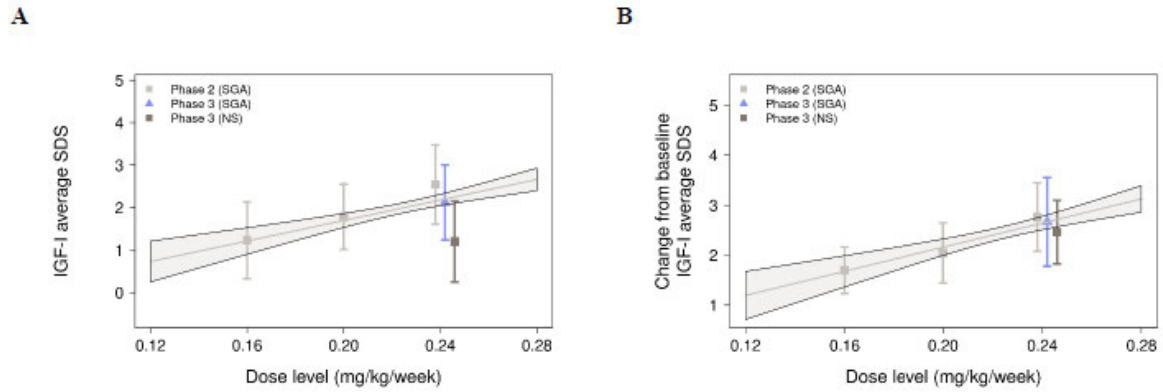


Notes: Symbols and bars indicate means with standard deviation of individual estimates. Lines are linear fit to individual estimates with 95% CIs from children born SGA in studies 4245 and 4467.

Abbreviations: CI: confidence interval, IGF-I average SDS: average IGF-I standard deviation score in a dosing interval.

Source: Applicant's Population PK and PK/PD Report, Figure 7-14

Figure 6. Dose-IGF-1 Response for Somapacitan in Children Born SGA or With NS



Notes: Symbols and bars indicate means with standard deviation of individual estimates. Lines are linear fit to individual estimates with 95% CIs from participants born SGA in studies 4245 and 4467.

Abbreviations: CI: confidence interval, IGF-I average SDS: average IGF-I standard deviation score in a dosing interval.

Source: Applicant's Population PK and PK/PD Report, Figure 8-14

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Yes. In addition to the exposure-response analysis described in the previous section, the once-weekly dosing regimen of 0.24 mg/kg is also supported by the results of phase 2 study 4245. Phase 2 study 4245 evaluated three somapacitan dose levels (0.16, 0.20, and 0.24 mg/kg/week) compared to Norditropin® controls in children with SGA. The study

demonstrated a clear dose-response relationship across all parameters. Specifically, IGF-I responses increased proportionally, with change from baseline IGF-I_{avg} SDS values of +1.70, +2.04, and +2.74 for the three dose levels. The linear dose-response modeling indicated that each 0.02 mg/kg/week dose increase resulted in a 0.24 SDS change in average IGF-I. In addition, the 0.24 mg/kg/week somapacitan dose provided optimal efficacy with an IGF-I response comparable to Norditropin® 0.067 mg/kg/day, the higher of the two daily control doses evaluated. Exposure-response analyses confirmed increasing height velocity with increasing somapacitan exposure and IGF-I response. No safety issues were identified across treatment arms up to somapacitan 0.24 mg/kg/week, including in participants obtaining IGF-I SDS levels above +3, and no safety issues were identified as compared to daily GH treatment.

Overall, the comprehensive evidence supported 0.24 mg/kg/week as the optimal dose for achieving therapeutic equivalence to standard daily growth hormone therapy while maintaining a favorable safety profile and long-term sustained efficacy.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

No. While body weight was identified as a significant covariate, the weight-based dosing (mg/kg/week) adequately accounts for this factor. Sex and race effects were minimal and do not require dose adjustments. See the PM review (Section 15.3) for further details.

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Not applicable for this submission. Drug-drug interactions were evaluated in the initial application for adult GHD.

Question on Clinically Relevant Specifications (TBD)?

None.

Does the Immunogenicity Impact the PK, PD or Efficacy?

The formation of anti-somapacitan antibodies does not meaningfully impact the pharmacokinetics, pharmacodynamics, or efficacy of somapacitan treatment. All detected antibodies were non-neutralizing, low-titer, and cross-reactive with human growth hormone, supporting that the immunogenic risk of somapacitan treatment is low and the benefit/risk ratio remains favorable for children with anti-somapacitan antibody formation. Refer to Section 8.3.11 for details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The following Table 1 summarizes the clinical development program somapacitan for the treatment of pediatric patients with short stature born SGA and with no catch-up growth by 2 years of age (S-012); treatment of pediatric patients with growth failure associated with NS (S-014); and treatment of pediatric patients with ISS (S-015).

Table 1. Listing of Clinical Trials Relevant to These Supplemental BLAs

Trial Identity	IND Number	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration	No. of Patients Enrolled	Study Population	No. of Centers and Countries
NN8640-4245	116327	Phase 2, randomized, open-label, dose finding, active control, parallel group trial.	0.16, 0.2, or 0.24 mg/kg/week SC somapacitan; or 0.035 or 0.067 mg/kg/day SC Norditropin	Primary: AHV at Week 26 Secondary: change in bone age, height SDS, AHV SDS, safety, and PD	Subjects remain on the drug and dose to which they were randomized for Weeks 0-26 (Main Period) and Weeks 27-52 (Extension I). Followed by Extension II (Weeks 52 to 260) where all subjects will be transitioned to 0.24 mg/kg/week SC somapacitan. If subjects complete Extension II prior to approval of somapacitan, they can continue 0.24 mg/kg/week somapacitan until somapacitan is approved or until December 2026 (Extension III).	Somapacitan: 37 Norditropin: 25 0.16 mg/kg/week somapacitan: 12 0.2 mg/kg/week somapacitan: 13 0.24 mg/kg/week somapacitan: 12 0.035 mg/kg/day Norditropin: 12 0.067 mg/kg/day Norditropin: 13	GH treatment naïve pre-pubertal children (2.5 to 10 [females] or 11 [males] years old) with short stature born SGA with no catch-up growth by 2 years of age	38 clinical sites in 12 countries (Austria, France, Hungary, India, Israel, Italy, Japan, Latvia, Russia, Thailand, Ukraine, and the United States).
Trial NN8640-4467	116327	Phase 3, randomized, open-label, active controlled, basket trial	SGA: 0.24 mg/kg/week somapacitan; or 0.035 or 0.067 mg/kg/day Norditropin	Primary: AHV at Week 52 Secondary: change in bone age, height SDS, and AHV SDS	Subjects remain on the drug and dose to which they were randomized for Weeks 0-52 (Main Period).	SGA: 0.24 mg/kg/week somapacitan: 69 0.035 mg/kg/day Norditropin: 37	GH treatment naïve pre-pubertal (2.5 to 10 [females] or 11 [males] years old)	133 clinical sites in 34 countries (Canada, The United States, Brazil, Lithuania, Germany, South Africa, Mexico,

Trial Identity	IND Number	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration	No. of Patients Enrolled	Study Population	No. of Centers and Countries
			NS and ISS: 0.24 mg/kg/week somapacitan; or 0.05 mg/kg/day Norditropin		Followed by a 104-week safety Extension Period (Weeks 52-156) where all subjects are treated with 0.24 mg/kg/week somapacitan (Extension I). If subjects complete Extension I prior to approval of somapacitan, they can continue 0.24 mg/kg/week somapacitan until somapacitan is approved or until October 2027 (Extension II).	0.035 mg/kg/day Norditropin: 35 NS: 0.24 mg/kg/week somapacitan: 49 0.05 mg/kg/day Norditropin: 28 ISS: 0.24 mg/kg/week somapacitan: 59 0.05 mg/kg/day Norditropin: 28	children with short stature born SGA with no catch-up growth by 2 years of age, NS, or ISS	Latvia, Austria, Belgium, Finland, France, Ireland, the Netherlands, Portugal, Spain, Switzerland, The United Kingdom, India, the Republic of Korea, Malaysia, Thailand, Bulgaria, Croatia, Greece, Israel, Italy, Poland, Russia, Saudi Arabia, Serbia, Slovenia, Japan, and China).
Trial NN8640-4469	116327	Phase 3 open-label, single arm, basket trial.	SGA, NS, ISS, TS: 0.24 mg/kg/week somapacitan	Primary: number of AEs from baseline to Week 26 Secondary: number of AEs from baseline to Week 156; AHV and change in height SDS, AHV SDS, IGF-1 SDS, and IGFBP-3 SDS at Week 26.	The trial includes a 26-week Main Period, 130-week Extension Period I (Weeks 26 to 156), and a 91-week Extension Period II (weeks 156 to 247)	SGA: 12 NS: 13 ISS: 11 TS: 11	GH treatment naïve or non-naïve children ≥ 10 (females) or ≥ 11 (males) years old to < 18 years old, with short stature born SGA with no catch-up growth by 2 years of age, NS, ISS, or TS	14 clinical sites in 5 countries (Malaysia, the Netherlands, South Korea, Spain, and the United States).

7.2. Review Strategy

Table 1 provides a list of the clinical trials in the somapacitan development program for the proposed indications, i.e., the treatment of pediatric patients with S-012) short stature born SGA and with no catch-up growth by 2 years of age; S-014) growth failure associated with NS; and S-015) ISS.

The completed 52-week Main Period of the pivotal phase 3 trial 4467 was a randomized, open label, active controlled (Norditropin; somatropin; BLA 021148), phase 3 basket trial in pediatric subjects aged 2.5 to 10 (females) or 11 (males) years old with short stature born SGA with no catch-up growth by 2 years of age, NS, ISS, or TS. Subjects were enrolled into one of four separate cohorts based on indication, and efficacy and safety analyses for each indication were conducted individually per cohort (sub-trial). (b) (4) As such, the Main Period of the sub-trials of the phase 3 trial 4467 for the SGA, NS, and ISS populations are the main focus of this review. The data and analysis from the TS cohort were not provided as the Applicant plans to submit an sBLA for this indication at a later date and are not discussed further in this review.

Additional growth and safety data for all indications were provided from the ongoing, open-label extension (OLE) period of trial 4467. For children born SGA, additional growth data were also provided from the Main and Extension Periods of the phase 2 trial 4245. Finally, supportive data on safety and efficacy in children older than 10 (females) or 11 (males) years old with short stature born SGA with no catch-up growth by 2 years of age, NS, ISS, or TS, were provided from the ongoing, open label phase 3 trial 4469. Trial 4469 and the OLE periods of trials 4467 and 4245 were open label and single arm without a comparator, there was no prespecified testing for efficacy endpoints, and the results of these periods were purely descriptive. Overall, information from the OLE periods of trials 4467 and 4245 was used to provide additional data on long-term safety and durability of response, while information from trial 4469 also was used to provide additional data from children older than those who were included in the pivotal phase 3 trial 4467.

The data from completed 26-week Main Period of trial 4245 have a database lock date of May 28, 2021, and data from the Extension Periods of trial 4245 have a database lock date of January 17, 2025. The data from the completed 52-week Main Period of trial 4467 have database lock dates of October 23, 2024, for the SGA and ISS sub-trials, and December 16, 2024, for the NS sub-trial (with the exception of some additional anti-somapacitan antibody data that had a lock date of December 16, 2024, and January 16, 2025, for the SGA and NS sub-trials, respectively). The database lock dates for all sub-trials of the ongoing OLE period of trial 4467 and for the ongoing trial 4469 is November 24, 2024. Additional safety data from the ongoing trials, with a database lock date of June 02, 2025, were included in the 120-Day Safety Update.

FDA has accepted data from one or more adequate and well-controlled trials to provide substantial evidence of effectiveness, thereby supporting concurrent approval of the drug for growth failure associated with these non-GHD conditions. Multiple hGH products with a native GH sequence have been approved that aim to mimic the function of endogenous GH secretion. The structure-function relationship of endogenous GH is well-understood. The wide variety of GH biological effects is mediated by one mechanism of action, i.e., GH binding to and activating GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, which stimulates the proliferation of chondrocytes and results in bone growth. No alternative receptors mediating GH activity have been identified. There is thus a strong mechanistic understanding of how hGH exerts its growth-stimulating effect in non-GHD conditions associated with short stature. FDA also accepts short-term changes in AHV that are not inferior to the active comparator (i.e., approved hGH formulations) for the evaluation of efficacy of hGH products with native GH sequences for these GH-sufficient indications. The use of AHV is supported by mechanistic evidence discussed above and clinical data from trials of short acting hGH formulations (e.g., data from Humatrope [BLA 019640] or Nutropin AQ [BLA 020522] treatment in subjects with ISS, and Norditropin treatment in subjects with SGA or NS) where some subjects had been treated to final adult height and demonstrated that improvement in short-term growth was associated with improvement in final adult height. The active moiety of somapacitan has the same primary amino acid sequence as native hGH and thus is expected to have the same action at the target receptor as native hGH.

As such, FDA accepts adequate and well controlled sub-trials from the basket trial 4467 in each proposed indication to provide the substantial evidence of effectiveness for the proposed indications. The rationale for this approach is briefly discussed here. SGA, ISS and NS are all non-GHD conditions that are associated with proportional short stature. While each condition results in short stature due to different etiologies, the treatment with exogenous hGH therapy to improve growth is expected to act along a similar mechanism of action, as discussed above. Each sub-trial met characteristics of adequate and controlled trial, and the data for each indication was analyzed separately. In addition, and similar to other hGH clinical programs in children with short stature associated with SGA, NS, or ISS, the same primary endpoint was used in individual sub-trials to evaluate the efficacy of somapacitan, i.e., AHV at Week 52. Short term improvement in AHV at 12 months was agreed as an acceptable endpoint to establish clinical benefit in patients with short stature associated with SGA, NS, and ISS. It is expected that hGH- and hGH analog-induced changes in AHV ultimately translate into increased final adult height.

This review includes the Applicant's primary and secondary efficacy results and analyses. Separate analyses were performed by the FDA statistician, Dr. Satyajit Ghosh, who confirmed the Applicant's findings of efficacy. The analyses were also reviewed by this medical reviewer.

The safety data were reviewed for each of the proposed indications separately and primarily included data from the pivotal phase 3 trial 4467, from the phase 2 trial 4469 (including long-term safety data up to 208 weeks), and from the open label trial 4469, all in children with short stature associated with SGA, NS, or ISS. This review includes the Applicant's safety

analyses as well as analyses generated by this medical reviewer using JMP Clinical, Medical Dictionary for Regulatory Activities (MedDRA)-Based Adverse Events Diagnostics (MAED) software, and Analysis Studio clinical software.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. Trial NN8640-4467 (Trial 4467)

A study comparing the effect and safety of once weekly dosing of somapacitan with daily Norditropin® as well as evaluating the long-term safety of somapacitan in a basket study design in children with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome, or idiopathic short stature

8.1.1.1. Trial Design

Trial 4467 is a randomized, open-labelled, active comparator (Norditropin; somatropin) phase 3 basket trial to evaluate the efficacy and safety of once-weekly somapacitan compared to daily somatropin after 52 weeks in GH-treatment naïve pre-pubertal children with short stature associated with being born SGA, NS, ISS, or TS. As mentioned above, the results of this trial evaluating Turner syndrome will not be discussed in this review. A similar trial design (randomized, active or placebo controlled) and duration (52 weeks) has been accepted by the Agency for the approval of other hGH formulations for short stature associated with non-GHD conditions (refer to Section 7.2).

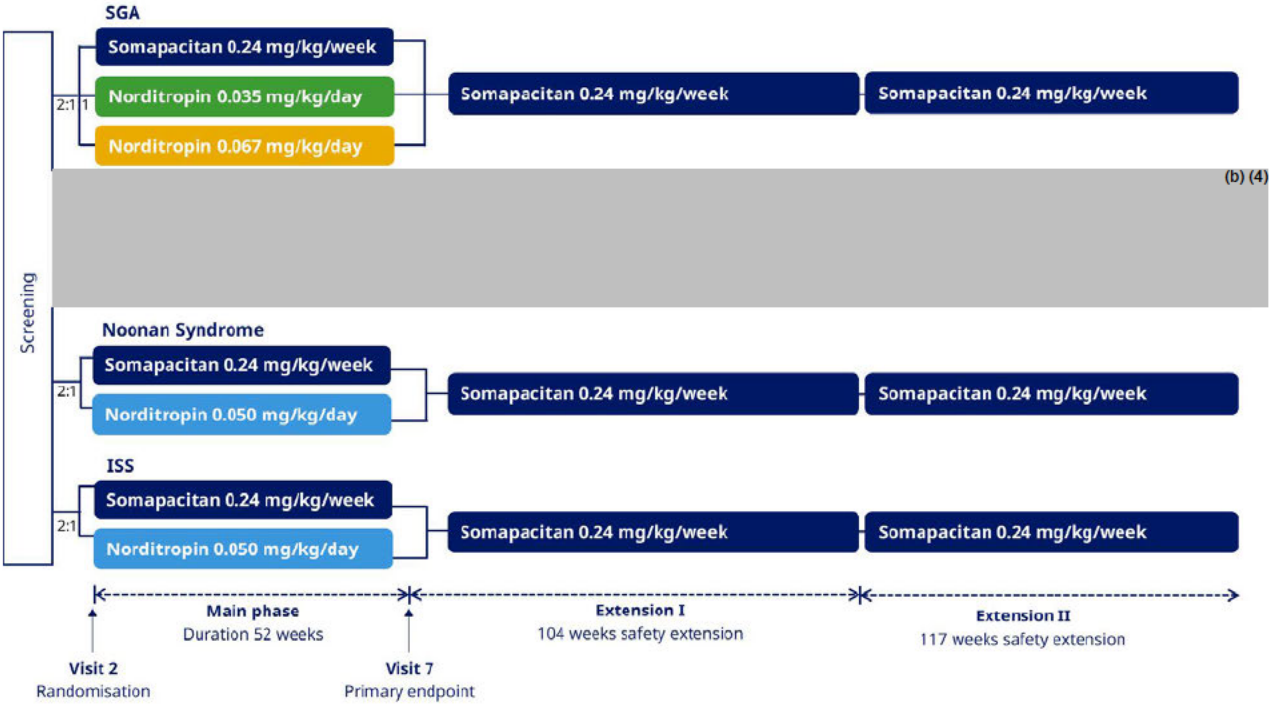
The primary objective of this trial is to evaluate the efficacy (non-inferiority) of once weekly somapacitan, compared to daily somatropin, measured by AHV at Week 52 in each subgroup of children with SGA, NS, ISS, or TS, assessed separately.

The secondary objectives were to compare the effect of weekly somapacitan and daily somatropin on change in height SDS, AHV SDS, bone age (BA), PK, PD, and safety over time in children with SGA, NS, ISS, or TS, in each subgroup separately.

The trial consisted of a screening period (up to 3 weeks for subjects born SGA or with ISS; up to 6 weeks for subjects with NS (b) (4)), a 52-week, randomized, active controlled Main Period, and a 104-week open label extension (OLE) period (Extension Period I), where all subjects are treated with somapacitan, to provide long-term data. Finally, for subjects who complete Extension Period I when somapacitan is not available for prescription for these indications in their country, they can continue therapy with somapacitan until it becomes available for prescription or October 2027, at the latest (up to 117 weeks). There was no washout period between periods.

Refer to Figure 7 below.

Figure 7. Schematic, Trial 4467



Source: Protocol for trial 4467, Figure 4-1, page 47 of 191

In the SGA cohort, subjects were randomized in a 2:1:1 ratio to either:

- 0.24 mg/kg/week somapacitan;
- 0.035 mg/kg/day (0.25 mg/kg/week) Norditropin; or
- 0.067 mg/kg/day (0.47 mg/kg/week) Norditropin.

In (b) (4) NS, and ISS cohorts, subjects were randomized in a 2:1 ratio to either:

- 0.24 mg/kg/week somapacitan; or
- 0.05 mg/kg/day (0.35 mg/kg/week) Norditropin.

Randomization was stratified by age (< 6 years old versus ≥ 6 years old), sex (male versus female), region (Japan versus non-Japan). Growth rate is generally dependent on age, with those younger than 6 typically having a higher AHV, and also by sex, with males on average growing at a slower rate and with delayed growth spurt.[32] As such, FDA has accepted a stratification by age and sex for trials evaluating hGH products with a native GH sequence for treatment indications related to short stature in children. As the eligibility criteria in Japan for each of the proposed indications varied somewhat from that of other countries (see Section 8.1.1.3, below), stratification by region was also acceptable.

[32] National Center for Health Statistics, 2022, Growth Charts, Centers for Disease Control and Prevention: https://www.cdc.gov/growthcharts/index.htm

Fixed doses of somapacitan and Norditropin were used. As discussed in Section 3.2, the Applicant chose the different doses of the comparator to align with the approved dosing of Norditropin for each indication in the various countries where the trial occurred: for short stature associated with SGA, 0.25 mg/kg/week daily Norditropin is the approved dose in the EU, while in the US (b) (4), the dose is approved up to 0.47 mg/kg/week; for subjects with short stature associated with NS and ISS, the Applicant used dosing of Norditropin that is within the accepted range of approved dosing of these indications in the US: up to 0.46 and up to 0.47 mg/kg/week for NS and ISS, respectively. In all cases, the dose chosen for Norditropin is within the labeled dosing range for Norditropin, and FDA did not have objections to the lower dose of Norditropin as the comparator but noted that using Norditropin at less than maximum dosing as a comparator may affect labeling.[33]

Per protocol, doses of somapacitan and Norditropin could be decreased by 25% for safety reasons, i.e., in subjects who experience IGF-1 levels > 3 SDS at two consecutive visits (visits occur at baseline, Week 4, Week 13, and every 13 weeks thereafter) or persistent AEs. If the AE or elevated IGF-1 resolves after dose reduction and the subject has been treated for at least 4 weeks at the reduced dose, the dose could be resumed at the original dose at the Investigator's discretion. If the AE or elevated IGF-1 did not resolve after the first dose reduction, an additional 25% reduction in dose may occur. If, after two dose reduction steps, the AE persists, the subject's treatment may be discontinued. Definition of persistence of AEs warranting dose reduction or treatment discontinuation was as per the Investigator's discretion. If IGF-1 remains > 3 SDS despite two dose reductions, continued treatment and dosing will be based on individual medical advice by the Investigator.

Subjects who stopped treatment prior to Week 52 were encouraged to complete the Main Period of the trial in order to collect the required data.

Treatment would be considered completed, and therapy stopped, if the subject reached near adult height (NAH), defined as AHV < 2 cm/year calculated over a period of at least 9 months and have reached a bone age ≥ 16 or ≥ 14 years for males or females, respectively. If bone age is not available, then the criteria used chronological ages of ≥ 17 and ≥ 15 for males and females, respectively.

Somapacitan was provided as a solution for SC injection *via* a marketed pen injector (PDS290). Three pen-injector strengths (5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL) were used in the trial based on body weight (2 to 8 kg, 6 to 15 kg, and 9 to 70 kg, respectively). Each of the three pen-injector strengths are approved for use in adults with GHD and children 2.5 years of age and older with growth failure due to GHD.

Norditropin provided via prefilled pen injector (Norditropin FlexPro; 10 mg/1.5 mL) for SC injection was used as the comparator in the trial.

[33] Norditropin, BLA 021148, label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021148s056s058lbl.pdf

Subjects or parents/guardians were trained in administration of study drugs by Investigators or delegates according to the directions for use (DFU) in how to handle the PDS290 or Norditropin FlexPro pen-injectors. Until a subject was deemed capable of self-administering, the parent/guardian administered the study drug. The protocol did not specify at what age subjects were expected to self-administer the product.

8.1.1.2. Trial Endpoints

Primary Endpoint

The primary efficacy endpoint was AHV after 52 weeks of treatment, analyzed for each indication individually. As discussed in Section 7.2, AHV is an accepted surrogate endpoint to demonstrate efficacy and establish clinical benefit of drugs with a native GH sequence for the treatment of short stature associated with SGA, NS, and ISS in children.

Secondary Endpoints

Supportive secondary efficacy, safety, and PD endpoints included growth parameters, biochemical marker measurements, AEs, and various laboratory parameters listed below, and were analyzed for each indication individually. These secondary endpoints are traditionally used in clinical programs of drugs meant to improve growth in children and were acceptable. The results from the analyses of secondary endpoints were intended to be supportive and were not included in a test for hierarchy.

Secondary Efficacy Endpoints

Change from baseline over time in:

- Height SDS
- AHV SDS
- Bone age
- PD (i.e., IGF-1)
- PK

Exploratory Endpoints

The Applicant also assessed parent/caregiver responses to the following clinical outcome assessments (COAs) over time: Growth Hormone Injection – Child Treatment Burden (GH-INJ-CTB), Growth Hormone Injection – Parent Treatment Burden (GH-INJ-PTB), Growth Hormone Parent Preference Questionnaire (GH-PPQ), Small for Gestational Age – Child Impact Measure-Observer (SGA-CIM-O), and Idiopathic Short Stature – Child Impact Measure-Observer (ISS-CIM-O).

8.1.1.3. Eligibility Criteria

For each sBLA, the eligibility criteria were consistent with the indication sought: treatment of short stature or growth failure associated with SGA, NS, or ISS. The trial included growth promoting-treatment naïve, pre-pubertal (Tanner I; aged 2.5 to < 10 (females) or < 11 (males) years of age) children with a diagnosis of SGA, NS, or ISS. Confirmation of these diagnoses required:

For SGA:

- Birth length, weight, or both, below -2 SDS
- Height SDS < -2.5 at screening
- AHV below 50th percentile
- BMI < 95th percentile

For NS:

- Height SDS < -2 SD at screening
- Clinical diagnosis of NS according to van der Burgt score list (see Table 50, in Section 15.4.1).

For ISS:

- Height < -2.5 SD at screening
- At least one GH peak > 7 ng/mL during GH stimulation test within the prior 18 months.

Overall, the inclusion criteria were consistent with current society guidelines on the diagnosis of each of these diagnoses.

For all indications, exclusion criteria appropriately excluded any known or suspected clinically significant abnormality or other diagnoses likely to affect growth or the ability to evaluate growth, such as hormone deficiencies, decreased growth due to nutritional deficiencies, chronic illness, chromosomal aneuploidies, or spinal deformities or skeletal dysplasias. The Applicant adequately excluded subjects in whom the use of hGH therapy may pose safety concerns (e.g., subjects with a history of, or active, malignancy; poorly controlled diabetes or diabetes complications). The Applicant also appropriately excludes subjects in whom interpretation of drug efficacy may be confounded by other factors, such as other medications or medical conditions.

See Section 15.4.1, Trial NN8640-4467 for the full inclusion and exclusion criteria for trial 4467.

8.1.1.4. Statistical Analysis Plan

The primary analysis of the primary and supportive secondary endpoints, conducted for each subgroup based on the proposed indication, was based on the full analysis set (FAS) which was defined as all randomized participants. In the primary analysis, intercurrent events (dose reduction due to IGF-I or AE, treatment discontinuation for any reason and initiation of ancillary therapy) were handled using treatment policy strategy and missing 52-week height

velocity was multiply imputed (number of imputation n=100) using the data from the corresponding Norditropin arm.

For each of the complete data sets, AHV at week 52 is analyzed using an analysis of covariance model with treatment, sex, age group, region, height SDS (<-3 or ≥- 3), and sex by age group by region interaction term as factors, and baseline height and baseline IGF-I SDS as covariates. For the supportive secondary endpoints - change in Height SDS, AHV SDS and bone age from baseline to week 52 were estimated using a model similar to the primary analysis of the primary endpoint. The following baseline covariates were used instead of the baseline height, all other covariates and factors remained same.

- For Height SDS - baseline Height SDS
- For AHV SDS - baseline Height Velocity SDS,
- For Bone age - bone age/chronological age at screening.

The least square mean treatment differences (somapacitan - Norditropin) and the 95% C.I. were reported by combining estimates based on each imputed dataset using Rubin's rule. The type I error was controlled at two-sided alpha = 0.05 using a hierarchical testing procedure within each sub-study. The secondary endpoints were not included in the testing hierarchy.

The steps in the hierarchical testing procedure for the SGA sub-study were as follows:

1. AHV at week 52 non-inferiority of somapacitan versus Norditropin low dose
2. AHV at week 52 non-inferiority of somapacitan versus Norditropin high dose
3. AHV at week 52 superiority of somapacitan versus Norditropin low dose
4. AHV at week 52 superiority of somapacitan versus Norditropin high dose.

For NS and ISS the testing hierarchy was as follows:

1. AHV at week 52 non-inferiority of somapacitan versus Norditropin
2. AHV at week 52 superiority of somapacitan versus Norditropin.

The non-inferiority margin for all the three sub-studies was pre-specified at 1.6 cm/year. This was based on a study in SGA where Norditropin 0.033 mg/kg/day provided mean increase of 3.3 cm at 1 year [95% CI: (2.9, 3.7) cm/year] versus no-treatment. The division considered the margin acceptable for the targeted indications.

8.1.1.5. Protocol Amendments

The protocol was amended 9 times. None of these amendments had an impact on the integrity of the trial or the interpretation of efficacy and safety results.

8.1.1.6. Trial Results

Compliance With Good Clinical Practices

The trial was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP) regulations/guidelines.

Financial Disclosure

The financial document was reviewed. No issues were identified that could influence the outcome of the trials. Refer to Section 15.1 of the Appendix.

8.1.1.7. Subject Disposition

The trial enrolled 307 subjects: 142 subjects with SGA, 77 subjects with NS, and 88 subjects with ISS.

SGA

Out of 167 subjects born SGA screened for the trial, 25 subjects were excluded as screening failures (the majority of which were related to not meeting eligibility criteria related to impaired AHV or a suspected abnormality that could affect growth).

A total of 142 subjects were randomized 2:1:1 to receive 0.24 mg/kg/week somapacitan, 0.035 mg/kg/day Norditropin, or 0.067 mg/kg/day Norditropin. However, one subject randomized to somapacitan was not exposed to treatment as this subject was randomized in violation of the inclusion criterion requiring height < -2.5 SD. Thus, 141 subjects were exposed to at least one dose of study drug in the 52-week Main Period: 69, 37, and 35 subjects in the 0.24 mg/kg/week somapacitan, 0.035 mg/kg/day Norditropin, and 0.067 mg/kg/day Norditropin groups, respectively. All 141 (141/142; 99.3%) completed 52 weeks of treatment in the Main Period of the trial.

A total of 140/141 subjects who completed 52 weeks of treatment continued into the ongoing Extension Period. One subject in the 0.067 mg/kg/day Norditropin group discontinued therapy after completion of the Main Period as the mother did not feel safe switching to somapacitan. Of 140 subjects in the Extension period, 1 subject, originally randomized to 0.035 mg/kg/day Norditropin, discontinued therapy and withdrew from the Extension Period early due to an adverse event (mood altered) (see Section 8.3.5).

Refer to Table 2 for subject disposition of subjects with SGA in trial 4467.

Table 2. SGA Subject Disposition, Trial 4467

Treatment	0.035 mg/kg/day Norditropin (N=37) n (%)	0.067 mg/kg/day Norditropin (N=35) n (%)	0.24 mg/kg/week Somapacitan (N=70) n (%)	Total (N = 142) n (%)
Exposed in 52-week Main Period	37 (100)	35 (100)	69 (98.5)	141 (99.3)
Completed treatment in the 52-week Main Period	37 (100)	35 (100)	69 (98.5)	141 (99.3)
Early withdrawal from treatment in 52-week Main Period	0	0	0	0
Early withdrawal from trial during the 52-week Main Period	0	0	0	0

Treatment	0.035 mg/kg/day Norditropin (N=37) n (%)	0.067 mg/kg/day Norditropin (N=35) n (%)	0.24 mg/kg/week Somapacitan (N=70) n (%)	Total (N = 142) n (%)
Rolled over into Extension Period	37 (100)	34 (97.1)	69 (98.5)	140 (98.6)
Early withdrawal from treatment in Extension Period	1 (2.7)	0	0	1 (0.7)
Adverse event	1 (2.7)	0	0	1 (0.7)
Early withdrawal from trial during the Extension Period	1 (2.7)	0	0	1 (0.7)
Adverse event	1 (2.7)	0	0	1 (0.7)

Source: Data compiled from trial 4467 ADSL datasets and from the Clinical Trial Report for trial 4467 SGA, Table 4-1, page 47.

Table 2 differs from what was provided by the Applicant regarding the subject in the 0.067 mg/kg/day Norditropin arm who did not roll over into the Extension Period of the trial. The Applicant reported that this subject discontinued treatment early during the 52-week Main Period but remained in the trial. However, it appears this subject actually completed 52 weeks of therapy in the Main Period and did not discontinue therapy until after analysis at Week 52. Therefore, this reviewer concluded that discontinuation of therapy, and from the trial, occurred after the 52-week Main Period, as is reflected in Table 2.

NS

Out of 85 subjects with NS who were screened for the trial, 8 subjects were excluded as screening failures (reasons for screening failures were spread across six different inclusion/exclusion criteria). A total of 77 subjects were randomized 2:1 to either 0.24 mg/kg/week somapacitan (N=49) or 0.05 mg/kg/day Norditropin (N=28).

A total of 76/77 (98.7%) subjects completed 52 weeks of treatment in the completed Main Period of the trial. One subject in the somapacitan group discontinued treatment and withdrew from the trial prematurely as they moved out of the country.

All 76 subjects who completed the 52-week Main Period of the trial rolled over into the Extension Period of the trial. Of the subjects enrolled in the ongoing Extension Period, 1/76 (1.3%) discontinued treatment prematurely in the Extension Period due to an AE (giant cell bone tumor, see Section 8.3.5), but remained in the trial.

Refer to Table 3 for subject disposition of subjects with NS in trial 4467.

Table 3. NS Subject Disposition, Trial 4467

Treatment	0.05 mg/kg/day Norditropin (N=28) n (%)	0.24 mg/kg/week Somapacitan (N=49) n (%)	Total (N = 77) n (%)
Exposed in 52-week Main Period	28 (100)	49 (100)	77 (100)
Completed treatment in the 52-week Main Period	28 (100)	48 (98)	76 (98.7)

Treatment	0.05 mg/kg/day Norditropin (N=28) n (%)	0.24 mg/kg/week Somapacitan (N=49) n (%)	Total (N = 77) n (%)
Early withdrawal from treatment in 52-week Main Period	0	1 (2)	1 (1.3)
Other	0	1 (2)	1 (1.3)
Early withdrawal from trial during the 52-week Main Period	0	1 (2)	1 (1.3)
Other	0	1 (2)	1 (1.3)
Rolled over into Extension Period	28 (100)	48 (98)	76 (98.7)
Early withdrawal from treatment in Extension Period	1 (3.6)	0	1 (1.3)
Adverse event	1 (3.6)	0	1 (1.3)
Early withdrawal from trial during the Extension Period	0	0	0

Source: Data compiled from trial 4467 ADSL datasets and from the Clinical Trial Report for trial 4467 NS, Table 4-1, page 46.

ISS

A total of 142 subjects were screened, of whom 54 subjects were screening failures (the majority of which were related to not meeting eligibility criteria related to bone age. A total of 88 subjects were randomized 2:1 to either 0.24 mg/kg/week somapacitan or 0.05 mg/kg/day Norditropin. However, one subject randomized to somapacitan was not exposed to treatment as this subject was randomized in violation of the inclusion criterion related to bone age. Thus, 87/88 randomized subjects were exposed to at least one dose of study drug: 59 and 28 subjects in the 0.24 mg/kg/week somapacitan and 0.05 mg/kg/day Norditropin groups, respectively.

A total of 85/88 (96.6%) randomized subjects completed 52 weeks of treatment in the completed Main Period of the trial. One subject who was not exposed to the drug is described above. Two additional subjects who stopped treatment early were in the somapacitan group: one subject discontinued treatment and withdrew from the trial prematurely after being lost to follow up and one subject stopped treatment prematurely, due to parent decision, but remained in the Main Period of the trial.

All 85 subjects who completed the 52-week Main Period of the trial rolled over into the Extension Period of the trial. Of the subjects enrolled in the ongoing Extension Period, 3/85 (3.5%) discontinued treatment prematurely in the Extension Period. One subject stopped treatment due to an AE (headache, see Section 8.3.5), but remained in the trial. Two subjects stopped treatment early in the Extension Period due to “withdrawal by subject” and both withdrew from the trial early.

Refer to Table 4 for subject disposition of subjects with ISS in trial 4467.

Table 4. ISS Subject Disposition, Trial 4467

Treatment	0.05 mg/kg/day Norditropin (N=28) n (%)	0.24 mg/kg/week Somapacitan (N=60) n (%)	Total (N = 88) n (%)
Exposed in 52-week Main Period	28 (100)	59 (98.3)	87 (98.9)
Completed treatment in the 52-week Main Period	28 (100)	57 (95)	85 (96.6)
Early withdrawal from treatment in 52-week Main Period	0	2 (3.3)	2 (2.3)
Parent decision	0	1 (1.7)	1 (1.1)
Lost to follow up	0	1 (1.7)	1 (1.1)
Early withdrawal from trial during the 52-week Main Period	0	1 (1.7)	1 (1.1)
Lost to follow up	0	1 (1.7)	1 (1.1)
Rolled over into Extension Period	28 (100)	57 (98)	85 (96.6)
Early withdrawal from treatment in Extension Period	1 (3.6)	2 (3.3)	3 (3.4)
Withdrawal by subject	0	2 (3.3)	2 (2.3)
Adverse event	1 (3.6)	0	1 (1.1)
Early withdrawal from trial during the Extension Period	0	2 (3.3)	2 (2.3)
Withdrawal by subject	0	2 (3.3)	2 (2.3)

Source: Data compiled from trial 4467 ADSL datasets and from the Clinical Trial Report for trial 4467 ISS, Table 4-1, page 48.

8.1.1.8. Protocol Violations/Deviations

SGA

The Applicant reported 22, 25, and 47 protocol deviations in the 37, 35, and 69 subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups, and the somapacitan group, respectively of the SGA population (see Table 51 in Section 15.4.2). The most common of these protocol deviations related to study procedures/assessments (related to missing entries in eDiaries, deviations to the maximum amount of blood to be drawn, late signing of lab reports, or PK and PD or Week 52 assessments outside the visit window), informed consent, treatment administration (related to missing doses or missing entries in eDiaries), or eligibility criteria (related to height SDS > -2 [the subject did not receive treatment], abnormalities likely to affect growth, lack of assessments of length at birth, BMI < -2 SDS, HbA1c assessment not available [when acquired, the value did not exceed the eligibility criteria]).

NS

The Applicant reported 34 and 56 protocol deviations in the 28 and 49 subjects of the 0.05 mg/kg/day Norditropin and somapacitan groups, respectively, of the NS population (see Table 52 in Section 15.4.2). The most common of these protocol deviations related to study procedures/assessments (related to missing entries in eDiaries, deviations to the maximum amount of blood to be drawn, missing echocardiograms, late signing of lab reports, or Week 52 assessments outside the visit window), informed consent, or treatment administration (related to missing doses or missing entries in eDiaries).

ISS

In the ISS population, the Applicant reported 17 and 26 protocol deviations in the 28 and 59 subjects of the 0.05 mg/kg/day Norditropin and somapacitan groups, respectively, and 5 protocol deviations in children who were not allocated in the trial (see Table 53 in Section 15.4.2). The most common of these protocol deviations related to study procedures/assessments (related to missing entries in eDiaries, deviations to the maximum amount of blood to be drawn, or Week 52 assessments outside the visit window), informed consent, eligibility criteria (height SDS > -2.5, bone age delayed more than 2 years, abnormalities likely to affect growth, or lacked a GH stimulation test within the prior 18 months), or treatment administration (related to missing doses or missing entries in eDiaries).

Conclusions

The protocol deviations were reviewed. Overall, the number of any one type of subject protocol deviation was small and relatively evenly distributed among the treatment arms, and therefore unlikely to have an impact on the overall results of trial 4467 for any proposed indication.

8.1.1.9. Baseline Demographic and Disease Characteristics

The demographic characteristics were overall well balanced between treatment groups in each sub-trial.

Of the 142 subjects born SGA who were enrolled and randomized in trial 4467, the proportion of enrolled females (50% to 55%) and males (45% to 50%) were comparable across all treatment arms. The majority of subjects (62.7%) were under 6 years old, and the mean (SD) age was 5.5 (1.9) years (range: 2.6 to 10.7 years of age).

Of the 77 subjects with NS who were enrolled and randomized in trial 4467, in both treatment arms there were more males (approximately 60%) than females (approximately 40%). Overall, there was a comparable proportion of subjects enrolled who were < 6 years of age (49.4%) compared to those ≥ 6 years of age (50.6%), with a mean (SD) age of 6.2 (2.3) years (range: 2 to 11.1 years old).

Of the 88 subjects with ISS who were enrolled and randomized in trial 4467, in both treatment arms there were more females (approximately 60%) than males (approximately 40%). The majority of subjects (63.6%) were ≥ 6 years old, and the mean (SD) age was 6.9 (2.1) years (range: 2.8 to 10.8 years of age).

Approximately 9.2%, 5.2%, and 13.6% of subjects born SGA, or diagnosed with NS or ISS, respectively, were from the United States (U.S.) and other subjects were from Mexico, South Africa, South America, Europe, and Asia. The preponderance of non-U.S. subjects is acceptable. In general, the diagnostic criteria within each individual diagnosis are not dependent on whether they are diagnosed in or outside of the U.S. Manifestations and management of each individual diagnosis also generally do not vary greatly based on the area

of enrollment. Thus, the efficacy and safety data on somapacitan use obtained from subjects from other countries are applicable to U.S. subjects.

Refer to Table 5, Table 6, and Table 7 for baseline demographics of the SGA, NS, and ISS populations, respectively, in trial 4467.

Table 5. Baseline Demographics of the SGA Population, Trial 4467

Demographics	0.035 mg/kg/day Norditropin (N=37)	0.067 mg/kg/day Norditropin (N=35)	0.24 mg/kg/week Somapacitan (N=70)	Total (N = 142)
Sex, n (%)				
Female	20 (54)	18 (51.4)	35 (50)	73 (51.4)
Male	17 (46)	17 (48.6)	35 (50)	69 (48.6)
Age, years				
Mean (SD)	5.6 (2)	5.4 (1.8)	5.6 (2)	5.5 (1.9)
Min, Max	2.8, 10.7	2.6, 9.4	2.6, 10.1	2.6, 10.7
Number of subjects above and below 6 years old, n (%)				
< 6 years	23 (62.2)	22 (62.9)	44 (62.9)	89 (62.7)
≥ 6 years	14 (37.8)	13 (37.1)	26 (37.1)	53 (37.3)
Race, n (%)				
Asian	18 (48.6)	10 (28.6)	23 (32.9)	51 (35.9)
Black or African American	0	0	2 (2.9)	2 (1.4)
White	17 (46)	24 (68.6)	42 (60)	83 (58.5)
Not reported	2 (5.4)	1 (2.9)	3 (4.3)	6 (4.2)
Ethnicity, n (%)				
Hispanic or Latino	6 (16.2)	2 (5.7)	6 (8.6)	14 (9.9)
Not Hispanic or Latino	30 (81.1)	30 (85.7)	59 (84.3)	119 (83.8)
Not reported	1 (2.7)	3 (8.6)	5 (7.1)	9 (6.3)
Country, n (%)				
Belgium	0	2 (5.7)	1 (1.4)	3 (2.1)
Brazil	0	0	4 (5.7)	4 (2.8)
Bulgaria	3 (8.1)	4 (11.4)	1 (1.4)	8 (5.6)
China	4 (10.8)	3 (8.6)	7 (10)	14 (9.9)
Croatia	0	1 (2.9)	0	1 (0.7)
Finland	3 (8.1)	0	0	3 (2.1)
France	1 (2.7)	1 (2.9)	2 (2.9)	4 (2.8)
Germany	0	1 (2.9)	0	1 (0.7)
Greece	3 (8.1)	1 (2.9)	2 (2.9)	6 (4.2)
India	3 (8.1)	1 (2.9)	1 (1.4)	5 (3.5)
Israel	0	0	6 (8.6)	6 (4.2)
Italy	1 (2.7)	0	3 (4.3)	4 (2.8)
Japan	5 (13.5)	3 (8.6)	8 (11.4)	16 (11.3)
Korea	2 (5.4)	1 (2.9)	1 (1.4)	4 (2.8)
Malaysia	0	1 (2.9)	3 (4.3)	4 (2.8)
Mexico	4 (10.8)	2 (5.7)	4 (5.7)	10 (7)
Poland	0	5 (14.3)	6 (8.6)	11 (7.8)
Portugal	0	1 (2.9)	1 (1.4)	2 (1.4)
Serbia	1 (2.7)	0	3 (4.3)	6 (4.2)

Demographics	0.035 mg/kg/day Norditropin (N=37)	0.067 mg/kg/day Norditropin (N=35)	0.24 mg/kg/week Somapacitan (N=70)	Total (N = 142)
Slovenia	0	0	1 (1.4)	1 (0.7)
South Africa	0	1 (2.9)	1 (1.4)	2 (1.4)
Spain	0	2 (5.7)	4 (5.7)	6 (4.2)
Switzerland	0	0	1 (1.4)	1 (0.7)
Thailand	3 (8.1)	1 (2.9)	3 (4.3)	7 (4.9)
United Kingdom	1 (2.7)	0	1 (1.4)	2 (1.4)
United States	3 (8.1)	4 (11.4)	6 (8.6)	13 (9.2)

Source: Clinical Trial Report for trial 4467, SGA, Table 4-4, page 53; and Table 4-5, page 54.

Table 6. Baseline Demographics of the NS Population, Trial 4467

Demographics	0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=49)	Total (N = 77)
Sex, n (%)			
Female	11 (39.3)	19 (38.8)	30 (39)
Male	17 (60.7)	30 (61.2)	47 (61)
Age, years			
Mean (SD)	6.1 (2.2)	6.2 (2.5)	6.2 (2.3)
Min, Max	2, 10.3	2.6, 11.1	2, 11.1
Number of subjects above and below 6 years old, n (%)			
< 6 years	15 (53.6)	23 (46.9)	38 (49.4)
≥ 6 years	13 (46.4)	26 (53.1)	39 (50.6)
Race, n (%)			
Asian	9 (32.1)	15 (30.6)	24 (31.2)
Black or African American	0	4 (8.2)	4 (5.2)
Multiple	1 (3.6)	0	1 (1.3)
White	14 (50)	25 (51)	39 (50.6)
Not reported	4 (14.3)	5 (10.2)	9 (11.7)
Ethnicity, n (%)			
Hispanic or Latino	0	1 (2)	1 (1.3)
Not Hispanic or Latino	24 (85.7)	44 (89.8)	68 (88.3)
Not reported	4 (14.3)	4 (8.2)	8 (10.4)
Country, n (%)			
Belgium	0	2 (4.1)	2 (2.6)
Brazil	1 (3.6)	4 (8.2)	5 (6.5)
Bulgaria	0	3 (6.1)	3 (3.9)
China	2 (7.1)	6 (12.2)	8 (10.4)
France	3 (10.7)	3 (6.1)	6 (7.8)
Greece	1 (3.6)	1 (2)	2 (2.6)
India	0	1 (2)	1 (1.3)
Israel	1 (3.6)	0	1 (1.3)
Italy	2 (7.1)	6 (12.2)	8 (10.4)
Japan	5 (17.9)	4 (8.2)	9 (11.7)
Korea	0	1 (2)	1 (1.3)
Latvia	1 (3.6)	1 (2)	2 (2.6)
Lithuania	0	1 (2)	1 (1.3)
Malaysia	1 (3.6)	1 (2)	2 (2.6)
Poland	2 (7.1)	2 (4.1)	4 (5.2)
Portugal	0	2 (4.1)	2 (2.6)

Demographics	0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=49)	Total (N = 77)
Saudi Arabia	0	1 (2)	1 (1.3)
Serbia	2 (7.1)	1 (2)	3 (3.9)
Slovenia	0	1 (2)	1 (1.3)
South Africa	1 (3.6)	2 (4.1)	3 (3.9)
Spain	1 (3.6)	2 (4.1)	3 (3.9)
Thailand	1 (3.6)	2 (4.1)	3 (3.9)
United Kingdom	1 (3.6)	1 (2)	2 (2.6)
United States	3 (10.7)	1 (2)	4 (5.2)

Source: Clinical Trial Report for trial 4467, NS, Table 4-4, page 52; and Table 4-5 page 53.

Table 7. Baseline Demographics of the ISS Population, Trial 4467

Demographics	0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=60)	Total (N = 88)
Sex, n (%)			
Female	17 (60.7)	35 (58.3)	52 (59.1)
Male	11 (39.3)	25 (41.7)	36 (40.9)
Age, years			
Mean (SD)	6.7 (2)	7.1 (2.1)	6.9 (2.1)
Min, Max	3.4, 10.5	2.8, 10.8	2.8, 10.8
Number of subjects above and below 6 years old (%)			
< 6 years	10 (35.7)	22 (36.7)	32 (36.4)
≥ 6 years	18 (64.3)	38 (63.3)	56 (63.6)
Race, n (%)			
American Indian or Alaska Native	0	1 (1.7)	1 (1.1)
Asian	7 (25)	19 (31.7)	26 (29.6)
Black or African American	0	1 (1.7)	1 (1.1)
Multiple	1 (3.6)	1 (1.7)	2 (2.3)
White	19 (67.9)	37 (61.7)	56 (63.6)
Not reported	1 (3.6)	1 (1.7)	2 (2.3)
Ethnicity, n (%)			
Hispanic or Latino	3 (10.7)	10 (16.7)	13 (14.8)
Not Hispanic or Latino	25 (89.3)	48 (80)	73 (83)
Not reported	0	2 (3.3)	2 (2.3)
Country, n (%)			
Brazil	2 (7.1)	5 (8.3)	7 (8)
Bulgaria	1 (3.6)	3 (5)	4 (4.5)
China	3 (10.7)	5 (8.3)	8 (9.1)
Germany	0	2 (3.3)	2 (2.3)
Greece	2 (7.1)	5 (8.3)	7 (8)
India	0	1 (1.7)	1 (1.1)
Israel	4 (14.3)	9 (15)	13 (14.8)
Japan	2 (7.1)	6 (10)	8 (9.1)
Korea	1 (3.6)	4 (6.7)	5 (5.7)
Latvia	1 (3.6)	0	1 (1.1)
Lithuania	1 (3.6)	0	1 (1.1)
Mexico	0	2 (3.3)	2 (2.3)
Poland	3 (10.7)	3 (5)	6 (6.8)
Portugal	0	1 (1.7)	1 (1.1)
Saudi Arabia	1 (3.6)	1 (1.7)	2 (2.3)

Demographics	0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=60)	Total (N = 88)
Slovenia	0	1 (1.7)	1 (1.1)
Spain	1 (3.6)	1 (1.7)	2 (2.3)
Thailand	0	3 (5)	3 (3.4)
United Kingdom	1 (3.6)	1 (1.7)	2 (2.3)
United States	5 (17.9)	7 (11.7)	12 (13.6)

Source: Clinical Trial Report for trial 4467, ISS, Table 4-4, pages 53; and Table 4-5, page 54.

In general, the baseline disease characteristics within each diagnosis were overall comparable across the treatment groups of each sub-trial. The baseline disease characteristics of subjects in each of the sub-trials of trial 4467 are generally consistent with those of pediatric patients with short stature associated with SGA, NS, and ISS routinely seen in clinical practice.

Mean baseline height SDS was below normal (i.e., height < -2 SDS) for all treatment arms in each sub-trial, consistent eligibility criteria and with a diagnosis of short stature and was comparable across treatment groups within each sub-trial. While the mean baseline AHV SDS was not below normal (i.e., normal: -2 < AHV SDS < 2) for all treatment groups in each sub-trial, this was not an eligibility criterion, nor is it necessary for these diagnoses. Further, mean baseline AHV was at the lower end of normal and comparable across treatment groups within each sub-trial. Finally mean baseline IGF-1 SDS values in all treatment groups of all sub-trials were within the normal range (i.e., -2 < IGF-1 SDS < 2), indicating sufficient GH status, and was comparable across treatment groups within each sub-trial.

Refer to Table 8, Table 9, and Table 10 for baseline characteristics of the SGA, NS, and ISS populations, respectively, in trial 4467.

For the SGA sub-trial, as discussion in Section 3.2, FDA recommended that the Applicant also stratify randomization based on baseline height SDS. This is because children with short stature associated with SGA who have more severe height deficiency at baseline may respond differently to growth promoting treatment. While the protocol did not include this stratification, it is reassuring that in the maximum dose (i.e., 0.067 mg/kg/day) Norditropin group and the somapacitan group, there is a comparable proportion of subjects with baseline height SDS -2.5 to -3 (51.4% and 54.3%, respectively) and with baseline height SDS < -3 (42.9% and 41.4%, respectively).

For the NS sub-trial, subjects were tested for pathogenic variants consistent with a diagnosis of NS. In 5/49 (10.2%) subjects in the somapacitan arm, no pathogenic variants were identified in the genetic panel tested; these subjects were enrolled based on clinical diagnosis. See Table 59, in Section 15.4.3, for results of genetic analyses. Overall, there is a wide distribution of different genetic variants among the treatment arms in the NS sub-trial, and, as discussed in Section 2.1, there is genotypic heterogeneity of NS. However, given comparable baseline characteristics between the treatment arms, specifically regarding height SDS and AHV, it is unlikely that the distribution of different genetic variants among the treatment arms will significantly impact assessment of trial results.

For ISS sub-trial, eligibility criteria required that all subjects have documented GH peak > 7 ng/mL after provocative testing. Only one randomized subject, in the somapacitan group, did

not meet this criterion, however, as discussed in Subject Disposition, above, this subject was not treated in the trial as this subject was randomized in violation of the inclusion criterion related to bone age. The mean (SD) GH peak was comparable between the two arms at 14.3 (7.1) ng/mL and 14.9 (6.4) ng/mL in the Norditropin and somapacitan arms, respectively.

Table 8. Baseline Characteristics of the SGA Population, Trial 4467

Characteristics	0.035 mg/kg/day Norditropin (N=37)	0.067 mg/kg/day Norditropin (N=35)	0.24 mg/kg/week Somapacitan (N=70)	Total (N = 142)
Mean (SD)				
AHV (cm/year)	5.1 (1.4)	5 (1.6)	5 (1.4)	5 (1.5)
AHV SDS	-1.7 (1.5)	-2.1 (1.4)	-2 (1.2)	-1.9 (1.3)
IGF-1 SDS	-0.6 (1.2)	-0.5 (1.1)	-0.5 (1.2)	-0.6 (1.2)
Height SDS	-3 (0.6)	-3.2 (0.8)	-3 (0.6)	-3 (0.7)
Height SDS, n (%)				
> -2.5	5 (13.5)	2 (5.7)	3 (4.3)	10 (7)
-2.5 to -3	21 (56.8)	18 (51.4)	38 (54.3)	77 (54.2)
< -3	11 (29.7)	15 (42.9)	29 (41.4)	55 (38.7)

Source: Clinical Trial Report for trial 4467, SGA, Table 4-4, page 53; Table 4-5, page 54; Table 8.2.8, pages 186 to 187; and Table 8.2.46, pages 229 to 230.

Table 9. Baseline Characteristics of the NS Population, Trial 4467

Characteristics	0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=49)	Total (N = 77)
Mean (SD)			
AHV (cm/year)	4.6 (1.8)	5.1 (2.1)	4.9 (2)
AHV SDS	-2.1 (2.2)	-1.6 (2.4)	-1.8 (2.3)
IGF-1 SDS	-1.5 (0.8)	-1.3 (1.1)	-1.3 (1)
Height SDS	-2.6 (0.7)	-2.7 (0.6)	-2.7 (0.6)
Height SDS, n (%)			
> -2	4 (14.3)	1 (2)	5 (6.5)
-2 to -3	16 (57.1)	34 (69.4)	50 (64.9)
< -3	8 (28.6)	14 (28.6)	22 (28.6)

Source: Clinical Trial Report for trial 4467, NS, Table 4-4, page 52; Table 4-5, page 53; Table 8.2.8, page 162; and Table 8.2.42, page 196.

Table 10. Baseline Characteristics of the ISS Population, Trial 4467

Characteristics	0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=60)	Total (N = 88)
Mean (SD)			
AHV (cm/year)	4.7 (1.6)	5.1 (1.8)	4.9 (1.7)
AHV SDS	-1.9 (1.5)	-1.2 (2.2)	-1.4 (2)
IGF-1 SDS	-1 (0.8)	-0.9 (0.9)	-0.9 (0.9)
GH peak (ng/mL)	14.3 (7.1)	14.9 (6.4)	14.7 (6.6)
Height SDS	-2.9 (0.5)	-2.8 (0.3)	-2.8 (0.4)

Characteristics	0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=60)	Total (N = 88)
Height SDS, n (%)			
> -2.5	5 (17.9)	3 (5)	8 (9.1)
-2.5 to -3	14 (50)	44 (73.3)	58 (65.9)
< -3	9 (32.1)	13 (21.7)	22 (25)

Source: Clinical Trial Report for trial 4467, ISS, Table 4-4, page 53; Table 4-5, page 54; Table 8.2.8, page 150; Table 8.2.42, page 184; and clinical reviewer assessment from JMP clinical analysis.

8.1.1.10. Comorbidities

The most commonly (≥ 5% of subjects in any treatment arm) reported comorbidities of the SGA population were small for dates baby (an expected diagnosis given the proposed indication), asthma, dermatitis atopic, eczema, rhinitis allergic, food allergy, atrial septal defect, cardiac murmur, conjunctivitis allergic, retinopathy of prematurity, cerebral palsy, constipation, and gastroesophageal reflux disease (GERD). See Table 60 in Section 15.4.3. Overall, the incidence of comorbidities in the SGA population is small and, with the exception of asthma, they are reported in comparable proportions across the treatment groups. Further, it is unlikely that that any of the most commonly reported comorbidities in the SGA population, including asthma, would have a significant impact on growth or thus the analysis of efficacy of somapacitan.

The most commonly (≥ 5% of subjects in either treatment arm) reported comorbidities of the NS population were Noonan syndrome (an expected diagnosis given the proposed indication), pulmonary valve and pulmonary artery stenosis, atrial septal defect and repair, ventricular septal defect, cryptorchidism and orchidopexy, constipation, pneumonia, psychomotor retardation, developmental delay, eyelid ptosis, and von Willebrand's disease. See Table 61 in Section 15.4.3. As discussed in Section 2.1, many of these comorbidities, such as congenital heart diseases and cryptorchidism, are not uncommon in patients diagnosed with NS. Significant congenital cardiac defects may have an impact on growth, however, overall, a comparable proportion of subjects in the Norditropin arm (13/28 [46.4%] subjects) compared to the somapacitan arm (20/49 [40.8%] subjects) reported at least one of these most commonly reported comorbidities related to congenital cardiac defects (i.e., pulmonary valve and pulmonary artery stenosis, atrial septal defect and repair, ventricular septal defect). The incidence of the other most commonly reported comorbidities in this population is small and include comorbidities unlikely to have a significant impact on the analysis of efficacy of somapacitan.

The most commonly (≥ 5% of subjects in either treatment arm) reported comorbidities of the ISS population were short stature, seasonal allergy, constipation, rhinitis, asthma, adenoidectomy, ear tube insertion, and tongue tie operation. See Table 62 in Section 15.4.3. Overall, the incidence of comorbidities in the SGA population is small and, with the exception of asthma, adenoidectomy, ear tube insertion, and tongue tie operation, they are reported in comparable proportions across the treatment groups. It is unlikely that any of the most commonly reported comorbidities in the ISS population would have a significant impact on growth or thus the analysis of efficacy of somapacitan.

8.1.1.11. Concomitant Medications

The most commonly reported (≥ 10% of subjects in any treatment group in any sub-trial) concomitant medications were consistent with medications taken in the general pediatric population and include analgesics/antipyretics (such as paracetamol and ibuprofen), mucolytics (such as ambroxol and carbocisteine), antihistamines/antiallergy medications (such as loratadine, chlorphenamine, and olopatadine), antibiotics (such as azithromycin, clarithromycin, and amoxicillin), antivirals (such as oseltamivir and acyclovir), antiasthma therapy (such as salbutamol, montelukast, and tulobutamol), cough suppressants (such as tipepidine and dextromethorphan), vitamin D supplements and other multivitamins, and steroids (such as budesonide and fluticasone). See Table 63, Table 64, and Table 65, in Section 15.4.3, for the most commonly reported concomitant medications in the SGA, NS, and ISS populations, respectively. While treatment with inhaled steroids and systemic corticosteroids may impact growth, the eligibility criteria excluded the use of such medications at doses that are likely to suppress growth (see Section 15.4.1 for the full inclusion and exclusion criteria for trial 4467). It is unlikely that any of the most commonly reported concomitant medications in any of the indicated populations had a significant impact on growth or thus the analysis of efficacy of somapacitan.

8.1.1.12. Treatment Compliance

Treatment compliance was assessed by recording of doses and missed doses, comparing prescribed and actual doses, adherence, drug accountability information (counting of returned trial product, visual inspection of pens), and review of the subjects' eDiaries, and all were documented at site visits and confirmed by site staff. Overall, appropriate measures were taken to ensure treatment compliance.

The majority of the subjects in the SGA, NS, and ISS sub-trials received the planned treatment. In the SGA sub-trial, the mean (SD) adherence was 94.7 (6.9)%, 93.6 (10.9)%, and 91.8 (18.8)% in the 0.035 mg/kg/day and 0.067 mg/kg/day Norditropin groups, and the somapacitan group, respectively. In the NS sub-trial, the mean (SD) adherence was 88.3 (1.3)% and 86.2 (19.9)% for the Norditropin and somapacitan groups, respectively. In the ISS sub-trial, the mean (SD) adherence was 88.8 (14.1)% and 84.8 (26.2)% in the Norditropin and somapacitan groups, respectively.

8.1.1.13. Efficacy Results–Primary Endpoint and Key Secondary Endpoints

This trial met the primary efficacy endpoint in all prespecified populations of subjects.

SGA

For the primary endpoint, the primary analysis confirmed the non-inferiority of 0.24 mg/kg/week somapacitan versus both the doses of Norditropin (0.067 mg/kg/day and 0.035 mg/kg/day) with respect to NI margin of -1.6 cm/year. Somapacitan demonstrated statistical superiority over low-dose Norditropin (treatment difference of 1.6 cm/year with 95% C.I.

[0.91; 2.23]) but failed to demonstrate superiority versus high-dose Norditropin (treatment difference of -0.1 cm/year with 95% CI [-0.75; 0.60]).

Table 11. Primary Analysis of Annualized Height Velocity (Cm/Year) at Week 52 (FAS): SGA Population

Characteristic	0.24 mg/kg/week Somapacitan (N=70)	0.035 mg/kg/day Norditropin (N=37)	0.067 mg/kg/day Norditropin (N=35)
Annualized Height Velocity (cm/year)(SE)	11.0 (0.23)	9.4 (0.25)	11.1 (0.30)
Treatment difference (95% CI)*		1.6 [0.91; 2.23] p-value < 0.001	-0.1 [-0.75; 0.60] p-value=0.823

Source: Statistical Reviewer's analysis
*Treatment difference (Height Velocity of somapacitan - daily Norditropin)
Height velocity at week 52 was analyzed using an ANCOVA model with treatment, [redacted], age group, region, height SDS (<-3 or >=-3) and [redacted] by age group by region interaction term as factors, and baseline height and baseline IGF-I SDS as covariates. There was no missing value at week 52, no multiple imputation was done.
SE: Standard Error

There was no missing Week 52 height assessment. Since the randomization ratio was 2:1:1, the Statistics reviewer performed an additional analysis of covariance (ANCOVA) with unequal variance to account for possible unequal residual variances between groups. However, the least square mean treatment differences (95% CI) obtained from ANCOVA model adjusted for unequal variances were 1.6cm/year (95% CI [0.94 ; 2.21]) and -0.1cm/year (95% C.I. [-0.77 ; 0.61]) versus low-dose and high-dose Norditropin respectively which are almost identical to what was observed in the primary analysis in Table 11.

NS

Non-inferiority of somapacitan versus Norditropin for the primary endpoint was confirmed for the primary analysis with respect to NI margin of -1.6cm/year. Superiority for AHV at Week 52 for somapacitan 0.24 mg/kg/week versus Norditropin was also demonstrated with statistically significant treatment difference of 1.2 cm/year (95% CI [0.32; 2.03]).

Table 12. Primary Analysis of Annualized Height Velocity (Cm/Year) at Week 52 (FAS): NS Population

Characteristic	0.24 mg/kg/week Somapacitan (N=49)	0.05 mg/kg/day Norditropin (N=28)
Annualized Height Velocity (cm/year)(SE)	10.4 (0.23)	9.2 (0.43)
Treatment Difference (95% CI)*		1.2 [0.32; 2.03] p-value=0.0071

Source: Statistical Reviewer's analysis
*Estimated treatment difference (Height Velocity of somapacitan - Daily Norditropin)
SE: Standard Error; CI: 95% Confidence Interval
Height velocity at week 52 was analyzed using an analysis of covariance model with treatment, [redacted], age group, region, height SDS (<-3 or >=-3) and [redacted] by age group by region interaction term as factors, and baseline height and baseline IGF-I SDS as covariates.
There was one missing value at week 52 from somapacitan arm and was multiply imputed using available data from the Norditropin arm.

One participant from the somapacitan group discontinued and withdrew from the study due to moving to a different country. This resulted in one missing height assessment at Week 52, corresponding to the same subject. A sensitivity analysis using multiple imputation under the non-inferiority null hypothesis (i.e. subtracting 1.6 cm/year from each imputed values) yielded treatment difference and 95% CI nearly identical to the primary analysis. An ANCOVA model adjusted for unequal variances produced similar results.

ISS

Non-inferiority of somapacitan versus Norditropin for the primary endpoint was confirmed for the primary analysis with respect to NI margin of -1.6cm/year. Superiority for AHV at Week 52 for somapacitan 0.24 mg/kg/week versus Norditropin was not demonstrated (treatment difference of -0.3 cm/year and 95% CI [-1.00; 0.42]).

Table 13. Primary Analysis of Annualized Height Velocity (Cm/Year) at Week 52 (FAS): ISS Population

Characteristic	0.24 mg/kg/week Somapacitan (N=60)	0.05 mg/kg/day Norditropin (N=28)
Annualized Height Velocity (cm/year) (SE)	10.2 (0.22)	10.5 (0.30)
Treatment difference (95% CI)*		-0.3 [-1.00; 0.42] p-value=0.4107

Source: Statistical Reviewer's analysis
*Estimated treatment difference (Height Velocity of somapacitan - Daily Norditropin)
SE: Standard Error; CI: 95% Confidence Interval
Height velocity at week 52 is analysed using an analysis of covariance model with treatment, [redacted], age group, region, height SDS (<-3 or >=-3) and [redacted] by age group by region interaction term as factors, and baseline height and baseline IGF-I SDS as covariates.
There was one missing value at week 52 from somapacitan arm and was multiply imputed using available data from the Norditropin arm.

Two participants in the somapacitan group discontinued the trial product. One participant withdrew from the study entirely, while the other completed the full 52-week treat period. One missing height assessment occurred at Week 52, corresponding to the participant who withdrew from the study. A sensitivity analysis using multiple imputation under the non-inferiority null hypothesis (i.e. subtracting 1.6 cm/year from imputed values) produced treatment differences and 95% CI nearly identical to the primary analysis. Similarly, an ANCOVA model adjusted for unequal variances showed similar results as what was observed in the primary analysis.

Subgroup Analyses

The efficacy of somapacitan on the primary endpoint (AHV after 52 weeks) was evaluated in different intrinsic subgroups including demographic factors (age, sex, race and region). The evaluation was based on study 4467. The results from sub-population analysis followed the same trends as for the entire study population in both the somapacitan and Norditropin group. We also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. A shrinkage estimates of the subgroup treatment effect, which borrows information from the other subgroups while

estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage).

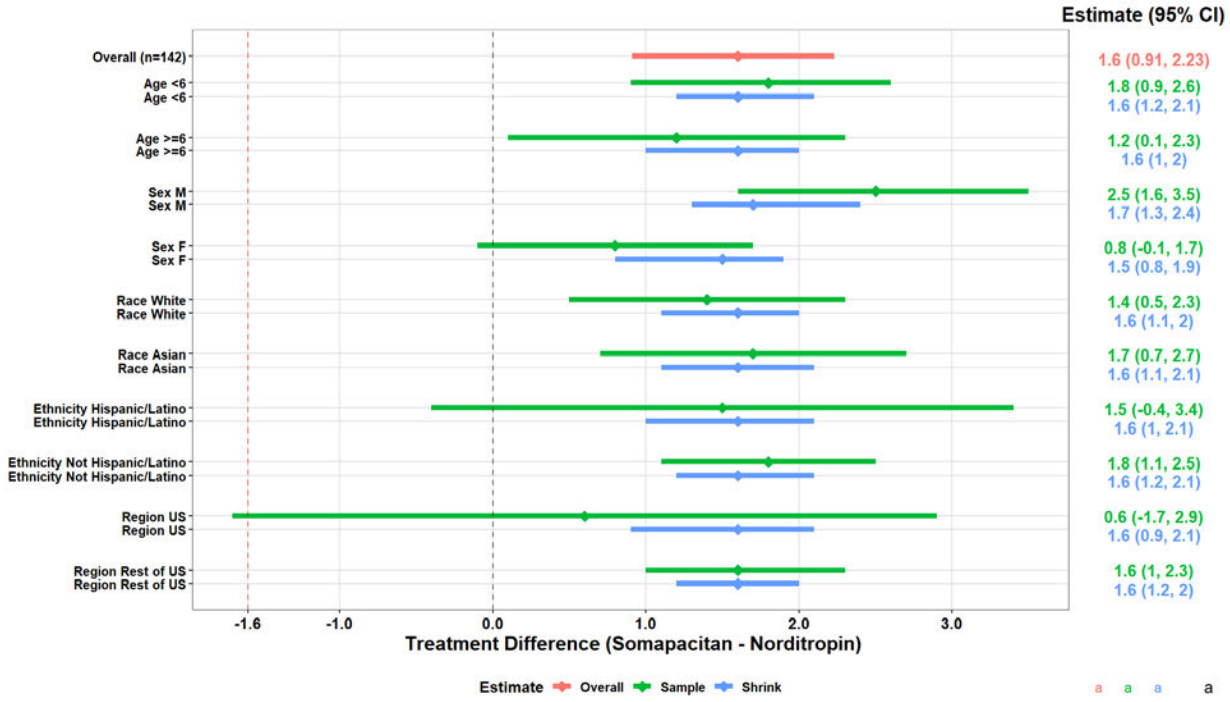
For i = 1, 2…, n; Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where:

- σ_i^2 are the observed variance for sample estimates,
- μ_i ~ N(μ, τ^2), and
- μ ~ N(0, 30), 1/τ^2 ~ Gamma(0.001, 0.001).

The variance of 30 for the hyper-prior $\mu \sim N(0,\ 30)$, was chosen as $4 \times n \times Observed\ S.E^2$. of the treatment effect.

SGA

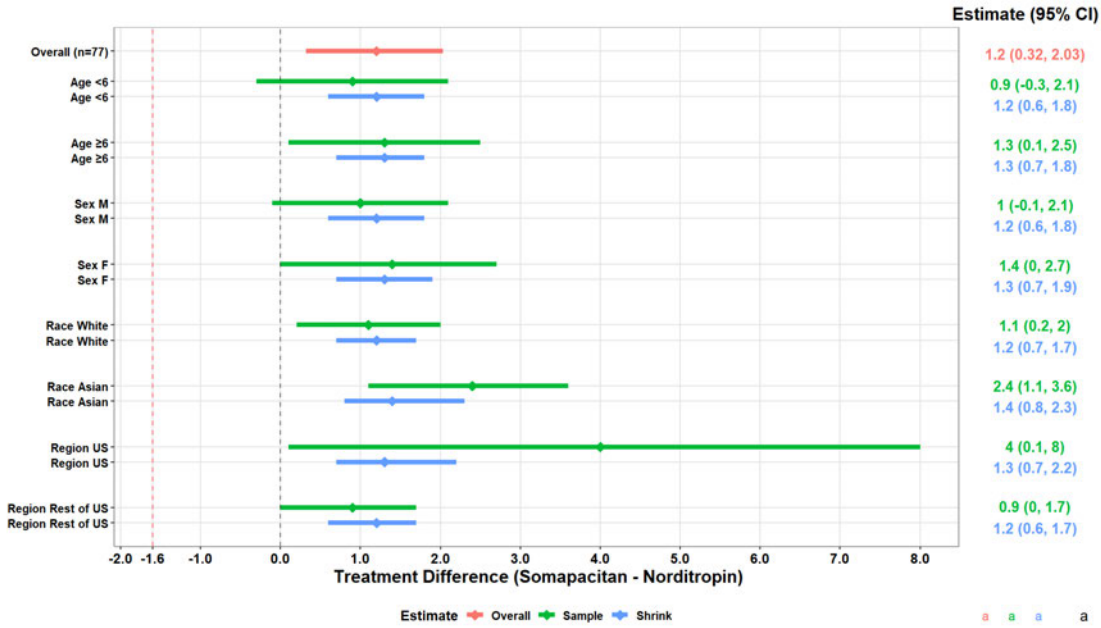
Figure 8. Subgroup Analyses AHV at Week 52 - Forest Plot (Full Analysis Set): Somapacitan vs Low Dose Norditropin (SGA Population)



Source: Statistical Reviewer's analysis.

NS

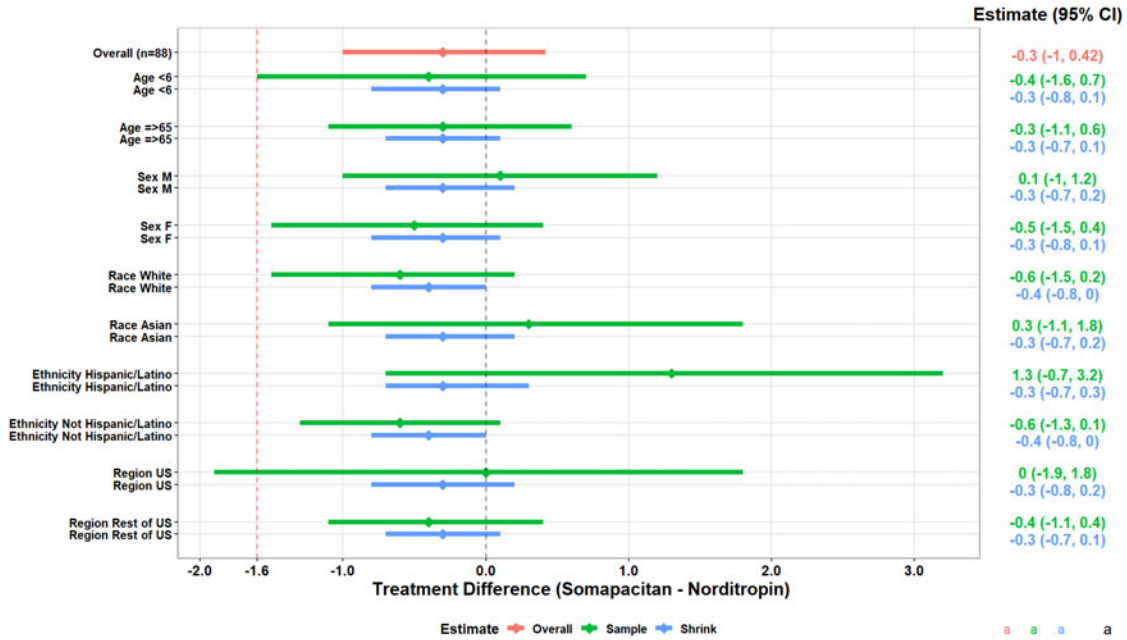
Figure 9. Subgroup Analyses AHV at Week 52 - Forest Plot (Full Analysis Set): NS Population



Source: Statistical Reviewer's analysis.
There was no sub-group analysis by ethnicity performed for the NS sub-study, since there was solely 1 participant in total with ethnicity Hispanic or Latino in this sub-study.

ISS

Figure 10. Subgroup Analyses AHV at Week 52 - Forest Plot (Full Analysis Set): ISS Population



Source: Statistical Reviewer's analysis.

8.1.1.14. Data Quality and Integrity

The Applicant's monitoring for data quality and integrity was acceptable. Refer to Office of Scientific Investigation review submitted to DARRTS on January 23, 2026.

8.1.1.15. Secondary Endpoints

The secondary efficacy endpoints were considered as supportive of the primary endpoint and will be summarized here. Overall, the analyses of data demonstrated improvement in all mean growth throughout the first 52 weeks in the pivotal phase 3 trial 4467 in subjects of all cohorts. However, given the secondary endpoints were not adjusted for multiplicity, caution is warranted when interpreting the results of the secondary endpoints.

SGA

For all the supportive secondary endpoints change from baseline in Height Velocity SDS, change from baseline in Height SDS and change from baseline in bone age to week 52, there were no statistically significant differences between the somapacitan group and the high-dose Norditropin group (Table 14). The change from baseline in Height SDS and Height Velocity SDS after 52 weeks was greater in the somapacitan group compared to the low-dose Norditropin group.

Table 14. Primary Analysis of Secondary Endpoints (Change From Baseline After 52 Weeks): SGA Population

Characteristic	0.24 mg/kg/week Somapacitan (N=70)	0.035 mg/kg/day Norditropin (N=37)	0.067 mg/kg/day Norditropin (N=35)	Treatment Difference (Somapacitan-0.035 mg/kg/day Norditropin) [95%CI]	Treatment Difference (Somapacitan-0.067 mg/kg/day Norditropin) [95%CI]
Height SDS	1.17	0.85	1.22	0.32 [0.18; 0.47]	-0.05 [-0.20; 0.10]
Height Velocity SDS	7.06	5.23	7.16	1.83 [1.06; 2.60]	-0.10 [-0.87; 0.68]
Bone age	0.07	0.03	0.08	0.04 [-0.01; 0.10]	-0.01 [-0.07; 0.04]

Source: Statistical Reviewer's analysis
Abbreviations: CI: confidence interval; ETD: estimated treatment difference; HSDS: height standard deviation score; HVSDS: height velocity standard deviation score

NS

For the supportive secondary endpoints, change from baseline to week 52 in Height Velicity SDS and in Height SDS, the changes were statistically significantly higher in the somapacitan group compared to the Norditropin group (Table 15). For the change from baseline to week 52 in bone age to chronological age ratio, there was almost no difference between somapacitan and Norditropin.

Table 15. Secondary Endpoints (Change From Baseline After 52 Weeks): FAS, NS Population

Characteristic	0.24 mg/kg/week Somapacitan (N=49)	0.05 mg/kg/day Norditropin (N=28)	Treatment Difference (Somapacitan-Daily Norditropin) [95% C.I.]
Height SDS	1.07	0.75	0.32 [0.16; 0.48]
Height Velocity SDS	6.30	5.24	1.06 [0.01; 2.10]
Bone age	0.02	0.03	-0.01 [−0.06; 0.03]

Source: Statistical Reviewer's analysis
Abbreviations: CI: confidence interval; ETD: estimated treatment difference; HSDS: height standard deviation score; HVSDS: height velocity standard deviation score

ISS

No differences were observed between somapacitan and Norditropin across all supportive secondary endpoints. (Table 16).

Table 16. Secondary Endpoints (Change From Baseline After 52 Weeks): FAS, ISS Population

Characteristic	0.24 mg/kg/week Somapacitan (N=60)	0.05 mg/kg/day Norditropin (N=28)	Treatment Difference (Somapacitan-Daily Norditropin) [95% C.I.]
HSDS	0.99	1.09	-0.10 [-0.24; 0.04]
HVSDS	5.98	6.51	-0.53 [-1.45; 0.39]
Bone age	0.04	0.01	0.03 [-0.01; 0.08]

Source: Statistical Reviewer's analysis
Abbreviations: CI: confidence interval; ETD: estimated treatment difference; HSDS: height standard deviation score; HVSDS: height velocity standard deviation score

8.1.1.16. Dose/Dose Response

As only one dose of somapacitan was evaluated in this trial, dose response cannot be assessed.

8.1.1.17. Durability of Response

Long-term response to somapacitan was assessed in the ongoing Extension Period of trial 4467, in which subjects randomized to somapacitan in the 52-week Main Period of the trial continued on 0.24 mg/kg/week somapacitan, and subjects randomized to any Norditropin arm of the 52-week Main Period of the trial were switched to 0.24 mg/kg/week somapacitan. Available data from subjects in the SGA, NS, and ISS populations who continued somapacitan therapy in the Extension Period demonstrated continued growth.

As of the database lock date, data from 32, 22, and 25 subjects in the SGA, NS, and ISS populations, respectively, who had been exposed to only 0.24 mg/kg/week somapacitan from the beginning of the trial, were available for up to 78 weeks (1.5 years) of therapy. Data from subjects only treated with 0.24 mg/kg/week somapacitan for 104 weeks (2 years) are more limited, as only 4, 2, and 9 subjects in the SGA, NS, and ISS populations, respectively, have available data, and thus interpretation of these data from Week 104 must be made with caution.

Data with continued treatment with somapacitan showed continued growth in all populations, though AHV decreased with continued treatment. This trend is expected, and a similar trend is observed during therapy with approved hGH products. Mean change in observed mean height SDS from baseline also showed continued improvement. Finally, mean bone age to chronological age ratio did not exceed one throughout therapy.

Growth parameters in subjects treated with 0.24 mg/kg/week somapacitan only :

- SGA cohort
  - Observed mean (SD) AHV at Week 52 was 11 (1.9) cm/year, at Week 78 was 8.8 (1.8) cm/year, and at Week 104 was 8.7 (1.4) cm/year.
  - Observed mean (SD) AHV SDS at Week 52 was 5.2 (2.1), at Week 78 was 2.9 (1.9), and at Week 104 was 2.6 (1.8).
  - Observed mean (SD) change from baseline in height SDS at Week 52 was 1.2 (0.4), at Week 78 was 1.5 (0.5), and at Week 104 was 2.2 (0.5).
- NS cohort
  - Observed mean (SD) AHV at Week 52 was 10.4 (1.6) cm/year, at Week 78 was 8.4 (1.5) cm/year, at Week 104 was 7.4 (0.7) cm/year.
  - Observed mean (SD) AHV SDS at Week 52 was 4.5 (2), at Week 78 was 2.7 (2), and at Week 104 was 0.6 (0.7).
  - Observed mean (SD) change from baseline in height SDS at Week 52 was 1.1 (0.3), at Week 78 was 1.3 (0.4), and at Week 104 was 1.1 (0.4).
- ISS cohort
  - Observed mean (SD) AHV at Week 52 was 10.2 (1.7) cm/year, at Week 78 was 8.6 (1.8) cm/year, at Week 104 was 7.6 (1.4) cm/year.
  - Observed mean (SD) AHV SDS at Week 52 was 4.5 (2.1), at Week 78 was 2.8 (2), and at Week 104 was 1.8 (1.2).
  - Observed mean (SD) change from baseline in height SDS at Week 52 was 1 (0.3), at Week 78 was 1.2 (0.4), and at Week 104 was 1.4 (0.4).

8.1.1.18. **Persistence of Effect**

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

8.1.1.19. **COA (PRO) Endpoints**

Five measures were used as exploratory endpoints to evaluate the change from baseline in treatment burden, parent preference, and impact on disease: GH-INJ-CTB, GH-INJ-PTB, GH-PPQ, SGA-CIM-O, and ISS-CIM-O. However, none of these PROs have been validated in the intended populations and thus interpretation of information derived from these PROs for the intended population is challenging, no meaningful conclusions can be drawn, and these data would not be eligible for inclusion in labeling.

8.1.2. Trial NN8640-4245 (Trial 4245)

A dose-finding trial evaluating the effect of and safety of once-weekly treatment of somapacitan compared to daily Norditropin® in children with short stature born small for gestational age with no catch-up growth by 2 years of age or older.

8.1.2.1. Trial Design

Trial 4245 is a dose-finding, randomized, open-label, five arm, active controlled, parallel group phase 2 trial that provides additional safety and efficacy data in GH treatment naïve pre-pubertal children with short stature born SGA with no catch-up growth by 2 years of age or older.

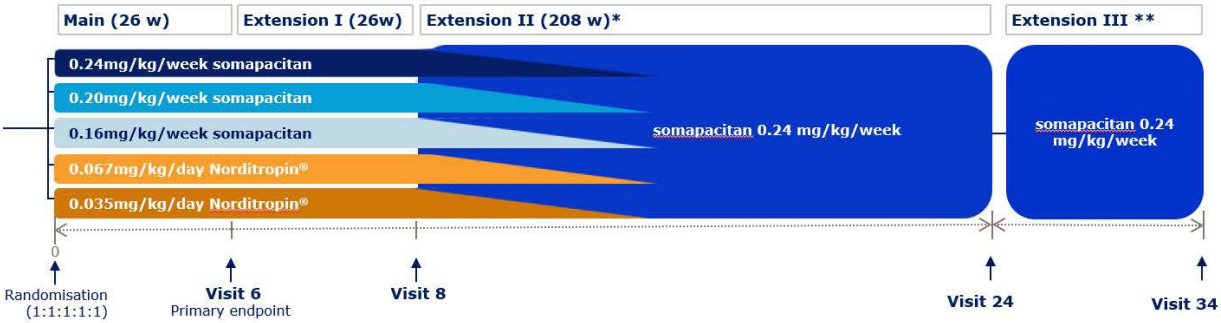
The primary objective of this trial is to evaluate the efficacy of 3 doses of once weekly somapacitan, compared to 2 doses of daily somatropin, as measured by AHV at Week 26 in children with short stature associated with SGA.

The secondary objectives were to compare the effect of 3 doses of weekly somapacitan and 2 doses daily somatropin on change in AHV, height SDS, AHV SDS, BA, PD, and safety over time in children with short stature associated with SGA.

The trial consisted of a screening period (up to 2 weeks), a 26-week, randomized, active controlled Main Period, and a 26-week Extension Period (Extension Period I), where all subjects are treated with the drug and dose to which they were randomized, followed by a 208-week single-arm Extension Period (Extension Period II) where all subjects were transitioned to treatment with the same dose of somapacitan. Additionally, subjects who complete Extension Period II before somapacitan is approved for treatment of children with short stature associated with SGA in their country can continue treatment with the same dose of somapacitan in Extension Period III, which will last until somapacitan is approved for the intended indication in their country, or until December 2026, at the latest.

Refer to Figure 11, below.

Figure 11. Schematic, Trial 4245



Source: Protocol for trial 4245, Figure 1, page 25 of 107
* Subjects completing the trial after the safety extension II (visit 24; week 260) will have a follow-up visit 30 days after the end of treatment.
** Subjects who remain on treatment in the extension III period until somapacitan becomes available for prescription for children with SGA or December 2026 at the latest. Subjects will have a follow-up visit 30 days after end of treatment.

Subjects were randomized in a 1:1:1:1:1 ratio to either:

- 0.16 mg/kg/week somapacitan
- 0.2 mg/kg/week somapacitan
- 0.24 mg/kg/week somapacitan
- 0.035 mg/kg/day (0.25 mg/kg/week) Norditropin
- 0.067 mg/kg/day (0.47 mg/kg/week) Norditropin

Subjects remained on their randomized treatment for 52 weeks (through the 26-week Main Period and the 26-week Extension Period I), then all subjects transitioned to 0.24 mg/kg/week somapacitan for treatment in Extension Periods II and III. Subjects were allowed to enter Extension Period II before switching to 0.24 mg/kg/week somapacitan and not all subjects transitioned to 0.24 mg/kg/week somapacitan on the same trial day. There was no washout period between periods.

Randomization was stratified by age (< 6 years old versus ≥ 6 years old), sex (male versus female), and region (Japan versus non-Japan), which was acceptable (see Section 8.1.1.1, above).

Fixed doses of somapacitan and Norditropin were used. See Section 8.1.1.1 for a discussion on the reasoning for multiple Norditropin arms with different doses. Per protocol, during the first 52 weeks of treatment (i.e., during the main and extension I periods) doses of somapacitan and Norditropin could be decreased by 25% for adverse events with a probable relationship to study drug. If after consecutive dose reduction steps, the adverse events persist, the subject's treatment may be discontinued. When the adverse event resolves, the dose can be resumed at the original randomized dose at the Investigator's discretion. Dose reduction criteria in the first 52 weeks of treatment did not include criteria related to IGF-1 SDS levels. During the Extension Periods II and III, dose reduction criteria were similar to those of trial 4467 and were based on persistent AEs and IGF-1 > 3 SDS (see Section 8.1.1.1). Definition of persistence of AEs warranting dose reduction or treatment discontinuation was as per the Investigator's discretion. Subjects who stopped treatment prior to Week 26 were encouraged to complete the Main Period of the trial in order to collect the required data.

Treatment would be considered complete, and therapy stopped, if the subject reached NAH, defined the same as in trial 4467 (see Section 8.1.1.1).

The somapacitan pens and strengths used in this trial were the same as in the pivotal phase 3 trial. Subjects or parents/guardians were trained in administration of study drugs by Investigators or delegates according to the DFU in how to handle the PDS290 or Norditropin FlexPro pen-injectors. The protocol did not specify at what age subjects were expected to self-administer the product. Until a subject was deemed capable of self-administering, the parent/guardian administered the study drug.

8.1.2.2. Trial Endpoints

Efficacy Endpoint

The efficacy endpoints were AHV after 26 weeks of treatment, BA after 52 weeks of treatment, and height SDS, AHV SDS, and PD assessment after 26 weeks of treatment.

The Applicant also assessed parent/caregiver responses to the following COA: GH-PPQ at 13 weeks after switching from Norditropin to somapacitan.

8.1.2.3. Eligibility Criteria

Eligibility criteria were consistent with the indication: treatment of short stature or growth failure associated with SGA. The trial included growth promoting-treatment naïve, pre-pubertal (Tanner I; aged 2.5 to < 10 (females) or < 11 (males) years old) children with a diagnosis of SGA. Confirmation of SGA required:

- Birth length, weight, or both, below -2 SDS
- Height SDS < -2.5 at screening
- AHV below 50th percentile
- BMI < 95th percentile

The eligibility criteria were largely consistent with the eligibility criteria for the SGA population in trial 4467 (see Section 8.1.1.3) and acceptable.

See Section 15.4.1, Trial NN8640-4245 for the full inclusion and exclusion criteria for trial 4245.

8.1.2.4. Statistical Analysis Plan

The trial was designed primarily as a dose-finding trial and not powered to evaluate efficacy. Prespecified analyses to characterize effects on growth are described below.

8.1.2.5. Analysis Population

The full analysis set (FAS) was used to analyze endpoints related to efficacy, defined as all randomized subjects exposed to trial products. The evaluation of safety was based on the safety analysis set (SAS), defined as all randomized subjects exposed to trial products.

8.1.2.6. Sample Size Justification

A sample size of approximately 60 subjects (12 subjects per each 0.16, 0.2, and 0.24 mg/kg/week somapacitan cohort and per each 0.035 and 0.067 mg/kg/day Norditropin cohort) was planned to be enrolled based on an assumption of SD of 2.6 cm/year for AHV after 26 weeks of treatment and use of a delta value of at least 3.25 cm/year between two treatment arms (i.e., somapacitan vs. Norditropin), and a 2-sided significance level of 5%. Assuming an 8% dropout during the trial, the Applicant calculated that 12 subjects randomized per treatment arm should provide 80% probability that the estimated treatment

difference lies completely above the chosen delta value when comparing a somapacitan treatment arm to a Norditropin treatment arm, assuming the two treatments are equal.

8.1.2.7. Efficacy Analysis

The efficacy endpoint of AHV (cm/year) at Week 26, was calculated as: AHV = (height at Week 26 visit minus height at baseline)/(time from baseline to Week 26 visit in years).

AHV at Weeks 13, 26, 39, and 52 are analyzed using a mixed model for repeated measurements (MMRM) with treatment, age group (< 6 years and ≥ 6 years), sex, region (Japan and rest of the world), and sex by age group interaction terms as factors and height at baseline as a covariate, all nested within week as a factor. From the MMRM treatment difference at Week 26 and Week 52 between the somapacitan arms and Norditropin arms was estimated the corresponding 95% CI. Children without post-randomization AHV data were not included in the primary analysis.

8.1.2.8. Supportive Efficacy Analyses

Height SDS, AHV SDS, and IGF-1 SDS from baseline to Weeks 26 and 52 were analyzed using an MMRM similar to that of the primary endpoint. An unstructured covariance matrix was used to describe the variability for the repeated measurements for a subject. Bone age was analyzed using an ANCOVA model on change from baseline in bone age (BA)/chronological age (CA) assessed at Week 52 and the model will include treatment, age group (< 6 years and ≥ 6 years), sex, region (Japan and rest of the world), and sex by age group interaction terms as factors and BA/CA at baseline as a covariate, all nested within week as a factor. The treatment difference estimate will be reported with corresponding 95% CI and p-value. Children without post-randomization AHV data were not included in the primary analysis.

There were no multiplicity adjustments made for the supportive secondary endpoints or the comparisons between each dose of somapacitan and Norditropin.

8.1.2.9. Safety Analyses

Safety endpoints were evaluated using descriptive statistics and were summarized by treatment, cohort, MedDRA system organ class, and MedDRA preferred term.

8.1.2.10. Protocol Amendments

The protocol was amended 11 times. These amendments were reviewed and did not appear to have an impact on the integrity of the trial or the interpretation of efficacy and safety results.

8.1.2.11. Trial Results

Compliance With Good Clinical Practices

The trial was conducted in accordance with ICH Good Clinical Practices regulations/guidelines.

Financial Disclosure

The financial document was reviewed. No issues were identified that could influence the outcome of the trials. Refer to Section 15.1 of the Appendix.

8.1.2.12. Subject Disposition

Out of 70 subjects born SGA screened for the trial, 8 subjects were excluded as screening failures (the majority of which were related to not meeting eligibility criteria related to impaired height or AHV or gestational age at birth). A total of 62 subjects were randomized approximately 1:1:1:1:1, and exposed, to 0.16 (n = 12), 0.2 (n = 13), or 0.24 mg/kg/week (n = 12) somapacitan or 0.035 (n = 12) or 0.067 mg/kg/day (n = 13) Norditropin.

A total of 61/62 (98.4%) subjects completed the 26-week Main Period; one subject in the 0.035 mg/kg/day Norditropin group prematurely withdrew from the trial by parent/guardian because they felt the laboratory tests were traumatizing. A total of 61/62 (98.4%) subjects continued in the trial and were exposed to randomized treatment in Extension Period I (Weeks 26 to 52). A total of 61/62 (98.4%) subjects completed 52 weeks of treatment.

A total of 60/62 (96.8%) subjects rolled over into, and were exposed to treatment, in Extension Period II. A total of 5/62 (8.1%) subjects discontinued treatment prematurely in Extension Period II after all subjects began treatment with 0.24 mg/kg/week somapacitan. The reasons for discontinuation of treatment and withdrawal from the trial for these subjects were all listed as 'other' and were not due to adverse events. A total of 55/62 (88.7%) subjects completed treatment in Extension Period II.

Refer to Table 17 for subject disposition of subjects in trial 4245.

Table 17. Subject Disposition, Trial 4245

Treatment	0.035 mg/kg/day Norditropin (N=12) n (%)	0.067 mg/kg/day Norditropin (N=13) n (%)	0.16 mg/kg/week Somapacitan (N=12) n (%)	0.2 mg/kg/week Somapacitan (N=13) n (%)	0.24 mg/kg/week Somapacitan (N=12) n (%)	Total (N = 62) n (%)
Exposed in 26-week Main Period	12 (100)	13 (100)	12 (100)	13 (100)	12 (100)	62 (100)
Completed treatment in the Main Period	11 (91.7)	13 (100)	12 (100)	13 (100)	12 (100)	61 (98.4)
Early withdrawal from treatment in 26-week Main Period	1 (8.3)	0	0	0	0	1 (1.6)
Early withdrawal from trial during the 26-week Main Period	1 (8.3)	0	0	0	0	1 (1.6)
Rolled over into 26-week Extension Period I	11 (91.7)	13 (100)	12 (100)	13 (100)	12 (100)	61 (98.4)
Completed treatment in the Extension Period I	11 (91.7)	13 (100)	12 (100)	13 (100)	12 (100)	61 (98.4)
Early withdrawal from treatment in 26-week Extension Period I	0	0	0	0	0	0
Early withdrawal from trial during the 26-week Extension Period I	0	0	0	0	0	0
Rolled over into 208-week Extension Period II and transitioned to 0.24 mg/kg/week somapacitan	11 (91.7)	13 (100)	12 (100)	12 (92.3)	12 (100)	60 (96.8)
Completed treatment in the Extension Period II	8 (66.7)	11 (84.6)	12 (100)	12 (92.3)	12 (100)	55 (88.7)
Early withdrawal from treatment in 208-week Extension Period II	3 (25)	2 (15.4)	0	0	0	5 (8.1)
Other	3 (25)	2 (15.4)	0	0	0	5 (8.1)
Early withdrawal from trial during the 208-week Extension Period II	3 (25)	2 (15.4)	0	0	0	5 (8.1)
Physician decision	0	1 (7.7)	0	0	0	1 (1.6)
Withdrawal by parent/guardian	2 (16.7)	0	0	0	0	2 (3.2)
Withdrawal by subject	1 (8.3)	1 (7.7)	0	0	0	2 (3.2)

Source: Data compiled from trial 4245 ADSL datasets and from the Clinical Trial Report for trial 4245, Table 4-1, pages 37 to 39.

8.1.2.13. Protocol Violations/Deviations

The Applicant reported 104 protocol deviations in all subjects enrolled in trial 4245 up to the end of Extension Period II, including 17, 30, 15, 23, and 19 protocol deviations reported in subjects originally randomized to 0.035 (n = 12) or 0.067 mg/kg/day (n = 13) Norditropin or 0.16 (n = 12), 0.2 (n = 13), or 0.24 mg/kg/week (n = 12) somapacitan, respectively (see Table 54 in Section 15.4.2). The most common of these protocol deviations related to trial procedures/assessments (primarily due to COVID19 restrictions or the timing of blood sampling not being in accordance with trial protocol), informed consent, treatment administration (primarily due to missed doses on multiple occasions), or SAE notification/safety procedure (related to non-submission of required photographs for injection site reactions, failure to follow safety procedures for AEs, deviations from European guidelines for blood sampling in relation to a subject's weight, and delays and reporting and challenges in adhering to protocol requirements).

The protocol deviations were reviewed and do not appear to have an impact on the overall results for trial 4245.

8.1.2.14. Baseline Demographic and Disease Characteristics

With the exception of the 0.035 mg/kg/day Norditropin group, which had 50% enrollment of males and 50% enrollment of females, there were more males (about 65% to 70%) than females (30% to 35%) enrolled in each arm of trial 4245. There was an even distribution of subjects < 6 years or ≥ 6 years of age (approximately 50% in each age group in each treatment arm), the mean (SD) age was 6.1 (2.4) years (range: 2.7 to 11 years of age).

Overall, the proportions and mean values between the different treatment groups were unlikely to have a significant impact on the results.

Approximately 9.7% of subjects were from the U.S. and other subjects were from Europe and Asia. As discussed in the Section 8.1.1.6, Baseline Demographic and Disease Characteristics, the predominance of non-U.S. subjects is acceptable and the efficacy and safety data on somapacitan use obtained from subjects from other countries are applicable to U.S. subjects.

Refer to Table 18 for baseline demographics of the SGA population in trial 4245.

Table 18. Baseline Demographics of the SGA Population, Trial 4245

Demographics	0.035 mg/kg/day Norditropin (N=12)	0.067 mg/kg/day Norditropin (N=13)	0.16 mg/kg/week Somapacitan (N=12)	0.2 mg/kg/week Somapacitan (N=13)	0.24 mg/kg/week Somapacitan (N=12)	Total (N = 62)
Sex, n (%)						
Female	6 (50)	4 (30.8)	4 (33.3)	4 (30.8)	4 (33.3)	22 (35.5)
Male	6 (50)	9 (69.2)	8 (66.7)	9 (69.2)	8 (66.7)	40 (64.5)
Age, years						
Mean (SD)	6.3 (2.8)	5.9 (2.4)	6.1 (2.4)	6.2 (2.2)	6 (2.5)	6.1 (2.4)
Min, Max	2.7, 11	3.3, 10.2	3.2, 9.6	3.6, 10.3	2.7, 9.9	2.7, 11

Demographics	0.035 mg/kg/day Norditropin (N=12)	0.067 mg/kg/day Norditropin (N=13)	0.16 mg/kg/week Somapacitan (N=12)	0.2 mg/kg/week Somapacitan (N=13)	0.24 mg/kg/week Somapacitan (N=12)	Total (N = 62)
Number of subjects above and below 6 years old, n (%)						
< 6 years	6 (50)	7 (53.8)	6 (50)	7 (53.8)	5 (41.7)	31 (50)
≥ 6 years	6 (50)	6 (46.2)	6 (50)	6 (46.2)	7 (58.3)	31 (50)
Race, n (%)						
White	9 (75)	8 (61.5)	4 (33.3)	7 (53.8)	6 (50)	34 (54.8)
Asian	3 (25)	5 (38.5)	6 (50)	4 (30.8)	6 (50)	24 (38.7)
Other	0	0	0	1 (7.7)	0	1 (1.6)
Not reported	0	0	2 (16.7)	1 (7.7)	0	3 (4.8)
Ethnicity, n (%)						
Hispanic or Latino	0	2 (15.4)	0	0	0	2 (3.2)
Not Hispanic or Latino	12 (100)	11 (84.6)	8 (66.7)	12 (92.3)	11 (91.7)	54 (87.1)
Not reported	0	0	4 (33.3)	1 (7.7)	1 (8.3)	6 (9.7)
Country, n (%)						
Austria	0	0	0	1 (7.7)	0	1 (1.6)
France	0	0	2 (16.7)	1 (7.7)	0	3 (4.5)
Hungary	0	0	1 (8.3)	0	0	1 (1.6)
India	0	1 (7.7)	1 (8.3)	0	0	1 (1.6)
Israel	1 (8.3)	1 (7.7)	1 (8.3)	0	0	3 (4.8)
Italy	0	1 (7.7)	1 (8.3)	0	1 (8.3)	3 (4.8)
Japan	3 (25)	4 (30.8)	3 (25)	4 (30.8)	3 (25)	17 (27.4)
Latvia	0	1 (7.7)	0	1 (7.7)	0	2 (3.2)
Russia	3 (25)	4 (30.8)	0	2 (15.4)	4 (33.3)	13 (21)
Thailand	0	0	2 (16.7)	0	1 (8.3)	3 (4.8)
Ukraine	2 (1.7)	0	0	3 (23.1)	1 (8.3)	6 (9.7)
United States	3 (25)	1 (7.7)	1 (8.3)	1 (7.7)	0	6 (9.7)

Source: Clinical Trial Report for trial 4245, Table 4-4, pages 47 to 48; and Table 4-5, pages 49 to 50.

In general, the baseline disease characteristics were overall comparable across the treatment groups in the phase 2 trial. Mean baseline height SDS was below normal (i.e., height < -2 SDS) for all treatment arms, consistent eligibility criteria and with a diagnosis of short stature and was comparable across treatment groups.

One subject in the 0.16 mg/kg/week somapacitan group had a wrong pre-screening height reported (107 cm rather than the correct 110 cm), resulting in a high AHV at baseline (8.1 cm/year rather than the correct 5.3 cm/year), and likely contributing to a higher mean AHV and AHV SDS at baseline in that dose cohort. Otherwise, overall, the mean baseline AHV was at the lower end of normal and comparable across treatment groups.

Finally, the mean baseline IGF-1 SDS values in all treatment groups were within the normal range (i.e., -2 < IGF-1 SDS < 2), indicating sufficient GH status.

Refer to Table 19 for baseline characteristics of the SGA population in trial 4245.

Table 19. Baseline Characteristics of the SGA Population, Trial 4245

Characteristics	0.035 mg/kg/day Norditropin (N=12)	0.067 mg/kg/day Norditropin (N=13)	0.16 mg/kg/week Somapacitan (N=12)	0.2 mg/kg/week Somapacitan (N=13)	0.24 mg/kg/week Somapacitan (N=12)	Total (N = 62)
Mean (SD)						
AHV (cm/year)	4.9 (1.6)	4.4 (1.3)	5.6 (1.5)	5.3 (1.4)	4.7 (2)	5 (1.6)
AHV SDS	-2 (1.6)	-2.1 (1.4)	-1.1 (2)	-1.2 (1.6)	-2.1 (1.1)	-1.7 (1.6)
IGF-1 SDS	-0.9 (1.1)	-0.6 (0.8)	-0.5 (0.8)	-0.3 (0.9)	-0.2 (0.1)	-0.5 (0.9)
Height SDS	-3.2 (0.6)	-3 (0.6)	-2.9 (0.5)	-3 (0.5)	-3.1 (0.8)	-3 (0.6)

Source: Clinical Trial Report for trial 4245, Table 4-6, page 51; Table 8.2.10, pages 219 to 222; Table 8.2.15, pages 231 to 234; Table 8.2.35, pages 279 to 282; Table 8.2.53, pages 321 to 324.

8.1.2.15. Comorbidities

The most commonly (≥ 2 subjects) reported comorbidities in subjects enrolled in trial 4245 were constipation, rhinitis allergic, asthma, foot deformity, short stature, adenoidal hypertrophy, autism spectrum disorder, febrile convulsion, hypoglycemia, iron deficiency anemia, and vitamin D deficiency. See Table 110 in Section 15.4.3. Overall, the incidence of comorbidities in the SGA population is small (no comorbidities were reported by more than 2 subjects in any single treatment arm), and it is unlikely that that any of the most commonly reported comorbidities would have a significant impact on growth or thus the analysis of efficacy of somapacitan.

8.1.2.16. Concomitant Medications

Similar to the phase 3 trial 4467, the most commonly reported (≥ 10% of subjects in any treatment group) concomitant medications were consistent with medications taken in the general pediatric population and include analgesics/antipyretics, mucolytics, antihistamines/antiallergy medications, antibiotics (such as azithromycin, clarithromycin, cefditoren, and amoxicillin), antivirals (such as oseltamivir and acyclovir), antiasthma therapy (such as salbutamol, montelukast, and tulobutamol), treatment of heavy menstrual, cough suppressants, vitamins, and steroids (such as budesonide and fluticasone). See Table 111, in Section 15.4.3, for the most commonly reported concomitant medications in the phase 2 trial 4245. While treatment with inhaled steroids and systemic corticosteroids may impact growth, the eligibility criteria excluded the use of such medications at doses that are likely to suppress growth (see Section 15.4.1 for the full inclusion and exclusion criteria for trial 4245). It is unlikely that any of the most commonly reported concomitant medications in this trial had a significant impact on growth or thus the analysis of efficacy of somapacitan.

8.1.2.17. Treatment Compliance

Treatment compliance was assessed by cross checking the following to expected use: drug accountability information (counting of returned trial product, visual inspection of pens), question of subjects, comparing prescribed and actual doses, and review of the subjects' dosing diaries. These were documented at site visits and confirmed by site staff. Overall, appropriate measures were taken to ensure treatment compliance.

The majority of the subjects in the phase 2 trial 4245 received the planned treatment; the mean (SD) adherence to randomized therapy was 84.4 (21.6)%, 92.3 (9.3)%, 96.2 (3.7)%, 92 (12.3)%, and 95.3 (4.7%)% in the 0.035 or 0.067 mg/kg/day Norditropin or 0.16, 0.2, or 0.24 mg/kg/week somapacitan arms, respectively. After subjects in the 0.035 or 0.067 mg/kg/day Norditropin or 0.16 or 0.2 mg/kg/week somapacitan groups were switched to 0.24 mg/kg/week somapacitan, the mean (SD) adherence was 80.2 (21.8)%, 86 (22.1)%, 92 (11.1)%, and 85.2 (20.6)%, respectively.

8.1.2.18. Efficacy Endpoint Results

The analyses of data demonstrated improvement in all mean growth parameters at Weeks 26 and 52 in the dose finding phase 2 trial in subjects born SGA.

Annualized Height Velocity

The mean AHV increased in all treatment groups (AHV at Weeks 26 and 52 are displayed in Table 20. The mean AHV in the 0.2 and 0.24 mg/kg/week somapacitan groups were comparable at each time point measured, and both were higher than 0.16 mg/kg/week somapacitan. The mean AHV after 52 weeks of treatment in the 0.24 mg/kg/week somapacitan group was comparable to the 0.067 mg/kg/day Norditropin group.

Table 20. Mean (SD) Annualized Height Velocity, Main Period and Extension Period I (Weeks 0 to 52), Full Analysis Set, Trial 4245

AHV (cm/year)		0.035 mg/kg/day Norditropin (N=12)	0.067 mg/kg/day Norditropin (N=13)	0.16 mg/kg/week Somapacitan (N=12)	0.2 mg/kg/week Somapacitan (N=13)	0.24 mg/kg/week Somapacitan (N=12)
Baseline	Mean (SD)	4.9 (1.6)	4.4 (1.3)	5.6 (1.5)	5.3 (1.4)	4.7 (2)
	n	12	13	12	13	12
Week 26	Mean (SD)	10.5 (2)	11.9 (2.4)	8.9 (1.8)	11.1 (2.6)	11.2 (3.4)
	n	11	13	12	12	12
Week 52	Mean (SD)	9.4 (1.7)	11.2 (1.6)	8.5 (1.5)	10.3 (1.9)	10.6 (2.5)
	n	11	13	12	13	12

Source: Clinical Trial Report for trial 4245, Table 4-6, page 51; Table 8.2.10, pages 219 to 222.
n = number of subjects with available data

Annualized Height Velocity SDS

The increase in mean AHV SDS at Weeks 26 and 52 showed a similar pattern of increase as was seen for AHV (see Table 21).

Table 21. Mean (SD) Annualized Height Velocity SDS, Main Period and Extension Period I (Weeks 0 to 52), Full Analysis Set, Trial 4245

AHV SDS		0.035 mg/kg/day Norditropin (N=12)	0.067 mg/kg/day Norditropin (N=13)	0.16 mg/kg/week Somapacitan (N=12)	0.2 mg/kg/week Somapacitan (N=13)	0.24 mg/kg/week Somapacitan (N=12)
Baseline	Mean (SD)	-2 (1.4)	-2.1 (1.4)	-1.1 (2)	-1.2 (1.6)	-2.1 (1.1)
	n	12	13	12	13	12
Week 26	Mean (SD)	4.4 (2.3)	5.8 (1.5)	2.9 (1.7)	5.4 (3.2)	5.2 (3.5)
	n	11	13	12	12	12
Week 52	Mean (SD)	3.3 (2.1)	5.5 (1.8)	2.7 (1.7)	5 (1.7)	5 (2.5)
	n	11	13	12	13	12

Source: Clinical Trial Report for trial 4245, Table 4-6, page 51; Table 8.2.15, pages 231 to 234.
n = number of subjects with available data

Height SDS

An improvement in height SDS was observed during treatment with somapacitan and Norditropin at Weeks 26 and 52 (Table 22). The change from baseline in mean height SDS was comparable between the 0.2 and 0.24 mg/kg/week somapacitan doses, and both were increased compared to the 0.16 mg/kg/week somapacitan dose and comparable to the 0.067 mg/kg/day Norditropin arm.

Table 22. Mean (SD) Height SDS, Main Period and Extension Period I (Weeks 0 to 52), Full Analysis Set, Trial 4245

		0.035 mg/kg/day Norditropin (N=12)		0.067 mg/kg/day Norditropin (N=13)		0.16 mg/kg/week Somapacitan (N=12)		0.2 mg/kg/week Somapacitan (N=13)		0.24 mg/kg/week Somapacitan (N=12)	
Height SDS		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**	**Value**	**Change From Baseline**	**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Baseline	Mean (SD)	-3.2 (0.6)	-	-3 (0.6)	-	-2.9 (0.5)	-	-3 (0.5)	-	-3.1 (0.8)	-
	n		12		13		12		13		12
Week 26	Mean (SD)	-2.6 (0.7)	0.6 (0.2)	-2.3 (0.7)	0.7 (0.3)	-2.5 (0.5)	0.4 (0.2)	-2.4 (0.6)	0.7 (0.3)	-2.4 (1)	0.7 (0.4)
	n		11		13		12		12		12
Week 52	Mean (SD)	-2.3 (0.7)	0.9 (0.3)	-1.8 (0.7)	1.3 (0.4)	-2.2 (0.6)	0.7 (0.3)	-1.9 (0.6)	1.1 (0.4)	-1.9 (1.1)	1.2 (0.5)
	n		11		13		12		13		12

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical, and Clinical Trial Report for trial 4245, Table 4-6, page 51; Table 8.2.35, pages 279 to 282.
Abbreviations: n = number of subjects with available data

Bone Age

There was minimal change in the bone age to chronological age ratio during the first year of therapy in the dose finding phase 2 trial, the amount of change was comparable between all Norditropin and somapacitan groups, and the mean ratio remained below 1 for all treatment groups. These results suggest that somapacitan does not advance bone age relative to chronological age (see Table 109, in Section 15.4.3, Trial NN8640-4245).

Long-Term Extension Periods

Subject continued to improve growth parameters with longer treatment of somapacitan. In the Extension period of phase 2 trial, subjects were transitioned to treatment with 0.24 mg/kg/week somapacitan. As of the database lock date, data on 12 subjects who had been exposed to only 0.24 mg/kg/week somapacitan from the beginning of the trial were available for up to 208 weeks (4 years) of therapy. For these subjects, observed mean (SD) AHV at Week 52 was 10.6 (2.5) cm/year, at Week 104 was 8.7 (1.3) cm/year, at Week 156 was 6.7 (1.6) cm/year, and at Week 208 was 6.6 (1.1) cm/year. Mean (SD) AHV SDS was 1 (1.7) by 208 weeks of treatment. Further, mean change in observed mean (SD) height SDS from baseline at Week 52 was 1.2 (0.6), at Week 104 was 1.8 (0.6), at Week 156 was 1.9 (0.6), and at Week 208 was 2 (0.6). Mean (SD) bone age to chronological age ratio was 0.81 (0.28), 0.89 (0.27), 0.93 (0.24), and 0.96 (0.21) after 52, 104, 156, and 208 weeks of treatment. Overall, the results showed continued growth, though AHV slowed with continued treatment. This trend is expected, and a similar trend is observed during therapy with approved hGH products as well as in phase 3 trial.

Conclusions

The results of the dose finding phase 2 trial 4245 were overall consistent with the results observed in the pivotal phase 3 trial 4467. Evaluations of growth parameters and bone age assessments from pre-treatment baseline to the end of 52 weeks of randomized treatment in the dose finding phase 2 trial 4245 were similar to those changes observed at the end of 52 weeks of randomized treatment in the pivotal phase 3 trial.

8.1.2.19. Dose/Dose Response

For a detailed evaluation of dose and dose response during the entire clinical development program of somapacitan for the proposed indications, refer to Section 6.

The somapacitan weekly dose selection of 0.24 mg/kg/week in the phase 3 trial 4467 was based on dose-response, exposure-response, and safety data analyses from this phase 2 dose-finding trial 4245 in children with short stature born SGA. Refer to Sections 6, 8.1.2.18, and 8.3.

8.1.2.20. Durability of Response

Long-term response to somapacitan was assessed in the Extension Period II of trial 4245. These results are discussed in Section 8.1.2.18, Long-Term Extension Periods.

8.1.2.21. Persistence of Effect

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

8.1.2.22. COA (PRO) Endpoints

The Applicant also assessed parent/caregiver responses to the following COA: GH-PPQ at 13 weeks after switching from Norditropin to somapacitan. However, this COA has not been validated in the intended population and thus interpretation of information derived from this COA for the intended population is challenging, no meaningful conclusions can be drawn, and these data would not be eligible for inclusion in labeling.

8.1.3. Trial NN8640-4469 (Trial 4469)

A study evaluating the safety and efficacy of once-weekly dosing of somapacitan in a basket study design in pediatric participants with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome or idiopathic short stature

8.1.3.1. Trial Design

Trial 4469 is an open-label, uncontrolled phase 3 trial with a basket design to evaluate the efficacy and safety of once-weekly dosing of 0.24 mg/kg/week somapacitan in treatment naïve or non-naïve children with short stature associated with SGA, NS, ISS, or TS, who are older than would be eligible for the phase 3 trial 4467 (i.e., ≥ 10 (females) or ≥ 11 (males) years of age and < 18 years of age).

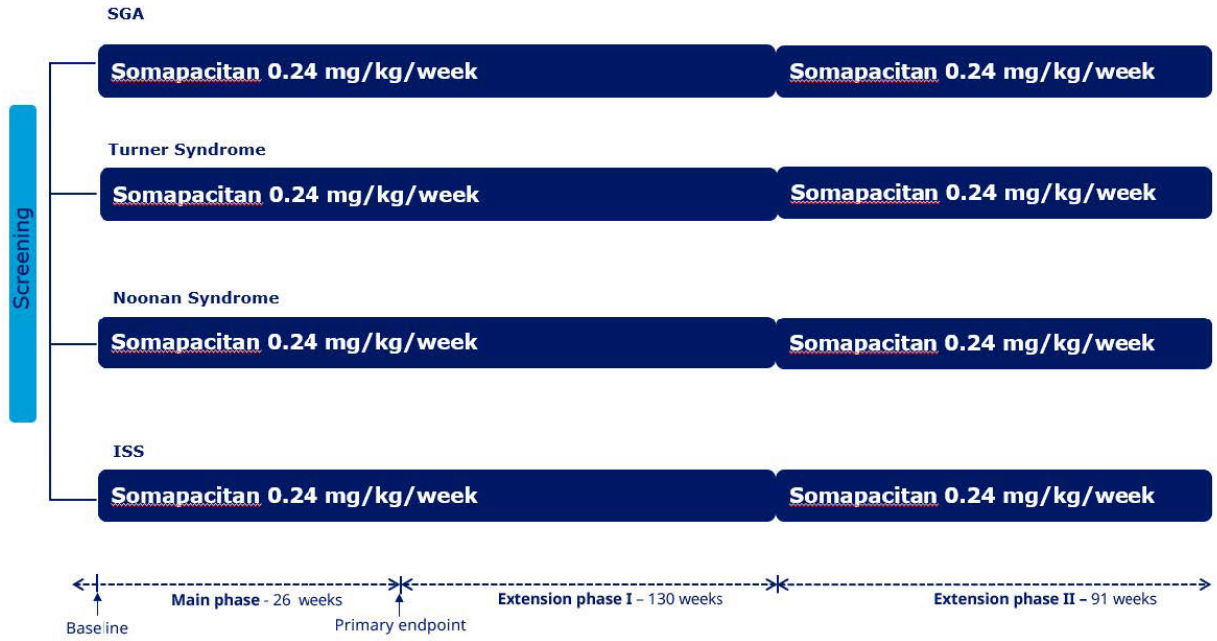
The primary objective of the trial is to evaluate the safety of once weekly somapacitan in children with treatment naïve or non-naïve children with short stature associated with SGA, NS, ISS, or TS, who are older than would be eligible for the phase 3 trial 4467.

The secondary objectives of the trial were to compare the effect of weekly somapacitan on AHV, height SDS, AHV SDS, BA, PK, PD, and safety over time in children with SGA, NS, ISS, or TS, separately.

The trial includes an up to 3-week screening period for subjects with ISS or born SGA and an up to 6-week screening period for subjects with TS or NS, a 26-week Main Period, and a 130-week Extension Period I. Subjects completing Extension Period I have the option to enroll in a 91-week Extension Period II, where they can continue treatment with somapacitan until it becomes available for prescription in their country, or October 2027 at the latest. All subjects of all diagnosis are treated with 0.24 mg/kg/week somapacitan in all treatment periods.

Refer to Figure 12 below.

Figure 12. Schematic, Trial 4469



Source: Protocol for trial 4469, Figure 4-1, page 42 of 155

Subjects in this trial receive fixed doses of somapacitan, and doses of somapacitan could be decrease as per protocol similar to those described in the pivotal phase 3 trial 4467 in Section 8.1.1.1.

Subjects who stopped treatment prior to Week 26 were encouraged to complete the Main Period of the trial in order to collect the required data.

Treatment would be considered completed, and therapy stopped, if the subject reached NAH, defined as AHV < 2 cm/year and have reached a bone age ≥ 16 or ≥ 14 years for males or females, respectively. If bone age is not available, then the criteria used chronological ages of ≥ 17 and ≥ 15 for males and females, respectively.

Somapacitan was provided as a solution for SC injection *via* a pen injector (PDS290). Subjects or parents/guardians were allowed to self-administer the drug.

8.1.3.2. Trial Endpoints

Efficacy Endpoints

Similar to the endpoints studied in the phase 3 trial 4467 and the phase 2 trial 4245, efficacy endpoints include evaluation of AHV, AHV SDS, height SDS, and PD and PK from baseline to Week 26.

Safety Endpoints

The safety endpoints include the number of AEs and the number of AEs possibly or probably related to somapacitan from baseline to Week 26.

8.1.3.3. Clinical Outcome Assessments

The Applicant also assessed outcome responses to the following COAs: Growth Hormone Injection – Child Treatment Burden – Child (GH-INJ-CTB-Child) and Growth Hormone Patient Preference Questionnaire – Child (GH-PPQ-Child).

8.1.3.4. Eligibility Criteria

The eligibility criteria were consistent with the diagnostic criteria for short stature or growth failure associated with SGA, NS, ISS, or TS. The eligibility criteria were largely consistent with those of the phase 3 trial 4467 (see Section 8.1.1.3), with the exceptions that in the phase 3 trial 4469 subjects may have previously been exposed to growth promoting treatment (i.e., treatment non-naïve) or treatment naïve, are older than would be eligible for the phase 3 trial 4467 (i.e., ≥ 10 (females) or ≥ 11 (males) years of age and < 18 years of age), and do not have to be pre-pubertal.

See Section 15.4.1, Trial NN8640-4469 for the full inclusion and exclusion criteria for trial 4469.

8.1.3.5. Statistical Analysis Plan

The trial was designed primarily as a safety trial.

No formal statistical hypotheses testing was performed in this trial. The safety data and data from clinical assessments were summarized using descriptive statistics.

The FAS (i.e., all subjects assigned to trial intervention) was used to analyze endpoints related to efficacy and the SAS (i.e., all subjects exposed to trial intervention) was used to analyze endpoints related to safety.

8.1.3.6. Protocol Amendments

The protocol was amended 4 times. These amendments were reviewed and did not appear to have an impact on the integrity of the trial or the interpretation of efficacy and safety results.

8.1.3.7. Trial Results

Compliance With Good Clinical Practices

The trial was conducted in accordance with ICH Good Clinical Practices regulations/guidelines.

Financial Disclosure

The financial document was reviewed. No issues were identified that could influence the outcome of the trials. Refer to Section 15.1 of the Appendix.

8.1.3.8. Subject Disposition

As of the cutoff date of January 29, 2025, a total of 47 subjects were exposed to 0.24 mg/kg/week somapacitan across the SGA, NS, ISS, and TS sub-trials in the ongoing phase 3 trial 4469. Of these, 15 subjects were naïve to growth promoting therapy (i.e., treatment naïve; including 4, 6, 2, and 3 subjects born SGA, or with NS, ISS, and TS, respectively) and 32 had previously received GH therapy (i.e., treatment non-naïve; including 8, 7, 9, and 8 subjects born SGA, or with NS, ISS, and TS, respectively). Of note, the data pertinent to subjects with TS will not be discussed further as indication for TS is not claimed in this submission.

SGA

A total of 12 subjects born SGA were screened and received treatment with 0.24 mg/kg/week somapacitan. There were no screening failures in the SGA population. All 12 subjects completed the 26-week Main Period and continued treatment in the Extension Period I. As of the cutoff date, no subjects in this population discontinued therapy or withdrew from the trial. See Table 124 in Section 15.4.3, Trial NN8640-4469.

NS

A total of 16 subjects with NS were screened, of which 3 subjects were excluded as screening failures (due to violations of eligibility criteria). A total of 13 subjects with NS received treatment with 0.24 mg/kg/week somapacitan. All 13 subjects completed the 26-week Main Period and continued treatment in the Extension Period I. As of the cutoff date, no subjects in this population discontinued therapy or withdrew from the trial. See Table 125 in Section 15.4.3, Trial NN8640-4469.

ISS

A total of 14 subjects with ISS were screened, of which 3 subjects were excluded as screening failures (due to violations of eligibility criteria). A total of 11 subjects with ISS received treatment with 0.24 mg/kg/week somapacitan. All 11 subjects completed the 26-week Main Period and continued treatment in the Extension Period I. As of the cutoff date, no subjects in this population discontinued therapy or withdrew from the trial. See Table 126 in Section 15.4.3, Trial NN8640-4469.

8.1.3.9. Protocol Violations/Deviations

The protocol deviations were reviewed and do not appear to have an impact on the overall results for the any subject population sub-trial (see Table 55 through Table 57, in Section 15.4.2).

8.1.3.10. Baseline Demographic and Disease Characteristics

The demographic characteristics of subjects enrolled in this trial were similar to demographic characteristics in trial 4467, except age of the enrolled subjects (as per eligibility criteria). Mean age of subjects enrolled in study 4469 was approximately 12, 12.5, 12, and 10.9 years for subjects in the SGA, NS, ISS, and TS populations, respectively.

Approximately 16.7%, 23.1%, and 27.3%, of subjects born SGA, or diagnosed with NS, or ISS, respectively, were from the U.S. and other subjects were from Europe or Asia. As discussed in the Section 8.1.1.6, Baseline Demographic and Disease Characteristics, the predominance of non-U.S. subjects is acceptable and the efficacy and safety data on somapacitan use obtained from subjects from other countries are applicable to U.S. subjects.

Refer to Table 23, Table 24, and Table 25, for baseline demographics of the SGA, NS, and ISS populations, respectively, in trial 4469.

Table 23. Baseline Demographics of the SGA Population, Trial 4469

Demographics	Treatment Naïve (N=4)	Treatment Non-Naïve (N=8)	Total (N = 12)
Sex, n (%)			
Female	2 (50)	3 (37.5)	5 (41.7)
Male	2 (50)	5 (62.5)	7 (58.3)
Age, years			
Mean (SD)	12.5 (2.1)	11.8 (1.7)	12 (1.8)
Min, Max	10, 15	10, 14	10, 15
Race, n (%)			
Asian	2 (50)	1 (12.5)	3 (25)
White	2 (50)	7 (87.5)	9 (75)
Ethnicity, n (%)			
Not Hispanic or Latino	4 (100)	8 (100)	12 (100)
Country, n (%)			
Korea	0	1 (12.5)	1 (8.3)
Malaysia	2 (50)	0	2 (16.7)
Poland	2 (50)	5 (62.5)	7 (58.3)
United States	0	2 (25)	2 (16.7)

Source: Clinical Trial Report for trial 4469, Table 4-5, page 58; and Table 4-6, pages 59 and 60.

Table 24. Baseline Demographics of the NS Population, Trial 4469

Demographics	Treatment Naïve (N=6)	Treatment Non-Naïve (N=7)	Total (N = 13)
Sex, n (%)			
Female	2 (33.3)	2 (28.6)	4 (30.8)
Male	4 (66.7)	5 (71.4)	9 (69.2)
Age, years			
Mean (SD)	12.7 (2.1)	12.3 (1.5)	12.5 (1.7)
Min, Max	10, 15	10, 14	10, 15
Race, n (%)			
Asian	1 (16.7)	1 (14.3)	2 (15.4)
White	5 (83.3)	6 (85.7)	1 (84.6)

Demographics	Treatment Naïve (N=6)	Treatment Non-Naïve (N=7)	Total (N = 13)
Ethnicity, n (%)			
Not Hispanic or Latino	6 (100)	7 (100)	13 (100)
Country, n (%)			
Korea	0	1 (14.3)	1 (7.7)
Malaysia	1 (16.7)	0	1 (7.7)
Poland	5 (83.3)	1 (14.3)	6 (46.1)
Spain	0	2 (28.6)	2 (15.4)
United States	0	3 (42.9)	3 (23.1)

Source: Clinical Trial Report for trial 4469, Table 4-7, page 61; and Table 4-8, pages 62 and 63.

Table 25. Baseline Demographics of the ISS Population, Trial 4469

Demographics	Treatment Naïve (N=2)	Treatment Non-Naïve (N=9)	Total (N = 11)
Sex, n (%)			
Female	0	6 (66.7)	6 (54.5)
Male	2 (100)	3 (33.3)	5 (45.5)
Age, years			
Mean (SD)	14.5 (0.7)	11.4 (1.2)	12 (1.7)
Min, Max	14, 15	10, 13	10, 15
Race, n (%)			
Asian	1 (50)	3 (33.3)	4 (36.4)
White	1 (50)	6 (66.7)	7 (63.6)
Ethnicity, n (%)			
Not Hispanic or Latino	2 (100)	9 (100)	11 (100)
Country, n (%)			
Korea	0	2 (22.2)	2 (18.2)
Malaysia	1 (50)	1 (11.1)	2 (18.2)
Poland	0	3 (33.3)	3 (27.3)
Spain	0	1 (11.1)	1 (9.1)
United States	1 (50)	2 (22.2)	3 ((27.3)

Source: Clinical Trial Report for trial 4469, Table 4-9, page 64; and Table 4-10, pages 65 and 66.

In general, for each diagnosis, the baseline disease characteristics of treatment naïve subjects demonstrated impaired linear growth and short stature. Mean baseline height SDS was below normal (i.e., height < -2 SDS) for treatment naïve subjects, consistent eligibility criteria and with a diagnosis of short stature. While the mean baseline AHV SDS was not below normal (i.e., normal: -2 < AHV SDS < 2) for treatment naïve subjects, this was not an eligibility criterion, nor is it necessary for these diagnoses. Further, mean baseline AHV was at the lower end of normal. Finally mean baseline IGF-1 SDS values in all treatment groups of all sub-trials were within the normal range (i.e., -2 < IGF-1 SDS < 2), indicating sufficient GH status.

For treatment non-naïve subjects, overall mean baseline height SDS was > -2 and mean baseline AHV and AHV SDS were consistent with normal growth, likely due to growth promoting therapy. As with treatment naïve subjects, mean baseline IGF-1 SDS values in all treatment groups of all sub-trials were within the normal range (i.e., -2 < IGF-1 SDS < 2), indicating sufficient GH status.

Refer to Table 26, Table 27, and Table 28, for baseline characteristics of the SGA, NS, and ISS, respectively, in trial 4469.

Table 26. Baseline Characteristics of the SGA Population, Trial 4469

Demographics	Treatment Naïve (N=4)	Treatment Non-Naïve (N=8)	Total (N = 12)
Mean (SD)			
AHV (cm/year)	4.6 (2.2)	7.2 (2.2)	6.3 (2.4)
AHV SDS	-0.1 (1.5)	0.8 (1.1)	0.5 (1.2)
IGF-1 SDS	-0.1 (1.3)	0.5 (1)	0.3 (1.1)
Height SDS	-2.9 (0.5)	-1.2 (0.6)	-1.8 (1)
Height SDS, n (%)			
< -2.5	4 (100)	0	4 (33.3)
≥ -2.5	0	8 (100)	8 (66.7)

Source: Clinical Trial Report for trial 4469, Table 4-5, page 58; Table 4-6, pages 59 and 60; Table 8.2.23, pages 202 to 203; and Table 8.2.67, pages 244 to 245.

Table 27. Baseline Characteristics of the NS Population, Trial 4469

Demographics	Treatment Naïve (N=6)	Treatment Non-Naïve (N=7)	Total (N = 13)
Mean (SD)			
AHV (cm/year)	4.2 (2.3)	6.2 (1.5)	5.3 (2.1)
AHV SDS	-0.4 (1.4)	0.5 (0.7)	0.1 (1.2)
IGF-1 SDS	-0.7 (1.2)	-1 (1.7)	-0.8 (1.4)
Height SDS	-2.7 (0.5)	-1.5 (0.8)	-2.1 (0.9)
Height SDS, n (%)			
< -2	6 (100)	1 (14.3)	7 (53.9)
≥ -2	0	6 (85.7)	6 (46.1)

Source: Clinical Trial Report for trial 4469, Table 4-7, page 61; Table 4-8, pages 62 and 63; Table 8.2.22, page 201; and Table 8.2.66, page 243.

Table 28. Baseline Characteristics of the ISS Population, Trial 4469

Demographics	Treatment Naïve (N=2)	Treatment Non-Naïve (N=9)	Total (N = 11)
Mean (SD)			
AHV (cm/year)	3.3 (0.4)	8 (2.9)	7.2 (3.2)
AHV SDS	-1.5 (0.2)	1.3 (1.1)	0.8 (1.5)
IGF-1 SDS	0.4 (0.4)	0.4 (1.4)	0.4 (1.2)
Height SDS	-2.7 (0.1)	-1.6 (1.3)	-1.8 (1.2)
Height SDS, n (%)			
< -2.5	2 (100)	3 (33.3)	5 (45.5)
≥ -2.5	0	6 (66.7)	6 (54.5)

Source: Clinical Trial Report for trial 4469, Table 4-9, page 64; Table 4-10, pages 65 and 66; Table 8.2.21, pages 199 to 200; and Table 8.2.65, pages 241 to 242.

8.1.3.11. Comorbidities

In the SGA population, only seasonal allergy (n=3) and vitamin D deficiency (n=2) are reported by more than 1 subject. In the NS population pulmonary valve stenosis (n=5), and cryptorchidism, eyelid ptosis, hypothyroidism, and vitamin D deficiency (n=2, each) are

reported by more than 1 subject. Hypothyroidism and seasonal allergy (n=2, each) are the only comorbidities reported by more than 1 subject in the ISS population. Overall, the incidence of comorbidities in any of the sub-trials in trial 4469 is small and unlikely to have a significant impact on the analysis of efficacy of somapacitan. See Table 127, Table 128, and Table 129, in Section 15.4.3 for comorbidities of subjects in the SGA, NS, and ISS populations of trial 4469, respectively.

8.1.3.12. Concomitant Medications

As in the phase 3 trial 4467, the only concomitant medications taken by more than one subject in any of the sub-trials of trial 4469 were consistent with medications taken in the general pediatric population and include analgesics/antipyretics, antibiotics, antihistamines/anti-allergy medications, melatonin, vitamin supplementation, and cough suppressants. Levothyroxine is also among the concomitant medications reported by at least 2 subjects in trial 4469 and is appropriate for subjects with hypothyroidism as a comorbidity. See Table 130, Table 131, and Table 132, in Section 15.4.3 for concomitant medications of subjects in the SGA, NS, and ISS populations of trial 4469, respectively. It is unlikely that the reported concomitant medications in this trial had a significant impact on the analysis of efficacy of somapacitan in this trial.

8.1.3.13. Treatment Compliance

Treatment compliance was assessed by cross checking the following to expected use: drug accountability information (counting of returned trial product, visual inspection of pens), question of subjects, comparing prescribed and actual doses, and review of the subjects' dosing diaries. These were documented at site visits and confirmed by site staff. Overall, appropriate measures were taken to ensure treatment compliance.

The majority of the subjects in the SGA, NS, and ISS sub-trials received the planned treatment. In the SGA sub-trial, the mean (SD) adherence was 99.3 (1.5)% and 98.9 (1.4)% for the treatment naïve and non-naïve groups, respectively. In the NS sub-trial, the mean (SD) adherence was 97.6 (3.7)% and 88.3 (18.5)% for the treatment naïve and non-naïve groups, respectively. In the ISS sub-trial, the mean (SD) adherence was 96.6 (0.5)% and 95.9 (7.4)% in the treatment naïve and non-naïve groups, respectively.

8.1.3.14. Efficacy Endpoint Results

The trial was designed as a safety trial, no efficacy analyses were prespecified. The trial was of a short duration (26 weeks), enrolled a small number of subjects and did not have a comparator group. Due to all these factors, the results are difficult to interpret. Lastly, many of these subjects were hGH treatment non-naïve, which confounds further the effect of somapacitan on growth. However, the results showed that subjects continued improvement in growth parameters in this study and the findings were similar to those in in the pivotal phase 3 trial 4467 and phase 2 dosing finding trial 4245.

Annualized Height Velocity

The mean (SD) AHV increased in all treatment naïve subjects at Weeks 26 for all populations, with mean (SD) AHV 11.3 (3.8) cm/year, 9.1 (2.3) cm/year, and 9.2 (3.5) cm/year, for the treatment naïve subjects of the SGA (n = 4), NS (n = 6), and ISS (n = 2) populations, respectively. For treatment non-naïve subjects, increase in AHV was small, however; AHV is known to wane after the initial catch up in growth once therapy has been initiated. Refer to Table 133, in Section 15.4.3.

Annualized Height Velocity SDS

The changes in AHV SDS at Week 26 showed a similar pattern of increase for treatment naïve subjects as was seen for AHV; the mean AHV SDS at baseline ranged from -1.5 to 0 for all treatment naïve populations and increased to mean (SD) AHV SDS of 3.5 (1.5), 3 (2.7), and 1.4 (0.6), for the treatment naïve subjects of the SGA (n = 4), NS (n = 6), and ISS (n = 2) populations, respectively. For treatment non-naïve subjects, mean AHV SDS values were consistent with continued growth as well. Refer to Table 134, in Section 15.4.3.

Height SDS

An improvement in height SDS was observed during 26 weeks of treatment with somapacitan in treatment naïve subjects of all populations, with mean (SD) change in 26-week height SDS from baseline of 0.5 (0.2), 0.4 (0.3), and 0.2 (0.2), for the treatment naïve subjects of the SGA (n = 4), NS (n = 6), and ISS (n = 2), populations, respectively (see Table 135, in Section 15.4.3). In general, the treatment non-naïve subjects of all populations also showed increases in height SDS with somapacitan therapy (see Table 136, in Section 15.4.3).

Bone Age

Very few subjects in trial 4469 have available bone age data following 1 year of treatment with somapacitan. However, in general, the available data do not indicate that somapacitan advanced bone age significantly relative to chronological age for treatment naïve or non-naïve subjects of the populations treated in the adolescent trial. See Table 137, in Section 15.4.3.

Conclusions

The interpretation of the results of the phase 3 trial 4469 in treatment naïve and non-naïve adolescents are overall limited by the small number of subjects in each treatment arm of each population enrolled, absence of comparator, trial design (safety trial without prespecified efficacy analyses) and the duration of the trial. However, the available data suggest that in adolescent subjects in the SGA, NS, and ISS, populations, treatment with somapacitan induced growth.

8.1.3.15. Dose/Dose Response

As only one dose of somapacitan was evaluated in this trial, dose response cannot be assessed.

8.1.3.16. Durability of Response

As discussed in Section 8.1.3.14, as of the cutoff date, very few subjects of any population were treated beyond 26 weeks in this trial. What data are available for treatment beyond 26 weeks are included in the tables discussed in that section and suggest that continued treatment with somapacitan results in increased growth in adolescents.

8.1.3.17. Persistence of Effect

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

8.1.3.18. COA (PRO) Endpoints

The Applicant also assessed parent/caregiver responses to the following COA: GH-INJ-CTB-Child and GH-PPQ-Child. However, these COAs have not been validated in the intended population and thus interpretation of information derived from this COA for the intended population is challenging, no meaningful conclusions can be drawn, and these data would not be eligible for inclusion in labeling.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

Primary Endpoints

The primary efficacy endpoint of each sub-trial of the phase 3 trial 4467 evaluated efficacy by comparing AHV after 52 weeks of 0.24 mg/kg/week somapacitan to approved, daily hGH treatment (0.035 or 0.067 mg/kg/day Norditropin for subjects in the SGA population, and 0.05 mg/kg/day Norditropin for subjects in the NS and ISS populations) in pediatric patients ≥ 2.5 years of age with 1) short stature born SGA and with no catch-up growth by 2 years of age; 2) growth failure associated with NS; and 3) ISS. For each of the proposed indications, the trial met the prespecified primary endpoint and demonstrated that somapacitan was non-inferior to Norditropin in the improvement in AHV:

- The mean AHV of subjects in the SGA population treated with somapacitan, 0.035 mg/kg/day Norditropin, and 0.067 mg/kg/day Norditropin was 11, 9.4, and 11.1 cm/year,

respectively, with estimated treatment differences of 1.6 cm/year (95% CI 0.91, 2.23) and -0.1 cm/year (95% CI -0.75, 0.6), respectively.

- The mean AHV of subjects in the NS population treated with somapacitan and Norditropin was 10.4 and 9.4 cm/year, respectively, with an estimated treatment difference of 1.2 cm/year (95% CI 0.32, 2.03).
- The mean AHV of subjects in the ISS population treated with somapacitan and Norditropin was 10.2 and 10.5 cm/year, respectively, with an estimated treatment difference of -0.3 cm/year (95% CI -1, 0.42).

However, somapacitan-induced AHV in subjects with ISS and NS was not compared to the maximum approved dose of Norditropin; doses of Norditropin for the ISS and NS populations in the trial were 0.05 mg/kg/day, and the maximum approved doses of Norditropin are 0.066 mg/kg/day for NS and 0.067 mg/kg/day for ISS. Therefore, language should be added to Section 14 of the label to clarify that the comparisons of somapacitan to Norditropin in the ISS and NS population were to less than maximum approved dosing of the comparator in order to inform the prescriber when selecting the product for the treatment.

The phase 2 trial 4245 in the SGA population provides additional efficacy data. TH trial demonstrated that AHV improved in all treatment groups at Weeks 26 and 52. The mean AHV at 52 weeks of the 0.16, 0.2, and 0.24 mg/kg/week somapacitan groups was 8.5, 10.3, and 10.6 cm/year, respectively, compared to the 0.035 and 0.067 mg/kg/day Norditropin groups with mean 52-week AHVs of 9.4 and 11.2 cm/year, respectively. The AHV at 52 weeks for subjects treated with.24 mg/kg/week somapacitan and 0.067 mg/kg/day Norditropin in the phase 2 trial 4245 was comparable to the 52-week AHV in the SGA population of the phase 3 trial 4467. Additional data from the phase 3 trial 4469 in the adolescent, treatment naïve SGA, NS, and ISS populations also showed similar data: 26 weeks of 0.24 mg/kg/week somapacitan resulted in a mean AHV of 11.3, 9.1, and 9.2 cm/year, respectively.

Finally, the drug-induced increases in AHV were sustained beyond the first year of treatment. In the extension period of the pivotal phase 3 trial 4467, data from continued treatment with somapacitan showed continued growth in all populations, though AHV decreased with continued treatment. This trend is expected and a similar trend is observed during therapy with approved hGH products: in children exposed to only 0.24 mg/kg/week somapacitan 1) in the SGA population, the observed mean AHV was 8.8 and 8.7 cm/year after 78 and 104 weeks, respectively; 2) in the NS population, the observed mean AHV was 8.4 and 7.4 cm/year after 78 and 104 weeks, respectively; and 3) in the ISS population, the observed mean AHV was 8.6 and 7.6 cm/year after 78 and 104 weeks, respectively.

Secondary and Other Endpoints

In the phase 3 trial 4467, the other growth parameters also improved at the end of 52 weeks of treatment (height SDS and AHV SDS) for the SGA, NS, and ISS populations. The mean changes in bone age were small and did not demonstrate rapid advancement of bone age with treatment. The overall results of these secondary endpoints were supportive of the primary endpoints and were consistent with improvement in growth in pediatric patients ≥

2.5 years of age with 1) short stature born SGA and with no catch-up growth by 2 years of age; 2) growth failure associated with NS; and 3) ISS treated with 0.24 mg/kg/week somapacitan.

Because the secondary endpoints were not adjusted for multiplicity, if secondary endpoints are reported in the label, it should be descriptive only.

The phase 2 trial 4245 also included evaluation of the growth parameters (height SDS and AHV SDS) in children of the SGA population. The largest improvements in these parameters were seen in the 0.2 and 0.24 mg/kg/week somapacitan groups and the 0.067 mg/kg/day Norditropin group, and the overall results were consistent with the changes seen in the phase 3 trial 4467. The mean changes in bone age were small and did not demonstrate rapid advancement of bone age with treatment. However, these results should be interpreted with caution because of multiple factors, including the small number of subjects per arm and the endpoints were not adjusted for multiplicity, therefore, these results should be interpreted with caution.

The interpretation of the results of the phase 3 trial 4469 in adolescents of the SGA, NS, and ISS populations are overall limited by the small number of subjects in each treatment arm of each population enrolled, absence of comparator, trial design (safety trial without prespecified efficacy analyses) and the duration of the trial. However, the available data suggest that in adolescent subjects in the SGA, NS, and ISS, populations, treatment with somapacitan induced growth (improvement in height SDS and AHV SDS, and small changes in bone age).

The open label extension periods of the pivotal phase 3 trial 4467, the phase 2 trial 4245 in subjects born SGA, and the phase 3 trial 4469 in children older than 10 years of age provided additional evidence of effectiveness. The results of these secondary endpoints demonstrated long-term improvement in growth parameters in children 2.5 years of age and older with short stature born SGA and no catch-up growth by 2 years of age, with growth failure associated with NS, or with ISS, and open epiphyses.

Subpopulations

Analyses of the primary endpoint of AHV after 52 weeks of treatment in the SGA, NS, and ISS populations of the pivotal phase 3 trial 4467 were conducted in the following subgroups: age (< or ≥ 6 years of age), sex (male or female), race (white or Asian), ethnicity (Hispanic/Latino or not Hispanic/Latino), and region (US or outside-US). The results from these sub-population analyses followed the same trends as for the entire trial population in both the somapacitan and Norditropin groups for each of the proposed indications (refer to Section 8.1.1.13).

Dose and Dose Response

In the phase 3 trial 4467 used for registrational purposes, all subjects treated with somapacitan received 0.24 mg/kg/week somapacitan throughout the trial. The dose could

only be decreased for safety reasons and titration targeting improved efficacy was not permitted.

As such, the recommended dose should be 0.24 mg/kg/week somapacitan for pediatric patients ≥ 2.5 years of age with 1) short stature born SGA and with no catch-up growth by 2 years of age; 2) growth failure associated with NS; and 3) ISS.

8.2.2. Additional Efficacy Considerations

The Applicant proposes this drug for all pediatric subjects with short stature born SGA and no catch-up growth by 2 years of age, and for pediatric subjects of all ages with growth failure associated with NS or with ISS, and open epiphyses. However, no subjects < 2.5 years of age were included. Further, for children born SGA, initiation of GH therapy is not recommended before 2 years of age as many of these children have appropriate catch-up growth by this time, and to allow for evaluation of underlying growth-limiting conditions if they do not have appropriate growth by this time. For children with ISS, this is a diagnosis of exclusion and an appropriate duration of time to evaluate for growth failure and evaluation of underlying growth-limiting conditions must also be conducted; it is also unlikely that there will be a major benefit to treatment before the age of 2.5 years. For children with NS, treatment of short stature with GH therapy during early childhood, including < 2.5 years of age, is controversial, in part due to safety concerns such as cardiac comorbidity and increased risk of certain malignancies. In addition, it is unknown if subjects < 2.5 years of age have a similar, greater, or lower IGF-1 response to somapacitan compared to subjects ≥ 2.5 years of age. Further, if subjects < 2.5 years of age were to have persistently elevated IGF-1 after treatment with somapacitan, given its longer half-life relative to currently available, daily hGH therapies, any AEs observed may not be as easily reversible upon discontinuation of the drug. Lastly, the magnitude of somapacitan-induced growth in this young population also unknown. Because of these concerns, somapacitan should not be indicated for patients born SGA, or with NS or ISS, who are < 2.5 years of age.

While the pivotal phase 3 trial 4467 did not include subjects older than 11 years of age, the phase 3 trial 4469 did include data safety and efficacy data from a limited number of children as old as 15 years of age. Given that the mechanism of action of GH is expected to be the same in all children (i.e., GH binds to and activates GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, and as GH and IGF-1 stimulate epiphyseal growth plates and the formation of new bone, resulting in increased linear growth), it is expected that these older subjects will respond with improved growth after exposure to somapacitan.

Therefore, the drug should be indicated only for pediatric patients ≥ 2.5 years of age with 1) short stature born SGA and with no catch-up growth by 2 years of age; 2) growth failure associated with NS; and 3) ISS.

8.2.3. Integrated Assessment of Effectiveness

Substantial evidence of effectiveness of somapacitan for the proposed indications was provided from the phase 3 trial 4467, which was a randomized, open-labelled, active comparator (Norditropin; somatropin) phase 3 basket trial to evaluate the efficacy and safety of once-weekly somapacitan compared to daily somatropin after 52 weeks in GH-treatment naïve pre-pubertal children with short stature associated with being born SGA, NS, ISS, or TS. As mentioned above, the results of this trial evaluating Turner syndrome will not be discussed in this review.

In the SGA cohort, subjects were randomized in a 2:1:1 ratio to either:

- 0.24 mg/kg/week somapacitan;
- 0.035 mg/kg/day (0.25 mg/kg/week) Norditropin; or
- 0.067 mg/kg/day (0.47 mg/kg/week) Norditropin.

In [redacted] (b) (4) NS, and ISS cohorts, subjects were randomized in a 2:1 ratio to either:

- 0.24 mg/kg/week somapacitan; or
- 0.05 mg/kg/day (0.35 mg/kg/week) Norditropin.

Trial 4467 was conducted in pediatric subjects with proportional short stature associated with non-GHD conditions. Each sub-trial was designed to demonstrate that somapacitan was non-inferior to AHV after 52 weeks of therapy with Norditropin independently in each subpopulation of subjects with short stature associated with non-GHD syndromes (i.e., born SGA, ISS, and NS). Each sub-trial included an active comparator group(s), i.e., Norditropin. The primary endpoint in all sub-trials were the same, i.e., AHV at the end of 52 weeks of treatment, and was conducted in subjects with the intended and closely related indications. Each sub-trial included prespecified independent primary efficacy analyses to establish the efficacy of the drug in each of the proposed indications.

Providing substantial evidence of effectiveness in each of these proposed indications of proportional short stature associated with a non-GHD condition from the individual adequate and well-controlled sub-trials is an acceptable approach. Each individual condition results in short stature not due to GHD and there is a strong mechanistic understanding of how hGH exerts its effect in children with short stature born SGA, associated with NS, or with ISS. Exogenous hGH therapy improves growth by acting along a similar mechanism of action in all three conditions. The structure-function relationship of endogenous GH is well-understood. The wide variety of GH biological effects is mediated by one mechanism of action, i.e., GH binding to and activating GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, which stimulates the proliferation of chondrocytes and results in bone growth. No alternative receptors mediating GH activity have been identified. It has been already demonstrated that treatment with approved hGH products improve linear growth in all three conditions (as per Section 2). Clinical trials evaluating the use hGH to improve growth in these indications use similar efficacy endpoints (i.e., AHV and/or height SDS at 52 or 104 weeks; as per Section 7.2). The active moiety of somapacitan has the same

primary amino acid sequence as native hGH and thus is expected to have the same action at the target receptor as native hGH.

In the phase 3 trial 4467, a fixed dose of 0.24 mg/kg/week somapacitan was used, regardless of age or severity of short stature at baseline. For each of the proposed indications, the trial met its primary endpoint of AHV at 52 weeks. Non-inferiority of somapacitan to Norditropin was established as the 95% CI of the estimated treatment differences of 52-week mean AHV between somapacitan and Norditropin for each group was ≥ -1.6 cm/year, the prespecified non-inferiority margin:

- The effect of 0.24 mg/kg/week somapacitan on AHV (11 cm/year) was non-inferior to the effect of 0.035 mg/kg/day Norditropin (9.4 cm/year) and 0.067 mg/kg/day Norditropin (11.1 cm/year) after 52 weeks of treatment in pediatric subjects with short stature born SGA.
  - Estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.035 and 0.067 mg/kg/day Norditropin was 1.6 cm/year (95% CI 0.91, 2.23; p-value < 0.001) and -0.1 cm/year (95% CI -0.75, 0.6; p-value = 0.823).
- The effect of 0.24 mg/kg/week somapacitan on AHV (10.4 cm/year) was non-inferior to the effect of 0.05 mg/kg/day Norditropin (9.4 cm/year) after 52 weeks of treatment in pediatric subjects with growth failure associated with NS.
  - Estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.05 mg/kg/day Norditropin was 1.2 cm/year (95% CI 0.32, 2.03; p-value = 0.0071).
- The effect of 0.24 mg/kg/week somapacitan on AHV (10.2 cm/year) was non-inferior to the effect of 0.05 mg/kg/day Norditropin (10.5 cm/year) after 52 weeks of treatment in pediatric subjects with ISS.
  - Estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.05 mg/kg/day Norditropin was -0.3 cm/year (95% CI -1, 0.42; p-value = 0.4107).

However, somapacitan-induced AHV in subjects with ISS and NS was not compared to the maximum approved dose of Norditropin; doses of Norditropin for the ISS and NS populations in the trial were 0.05 mg/kg/day, and the maximum approved doses of Norditropin are 0.066 mg/kg/day for NS and 0.067 mg/kg/day for ISS. Therefore, language should be added to Section 14 of the label to clarify that the comparisons of somapacitan to Norditropin in the ISS and NS population were to less than maximum approved dosing of the comparator in order to inform the prescriber when selecting the product for the treatment.

The results of the secondary analyses were supportive of the primary analysis for each indication; the phase 3 trial 4467 demonstrated improvement in all other growth parameters (height SDS and AHV SDS). Secondary endpoints were not included in any test hierarchy and there were no adjustments for multiplicity. As such, results of statistical analyses could be due to chance, consistent with the principle and limitations of multiple endpoints testing, so interpretation of results should be made with caution. Further, statistical claims based on the supportive secondary endpoints should not be included in the label.

Treatment effects were generally consistent across subgroups (age (< or ≥ 6 years of age), sex

(male or female), race (white or Asian), ethnicity (Hispanic/Latino or not Hispanic/Latino), and region (US or outside-US)) in each of the proposed indicated populations.

Additional evidence of efficacy provided by the phase 2 trial 4245 revealed a similar mean AHV at the end of 52 weeks of treatment with 0.24 mg/kg/week somapacitan for the SGA population: 10.6 cm/year. The improvement in the other growth parameters observed in this trial at Week 52 were in general consistent with the improvements in these parameters in the phase 3 trial 4467. Additionally, in adolescent children of the SGA, NS, and ISS populations in the phase 3 trial 4469, improvement in mean AHV, height SDS, and AHV SDS were seen with 0.24 mg/kg/week somapacitan treatment.

Durability of response to somapacitan was addressed in the open label extension periods of the pivotal phase 3 trial 4467, the phase 2 trial 4245 in subjects born SGA, and the phase 3 trial 4469 in children older than 10 years of age provided additional evidence of effectiveness. The results of these secondary endpoints demonstrated long-term improvement in growth parameters in children 2.5 years of age and older with short stature born SGA and no catch-up growth by 2 years of age, with growth failure associated with NS, or with ISS, and open epiphyses. In the extension period of the pivotal phase 3 trial, data with continued treatment with somapacitan showed continued growth in all populations, though AHV decreased with continued treatment. This trend is expected and a similar trend is observed during therapy with approved hGH products: in children exposed to only 0.24 mg/kg/week somapacitan 1) in the SGA population, the observed mean AHV was 8.8 and 8.7 cm/year after 78 and 104 weeks, respectively; 2) in the NS population, the observed mean AHV was 8.4 and 7.4 cm/year after 78 and 104 weeks, respectively; and 3) in the ISS population, the observed mean AHV was 8.6 and 7.6 cm/year after 78 and 104 weeks, respectively.

No subjects < 2.5 years of age were included. Further, for children born SGA, initiation of GH therapy is not recommended before 2 years of age as many of these children have appropriate catch-up growth by this time, and to allow for evaluation of underlying growth-limiting conditions if they do not have appropriate growth by this time. For children with ISS, this is a diagnosis of exclusion and an appropriate duration of time to evaluate for growth failure and evaluation of underlying growth-limiting conditions must also be conducted; it is also unlikely that there will be a major benefit to treatment before the age of 2.5 years. For children with NS, treatment of short stature with GH therapy during early childhood, including < 2.5 years of age, is controversial, in part due to safety concerns such as cardiac comorbidity and increased risk of certain malignancies. In addition, it is unknown if subjects < 2.5 years of age have a similar, greater, or lower IGF-1 response to somapacitan compared to subjects ≥ 2.5 years of age. Further, if subjects < 2.5 years of age were to have persistently elevated IGF-1 after treatment with somapacitan, given its longer half-life relative to currently available, daily hGH therapies, any AEs observed may not be as easily reversible upon discontinuation of the drug. Lastly, the magnitude of somapacitan-induced growth in this young population also unknown. Because of these concerns, somapacitan should not be indicated for patients born SGA, or with NS or ISS, who are < 2.5 years of age. For older children, while the pivotal phase 3 trial 4467 did not include subjects older than 11 years of age, the phase 3 trial 4469 did include data safety and efficacy data from a limited number of

children as old as 15 years of age. Given that the mechanism of action of GH is expected to be the same in all children (i.e., GH binds to and activates GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, and as GH and IGF-1 stimulate epiphyseal growth plates and the formation of new bone, resulting in increased linear growth), it is expected that these older subjects will respond with improved growth after exposure to somapacitan.

In conclusion, the efficacy results provided from adequate and well controlled sub-trials (included in phase 3 basket trail 4467) conducted in each of the intended populations support approval of somapacitan in pediatric patients ≥ 2.5 years of age with 1) short stature born SGA and with no catch-up growth by 2 years of age; 2) growth failure associated with NS; and 3) ISS.

8.3. Review of Safety

8.3.1. Safety Review Approach

The safety data were derived from the pivotal phase 3 trial 4467 (completed Main Period and ongoing Extension Periods), the phase 2 dose finding trial 4245 (completed Main Period, Extension Period I, and Extension Period II), and the phase 3 trial 4469 (completed Main Period and ongoing Extension Periods). The data from completed 26-week Main Period of trial 4245 have a database lock date of May 28, 2021, and data from the Extension Periods of trial 4245 have a database lock date of January 17, 2025. The data from the completed 52-week Main Period of trial 4467 have database lock dates of October 23, 2024, for the SGA and ISS sub-trials, and December 16, 2024, for the NS sub-trial (with the exception of some additional anti-somapacitan antibody data that had a lock date of December 16, 2024, and January 16, 2025, for the SGA and NS sub-trials, respectively). The database lock date for all ongoing OLE periods of these trials is November 24, 2024. Additional safety data from the ongoing trials, provided in the 120-Day Safety Update with a database lock date of June 02, 2025, were also reviewed.

The prespecified safety analysis plan and definitions were reviewed during the clinical development program and were acceptable. The safety population was defined by the Applicant as the SAS and was defined as all subjects exposed to study intervention/trial product (i.e., somapacitan or Norditropin of any dose).

The Applicant presented safety data by individual trial. In the phase 3 trials (trials 4467 and 4469) that included a basket design with sub-trials based on the proposed indications, the Applicant presented safety data by individual diagnosis, i.e., by SGA, NS, ISS, or TS populations. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 27.1.

This medical reviewer used safety data originating from the completed, randomized, active-controlled Main Period of the pivotal phase 3 trial 4467 as the primary source of safety assessment. The Main Period of this trial provides the most informative data on common product-related safety issues because it allows a direct comparison of somapacitan to

Norditropin (with an established safety profile in the proposed indications), the data were obtained in randomized groups with frequent assessments and had a Main Period with a 52-week duration of controlled observation. Supportive and long-term safety data are obtained from the ongoing Extension Periods of the phase 3 trial 4467, the phase 2 trial 4245 (completed Main Period, Extension Period I, and Extension Period II), and the phase 3 trial 4469 in subjects that were older than those in, but otherwise eligible for, trial 4467 (completed Main Period and ongoing Extension Periods). However, the overall analysis of safety data from the supportive phase 2 trial 4245 is complicated because of the different lengths of exposure to the proposed dose (0.24 mg/kg/week somapacitan) and the use of lower doses for 52 weeks in portion of the enrolled subjects. The analysis of safety data from the ongoing Extension Periods of the phase 3 trial 4467 is complicated by the lack of a control arm. Additionally, the safety data from the phase 3 trial 4469 is complicated by the fact that the majority of enrolled subjects were exposed to previous treatment with growth-promoting therapies that potentially confound the results, the small number of subjects enrolled with limited exposure to somapacitan, and by the lack of a control group. Thus, the supportive safety data should be interpreted with caution. This clinical reviewer also analyzed and presented the safety data separately for each individual trial and population-based sub-trial.

Clinical trial data were analyzed independently by the clinical reviewer using JMP clinical, Analysis Studio, and MAED software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

This safety review also focused on class-specific AEs seen with currently approved growth hormone therapies, namely, severe hypersensitivity, neoplasms, glucose intolerance, intracranial hypertension (IH), fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis (SCFE) and osteonecrosis, progression of preexisting scoliosis, pancreatitis, and injections site reactions (including lipoatrophy).

Finally, the clinical reviewer conducted an analysis of AEs occurring during the clinical development program using Office of New Drugs (OND) Custom Medical Queries (OCMQ) or grouped queries (GQ). OCMQs were developed by FDA to improve the capture of synonymous AE terms and to improve overall safety signal detection. This medical reviewer performed the OCMQ analysis using JMP Clinical. To further improve safety signal detection, the clinical reviewer also created GQs which consisted of AEs that were not already part of an OCMQ but were synonymous. Subjects who reported more than 1 individual preferred term (PT) grouped in a single OCMQ or GQ are only counted once in the number of subjects reporting that combined term.

8.3.2. Review of the Safety Database

Overall Exposure

SGA

Throughout the pivotal phase 3 trial 4467, the phase 2 trial 4245, and the phase 3 trial 4469, a total of 212 pediatric subjects with short stature born SGA received at least one dose of 0.24 mg/kg/week somapacitan. The mean (SD) of exposure of subjects born SGA to 0.24 mg/kg/week somapacitan in trial 4245 was 125 (63) weeks (range 18.1 to 279 weeks), in trial 4467 was 51.8 (29) weeks (range 0.1 to 107 weeks), and in trial 4469 was 59 (14) weeks (range 47.1 to 90.1 weeks).

Of the 212 subjects born SGA exposed to at least one dose of 0.24 mg/kg/week somapacitan, 173 (81.6%), 132 (62.3%), 78 (36.8%), 46 (21.7%), 13 (6.1%), 12 (5.7%), 12 (5.7%), 12 (5.7%), 7 (3.3%), and 1 (0.5%) subject received 0.24 mg/kg/week somapacitan for ≥ 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months, respectively.

NS

Throughout the pivotal phase 3 trial 4467 and the phase 3 trial 4469, a total of 88 pediatric subjects with NS received at least one dose of 0.24 mg/kg/week somapacitan. The mean (SD) of exposure of subjects with NS to 0.24 mg/kg/week somapacitan in trial 4467 was 58.1 (28) weeks (range 4.1 to 109 weeks) and in trial 4469 was 48 (15) weeks (range 36.9 to 88.4 weeks).

Of the 88 subjects with NS exposed to at least one dose of 0.24 mg/kg/week somapacitan, 71 (80.7%), 52 (59.1%), 22 (25%), and 2 (2.3%) subjects received 0.24 mg/kg/week somapacitan for ≥ 6, 12, 18, and 24 months, respectively.

ISS

Throughout the pivotal phase 3 trial 4467 and the phase 3 trial 4469, a total of 97 pediatric subjects with ISS received at least one dose of 0.24 mg/kg/week somapacitan. The mean (SD) of exposure of subjects with ISS to 0.24 mg/kg/week somapacitan in trial 4467 was 63.6 (28) weeks (range 9.3 to 116 weeks) and in trial 4469 was 67.4 (14) weeks (range 38.1 to 89.1 weeks).

Of the 97 subjects with ISS exposed to at least one dose of 0.24 mg/kg/week somapacitan, 81 (83.5%), 68 (70.1%), 26 (26.8%), and 7 (7.2%) subjects received 0.24 mg/kg/week somapacitan for ≥ 6, 12, 18, and 24 months, respectively.

Adequacy of the Safety Database

Overall, while the level of exposure to 0.24 mg/kg/week somapacitan during the clinical development program does not satisfy the ICH E1 guidelines[34] for safety assessment of chronically administered medications, similar exposures have been accepted to support approval of other hGH products for the same indications (SGA – Genotropin: 169 subjects over two different doses, Humatrope: 214 subjects of 3 different dosing regimens; NS – Norditropin: 21 subjects over two different doses; ISS – Genotropin: 177 subjects randomized to receive one of two doses, or no treatment). [35, 36, 37] Thus, the safety database from the pivotal phase 3 trial 4467, the phase 2 trial 4245, and the phase 3 trial 4469 is considered adequate for a comprehensive safety assessment of 0.24 mg/kg/week somapacitan for the proposed indications, patient population, and dosage regimen at the time of BLA submission.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

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

Categorization of Adverse Events

The Applicant's definitions of AEs and serious AEs (SAEs) in the protocols were accurate and the process for recording, coding, and categorizing AEs was overall reasonable and appropriate.

- An AE was defined any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of investigational medicinal product (IMP), whether or not considered related to the IMP. AN AE can therefore be any unfavorable and unintended sign, symptoms, or disease (new or exacerbated) temporally associated with the use of an IMP.
- The Applicant did not use the term treatment emergent adverse event (TEAE) but instead used an "on-treatment observation period" to analyze AEs. The Applicant defined the on-treatment observation period as all observed data that occurs from first administration of

[34] Guideline for Industry *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995).

[35] Genotropin (BLA 020280) label available at:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ffebf88b-d257-4542-9808-74d9b7167765

[36] Humatrope (BLA 019640) label available at:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a774e1ae-3997-49ee-8b0e-99a2b315d409

[37] Norditropin (BLA 021148) label available at:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1058e17c-9261-459c-a3e6-fae38d196c14

IMP and up until the last visit of the trial, last contact, or 14 days after the last administration, whichever occurs first. Unless otherwise stated, all reporting of AEs in this review will be those that occur during this "on-treatment observation period" as, in the opinion of this reviewer, such AEs are consistent with TEAEs.

- SAEs were defined as an AE that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, is a congenital anomaly/birth defect, or is a significant medical event.
- Severity of SAEs and AEs were assessed and reported by the Investigator as one of the following severity categories:
  - Mild: an event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
  - Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
  - Severe: An event that prevents normal everyday activities.
- Given that the protocols do not use a specific grading criteria to grade severity of AEs, and severity is instead based upon the Investigator's assessment, it is possible that assessment of the severity of each AE may not be objective. This complicates the assessment of severity during this review and must be taken into consideration.
- SAEs and AEs were followed until the outcome of the event was "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", "not recovered/not resolved", "fatal", or if the subject is lost to follow up, "unknown".
- Verbatim terms were included in the data files and were appropriately categorized in the AEDECOD (dictionary-derived term) data file.

Routine Clinical Tests

Overall, clinical safety testing was appropriate. Evaluations included regular assessments of hematology parameters, biochemistry parameters, hormones (cortisol, free T4 [Ft3], free T4 [FT4], thyroid stimulating hormone [TSH]), glucose and lipid metabolism, anti-drug antibodies (ADA), bone age x-rays, IGF-1, IGFBP-3, echocardiograms (NS and TS), electrocardiograms, and coagulation parameters (NS, only due to an increased risk for abnormalities of blood coagulation in this population; see Section 2.1). Assessment of injection sites, physical exams, and vital signs were also conducted throughout the trial for safety assessments.

8.3.4. Safety Results

Deaths

There were no deaths reported during any period of the pivotal phase 3 trial, the dose finding phase 2 trial 4245, or the phase 3 trial 4469.

Serious Adverse Events

Overall, the incidence of SAEs was low in the somapacitan clinical program and did not raise new safety concerns related to the use of somapacitan in the indicated populations. Most SAEs either appeared to be unrelated to somapacitan, or there were other confounders that precluded a definitive causal association. The majority of SAEs were reported in one subject, each, though tonsillar and/or adenoid hypertrophy was reported as an SAE in a total of 5 subjects treated with somapacitan in the clinical program. Although the adenoid/tonsillar hypertrophy is not uncommon in the general pediatric population, given the known tissue growth-stimulating effect of IGF-1, and the fact that hyperplasia/hypertrophy is a labeled AE with use of hIGF-1 (Increlex [mecasermin]; BLA 021839) in pediatric patients, the casualty between the drug and the event cannot be ruled out completely. One more SAE that was possibly related to somapacitan of type 1 diabetes mellitus in a subject born SGA and treated with 0.2 mg/kg/week somapacitan in the phase 2 trial resulted in premature study drug discontinuation (see discussion below).

8.3.4.1. Phase 3 Trial 4467

Overall, only a few subjects in this trial, of any diagnosis, reported SAEs. For 1 subject each in the SGA and ISS populations during the Main Period of the trial and 1 and 2 subjects in the SGA and ISS populations, respectively, during the Extension Period, a causal association between SAEs of adenoidal or tonsillar hypertrophy could not be ruled out completely. However, adenoidal and tonsillar hypertrophy are also not uncommon in this population and for several of these subjects, adenoidal and tonsillar hypertrophy were noted prior to somapacitan exposure or concomitant tonsillitis was also noted, confounding assessment. All other SAEs appeared to be unrelated to somapacitan therapy.

SGA

In the 52-week Main Period of the pivotal phase 3 trial, a total of 10/141 (7.1%) subjects born SGA reported 16 SAEs (see Table 29). A higher proportion of subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups reported SAEs than in the somapacitan group: 3/37 (8.1%), 4/36 (11.4%), and 3/69 (4.3%) subjects, respectively.

Table 29. Serious Adverse Events, Main Period of Trial 4467, SGA Safety Population

Preferred Term	Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)	Total (N=141) n (%)
Any SAE	3 (8.1)	4 (11.4)	3 (4.3)	10 (7.1)
Tonsillar hypertrophy	1 (2.7)	2 (5.7)	1 (1.4)	4 (2.8)
Adenoidal hypertrophy	0	1 (2.9)	1 (1.4)	2 (1.4)
Bronchiolitis	0	1 (2.9)	0	1 (0.7)
Choking	0	0	1 (1.4)	1 (0.7)
Influenza	1 (2.7)	0	0	1 (0.7)

Preferred Term	Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)	Total (N=141) n (%)
Melanocytic naevus	0	0	1 (1.4)	1 (0.7)
Metapneumovirus infection	0	1 (2.9)	0	1 (0.7)
Pneumonia Hemophilus	1 (2.7)	0	0	1 (0.7)
Pneumonia mycoplasmal	0	0	1 (1.4)	1 (0.7)
Pneumonia streptococcal	1 (2.7)	0	0	1 (0.7)
Upper respiratory tract infection	1 (2.7)	0	0	1 (0.7)
Viral infection	0	1 (2.9)	0	1 (0.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

Tonsillar hypertrophy (reported in 1, 2, and 1 subject in the somapacitan and high and low dose Norditropin groups, respectively) and adenoidal hypertrophy (reported in 1 subject each in the somapacitan and high dose Norditropin groups) were the only SAEs reported by more than 1 subject born SGA. Six subjects reported only 1 SAE, while 4 subjects reported more than 1 SAE (0.035 mg/kg/day Norditropin: 1 subject – influenza, pneumonia Hemophilus, and pneumonia streptococcal; 0.067 mg/kg/day Norditropin: 1 subject adenoidal hypertrophy, tonsillar hypertrophy, and metapneumovirus infection; and somapacitan: 1 subject – adenoidal hypertrophy and tonsillar hypertrophy, 1 subject – melanocytic naevus and pneumonia mycoplasmal).

During the Extension Period of trial 4467 a total of 5/140 (3.6%) subjects born SGA reported 7 SAEs. These SAEs included pneumonia (2/140 [1.4%] subjects), and adenoidal hypertrophy, tonsillar hypertrophy, tonsillitis, tonsillitis bacterial, and mesenteric lymphadenitis (1/140 [0.7%] subject, each). Only 2 subjects reported more than one SAE (1 subject - tonsillar hypertrophy and adenoidal hypertrophy; 1 subject – tonsillitis and mesenteric lymphadenitis).

All narratives of these SAEs were reviewed by this medical reviewer, and with the exception of the SAEs of adenoidal and tonsillar hypertrophy, were all determined as unlikely to be related to somapacitan. The narratives for the SAEs related to adenoidal and tonsillar hypertrophy in subjects treated with somapacitan are summarized here. All other SAEs are briefly reviewed in Section 15.4.4, Narratives From SAEs Reported in the Pivotal Phase 3 Trial 4467, SGA.

Main Period

Adenoidal Hypertrophy and Tonsillar Hypertrophy

These SAEs (both of moderate severity) were reported in a 3-year-old male with a history of chronic serous otitis media and chronic disease of adenoid vegetations. He also had known chronic tonsillitis prior to entering the trial that were related to multiple upper respiratory tract infections, which led to an examination by an otolaryngologist about 3 months after starting somapacitan therapy. At this visit, the otolaryngologist recommended adenoidectomy and tonsillectomy and was set as the date of onset for these SAEs. The

recommended surgeries occurred about a week and a half after the visit. The SAEs were recovered, and somapacitan dosing was unchanged. While this subject had a history of adenoid vegetations and chronic tonsillitis prior to entering the trial and adenoidal and tonsillar hypertrophy are not uncommon findings in the general pediatric population, given known tissue growth-stimulating effect of IGF-1 (effects of growth hormone are mediated through IGF-1, and this is already a labeled adverse event with use of recombinant human IGF-1, Increlex), the reviewer cannot completely rule out a possible causal association between somapacitan use and these events.

Extension Period

Adenoidal Hypertrophy and Tonsillar Hypertrophy

These severe SAEs were reported in a 4-year-old male with a history of testicular retraction who was originally randomized to the 0.035 mg/kg/day Norditropin group in the Main Period of trial 4467. Approximately 4 months after switching to somapacitan in the Extension Period, he had onset of snoring and sleep apnea and was diagnosed with adenoidal hypertrophy. About 2 months later, he visited an otolaryngologist who also diagnosed tonsillar hypertrophy. About 12 months after the switch to somapacitan (about 24 months of total treatment in the trial), he was hospitalized for adenoidectomy and tonsillectomy, after which both SAEs were reported as recovered. There was no change to somapacitan dosing. Adenoidal and tonsillar hypertrophy are not uncommon findings in pediatric patients, however, given onset of adenoidal hypertrophy within 4 months, and tonsillar hypertrophy within 6 months, of starting somapacitan and the known tissue growth- stimulating effect of IGF-1, the reviewer cannot rule out a possible causal association between somapacitan use and these events.

NS

In the 52-week Main Period of the pivotal phase 3 trial, a total of 7/77 (9.1%) subjects with NS reported 8 SAEs in the pivotal phase 3 trial (see Table 30). A higher proportion of subjects in the Norditropin group reported SAEs than in the somapacitan group: 3/28 (10.7%) vs. 4/49 (8.2%) subjects, respectively.

Table 30. Serious Adverse Events, Main Period of Trial 4467, NS Safety Population

Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)	Total (N=77) n (%)
Any SAE	3 (10.7)	4 (8.2)	7 (9.1)
Adenoidal hypertrophy	1 (3.6)	0	1 (1.3)
Asthma	0	1 (2.0)	1 (1.3)
Cholesteatoma	0	1 (2.0)	1 (1.3)
Febrile convulsion	0	1 (2.0)	1 (1.3)
Gastroenteritis	0	1 (2.0)	1 (1.3)
Lower respiratory tract infection	1 (3.6)	0	1 (1.3)

Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)	Total (N=77) n (%)
Obstructive sleep apnea syndrome	1 (3.6)	0	1 (1.3)
Pneumonia	0	1 (2.0)	1 (1.3)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

No SAEs in the Main Period of the trial were reported by more than 1 subject with NS, and only 1 subject, in the somapacitan group, reported more than 1 SAE (asthma and pneumonia).

During the Extension Period of trial 4467, a total of 4/76 (5.3%) subjects with NS reported 5 SAEs. These SAEs included bone cell giant tumor, diarrhea, nasopharyngitis, pneumonia, and pneumonia aspiration (1/76 [1.3%] subject, each). Only 1 subject reported more than one SAE (diarrhea and nasopharyngitis).

All narratives of these SAEs reported by subjects with NS were reviewed by this medical reviewer and were all determined as unlikely to be related to somapacitan. The narratives for these SAEs are not discussed further here but briefly reviewed in Section 15.4.4, Narratives From SAEs Reported in the Pivotal Phase 3 Trial 4467, NS.

ISS

In the 52-week Main Period of the pivotal phase 3 trial, a total of 3/87 (3.4%) subjects with ISS reported 4 SAEs in the pivotal phase 3 trial (see Table 31). All 3 subjects were in the somapacitan group (3/59 subjects; 5.1%); no subjects in the Norditropin group reported SAEs.

Table 31. Serious Adverse Events, Main Period of Trial 4467, ISS Safety Population

Preferred Term	Norditropin 0.050 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=59)	Total (N=87)
Any SAE	0	3 (5.1)	3 (3.4)
Adenoidal hypertrophy	0	1 (1.7)	1 (1.1)
Influenza	0	1 (1.7)	1 (1.1)
Inguinal hernia	0	1 (1.7)	1 (1.1)
Tonsillar hypertrophy	0	1 (1.7)	1 (1.1)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

No SAEs in the Main Period of the trial were reported by more than 1 subject with ISS, and only 1 subject reported more than 1 SAE (adenoidal hypertrophy and tonsillar hypertrophy).

During the Extension Period of trial 4467, a total of 3/85 (3.5%) subjects with ISS reported 5 SAEs. These SAEs included adenoidal hypertrophy (2/85 [2.4%] subjects), and tonsillar hypertrophy, chronic tonsillitis, and pneumonia bacterial (1/85 [1.2%] subject, each). Two subjects reported more than one SAE (1 subject: adenoidal hypertrophy and tonsillar hypertrophy; 1 subject – adenoidal hypertrophy and chronic tonsillitis).

All narratives of these SAEs were reviewed by this medical reviewer and, with the exception of the SAEs related to adenoidal and tonsillar hypertrophy, were all determined as unlikely to be related to somapacitan. The narratives for the SAEs related to adenoidal and tonsillar

hypertrophy in subjects treated with somapacitan are summarized here. All other SAEs are briefly reviewed in Section 15.4.4, Narratives From SAEs Reported in the Pivotal Phase 3 Trial 4467, ISS.

Main Period

Adenoidal Hypertrophy and Tonsillar Hypertrophy

These moderate SAEs were reported in a 4-year-old female subject with a history of rhinitis, nasosinusitis, asthma, and adenoidal and tonsillar hypertrophy. She was first diagnosed with adenoidal and tonsillar hypertrophy approximately 6 and 1 month, respectively, prior to starting therapy with somapacitan in the pivotal phase 3 trial. Approximately 7 months after starting somapacitan therapy, she was hospitalized for "acute worsening of the condition" and underwent bilateral total tonsillectomy and palatopharyngoplasty. Approximately 1 week after admission she was discharged, and the adenoidal and tonsillar hypertrophy SAEs were reported as recovered. Somapacitan therapy was unchanged. While adenoidal and tonsillar hypertrophy are not uncommon findings in pediatric patients, and both were present prior to starting therapy in this trial, given the need for adenoidectomy and tonsillectomy within 7 months after the initiation of somapacitan and the known tissue growth-stimulating effect of IGF-1, this reviewer cannot rule out a possible causal association between somapacitan use and these events.

Extension Period

Chronic Tonsillitis and Adenoidal Hypertrophy

These severe SAEs were reported in a 4-year-old male originally randomized to Norditropin in the Main Period of the pivotal phase 3 trial 4467 who had no significant past medical history. Approximately 5 days after switching to somapacitan therapy, he was noted to have snoring. About a month later he was examined and found to have tonsillitis and adenoidal hypertrophy, as well as non-serious chronic pharyngitis and secretary otitis media. Four days after examination he was hospitalized for adenoidectomy (tonsillectomy was not noted), after which both SAEs were reported as recovered. Somapacitan therapy was temporarily interrupted. While adenoidal hypertrophy and tonsillitis are not uncommon findings in pediatric patients, and this individual had concurrent findings of pharyngitis and otitis media which may indicate an infection as a cause of the tonsillitis and adenoidal hypertrophy, given the need for adenoidectomy within 1 month after the initiation of somapacitan and the known tissue growth-stimulating effect of IGF-1 , we cannot rule out a possible causal association between somapacitan use and adenoidal hypertrophy.

Tonsillar Hypertrophy and Adenoidal Hypertrophy

These moderate SAEs were reported in a 6-year-old male subject without significant medical history who was originally randomized to somapacitan in the Main Period of the pivotal phase

3 trial 4467. Seventeen months after initially starting somapacitan therapy, an otolaryngologist advised the subject to undergo surgery for tonsillar hypertrophy due to symptoms of snoring and nausea. Approximately one month later, during a clinic visit for the trial, adenoidal and tonsillar hypertrophy were reported as adverse reactions, and he was referred for surgery. He was admitted for surgery 21 months after starting somapacitan therapy for tonsillectomy and adenoidectomy. Both SAEs were reported as recovered afterwards and he was discharged. Somapacitan dosing was unchanged. While adenoidal and tonsillar hypertrophy are not uncommon findings in pediatric patients, given a lack of alternative possible causes and the known tissue growth-stimulating effect of IGF-1, we cannot rule out a possible causal association between somapacitan use and adenoidal hypertrophy.

8.3.4.2. Dose Finding Phase 2, Trial 4245

In the Main Period and Extension Period I, from Weeks 0 to 52, one subject randomized to 0.035 mg/kg/day Norditropin reported 1 SAE of inguinal hernia. No SAE were reported in somapacitan groups.

In the 208-week Extension Period II, where all subjects were transitioned to 0.24 mg/kg/week somapacitan, an additional 4/60 (6.7%) subjects reported 4 SAEs: tonsillar hypertrophy, asthma, development hip dysplasia, and type 1 diabetes mellitus; each reported by only 1 subject, and no subjects reported more than 1 SAE. With the exception of the SAE of type 1 diabetes mellitus (reported in 1/13 [1.6%] subject originally randomized to 0.2 mg/kg/week somapacitan) and the SAE of tonsillar hypertrophy (reported in 1/13 [1.6%] subject originally randomized to 0.067 mg/kg/week Norditropin), this reviewer considered all these SAEs as unlikely to be related to study drug therapy.

The SAEs of type 1 diabetes and tonsillar hypertrophy in subjects treated with somapacitan are discussed briefly, below. The narratives for SAEs not considered to be related to somapacitan therapy are not discussed further here but briefly reviewed in Section 15.4.4, Narratives From SAEs Reported in the Phase 2 Dose Finding Trial 4245.

Extension Period II

Type 1 Diabetes Mellitus

This case relates to a 10-year-old male with a history of bronchial asthma and allergic rhinitis who was originally randomized to 0.2 mg/kg/week somapacitan who reported polyuria, thirst, and weight loss beginning about 11 months after starting 0.2 mg/kg/week somapacitan. He was noted to have ketonuria, elevated blood glucose, and tested positive for islet cell antibodies (ICA), antibodies to insulin, glutamic acid decarboxylase (GAD) antibodies, and he was diagnosed with new onset type 1 diabetes of moderate severity and admitted to the hospital. He received insulin therapy, and hyperglycemia and ketonuria improved, and a week after admission he was discharged from the hospital. The event is ongoing/not recovered. Somapacitan therapy was discontinued.

While this was listed as an SAE in Extension Period II, it appears this SAE was reported at the end of the first 52 weeks of therapy, and it does not appear that this subject ever received 0.24 mg/kg/week somapacitan.

Glucose intolerance and diabetes mellitus are known risks and labeled warnings of rhGH products and their analogs, including somapacitan. Growth hormone therapy may decrease insulin sensitivity, and patients with undiagnosed prediabetes or diabetes mellitus may experience worsened glycemic control and become symptomatic. While somapacitan therapy in this subject likely was not the cause of the Type 1 diabetes itself and autoantibodies that are pathognomonic of type 1 diabetes mellitus, it likely contributed to a worsening of glycemic control and onset of acute symptoms that unmasked the diagnosis in this subject.

Tonsillar Hypertrophy

This case relates to a 7-year-old female with a history of zinc deficiency who was originally randomized to 0.067 mg/kg/day Norditropin in the dose finding phase 2 trial and began therapy in August 2019. She switched to 0.24 mg/kg/week somapacitan in August 2022. Approximately 9 months after switching to somapacitan, she was evaluated by her doctor for snoring, and 7 months after this she was hospitalized for tonsillectomy following the diagnosis of mild tonsillar hypertrophy (after approximately 40 months in the trial). She was discharged from the hospital after about 7 days. Somapacitan dosing was not interrupted or changed, and the SAE resolved. While tonsillar hypertrophy is not an uncommon finding in pediatric patients, given a lack of alternative possible causes and the known tissue growth-stimulating effect of IGF-1, we cannot rule out a possible causal association between somapacitan use and adenoidal hypertrophy.

Overall, the incidence of SAEs was low in the phase 2 dose finding trial with subjects born SGA and did not raise new safety concerns related to the use of somapacitan in the indicated population.

8.3.4.3. Phase 3, Trial 4469

During the 26-week Main Period of this trial, a total of 2/47 (4.3%) subjects reported 4 SAEs, including 1/9 (11.1%) treatment non-naïve subject with ISS who reported an SAE of pneumonia and 1/8 (12.5%) treatment non-naïve subject born SGA who reported SAEs of constipation, gastroesophageal reflux disease, and gastrointestinal microorganism overgrowth.

During the subsequent 130-week Extension Period I, no subjects in the SGA, NS, or ISS populations reported SAEs.

No treatment naïve subjects reported SAEs in trial 4469.

All narratives of SAEs reported by subjects in trial 4469 were reviewed by this medical reviewer and were all determined as unlikely to be related to somapacitan. The narratives for these SAEs are not discussed further here but briefly reviewed in Section 15.4.4, Narratives From SAEs Reported in the Phase 3 Trial 4469.

8.3.4.4. 120-Day Safety Update

The 120-Day Safety Update report, with a cutoff date of June 02, 2025, reported that, in the ongoing extension period of trial 4467 the following subjects had SAE: 3 subjects in the SGA population (influenza in 1 subject, viral infection in 1 subject, and bronchitis mycoplasmal and leukopenia in 1 subject), 2 subjects in the NS population (abdominal pain in 1 subject and pneumonia in 1 subject), and 3 subjects in the ISS population (appendicitis in 1 subject, bronchitis in 1 subject, and mesenteric lymphadenitis in 1 subject) .

One subject in trial 4469 in the NS population reported an SAE of seizure.

The narratives of all SAEs that occurred in the 120-Day Safety update period were reviewed by this reviewer. Due either to a lack of sufficient information, other possible etiologies or concomitant medications, or negative de- or rechallenges, a causal association between somapacitan therapy and these SAEs cannot be conclusively made.

8.3.5. Dropouts and/or Discontinuations Due to Adverse Effects

Few subjects with NS, ISS, or born SGA discontinued treatment with somapacitan due to AEs during the clinical development program for somapacitan. The AEs leading to discontinuation of trial treatment do not represent new safety signals for somapacitan in the proposed populations.

8.3.5.1. Pivotal Phase 3 Trial 4467

Overall, relatively few subjects in this trial, of any diagnosis, reported AEs that resulted in permanent discontinuation of trial therapy, and only 1 of these (headache) was an AE where a causal relationship between somapacitan and the AE could not be ruled out (discussed below).

Main Period

During the 52-week Main Period of the pivotal phase 3 trial, none of subjects treated with somapacitan discontinued the study due to AE. One of 37 (2.7%) subject in the SGA population randomized to the 0.035 mg/kg/day Norditropin arm reported 1 non-serious AE (PT: mood altered) that led to permanent discontinuation of trial therapy.

Extension Period

During the 208-week Extension Period, where all subjects were transitioned to 0.24 mg/kg/week somapacitan, an additional 2 subjects discontinued therapy due to an AE, including 1/76 (1.3%) subject with NS (PT: bone giant cell tumor; SAE) and 1/85 (1.2%) subject with ISS (PT: headache; non-serious AE).

As discussed in Section 15.4.4, Narratives From SAEs Reported in the Pivotal Phase 3 Trial 4467, NS, the SAE of bone giant cell tumor leading to premature treatment discontinuation in a subject with NS is unlikely to be related to somapacitan therapy.

The non-serious, moderate AE of headache in a subject with ISS was reported in a 7-year-old female without significant past medical history. She completed 12 months of 0.05 mg/kg/day Norditropin during the Main Period of the pivotal phase 3 trial, then, approximately two months after this subject transitioned to 0.24 mg/kg/week somapacitan in the Extension Period, she reported the non-serious AE of headache. The investigator concluded that it was possible that the AE was related to somapacitan therapy, and discontinued somapacitan. This AE is reported as not resolved. This subject had previously also reported 2 prior, non-serious AEs of headache about 8 and 52 days after starting Norditropin in the Main Period that resolved after 2 and 5 days, respectively. There was no change in dosing following the first AE of headache, but the dosing of Norditropin was temporarily interrupted for about 2 weeks with the second AE of headache. All AEs of headache were considered possibly related to therapy by the investigator. Given the multiple episodes of headache with both Norditropin and somapacitan therapy, a lack of a clear alternative cause, and the temporary interruption, or permanent discontinuation, of therapy, this reviewer cannot rule out somapacitan therapy as a possible cause of the headache. However, as discussed in Section 8.3.7, overall, the proportion of subjects reporting AEs of headache was comparable between subjects treated with Norditropin and somapacitan, and as only 1 subject with reported an AE of headache leading to discontinuation of therapy, it is unlikely that this case represents a new safety signal for somapacitan therapy.

8.3.5.2. Dose Finding Phase 2, Trial 4245

Throughout the Main Period, and Extension Periods I and II, only 1/62 (1.6%) subject permanently discontinued therapy due to an AE (PT: type 1 diabetes mellitus). This AE occurred in 1/13 (7.7%) subject in the group originally randomized to 0.2 mg/kg/week somapacitan. Refer to Section 8.3.4.2, Dose Finding Phase 2, Trial 4245.

8.3.5.3. Phase 3, Trial 4469

No AEs resulted in premature discontinuation of trial drug in any subject of any diagnosis during this trial.

8.3.5.4. 120-Day Safety Update (a Cutoff Date of June 02, 2025)

No subject discontinued somapacitan or withdrew from any clinical trial (i.e., trials 4467, 4245, or 4469) due to an AE during the reporting period of the 120-day safety update.

8.3.6. Significant Adverse Events

8.3.6.1. Severe Adverse Events

Overall, a small proportion of subjects born SGA, or with NS or ISS, treated with somapacitan and Norditropin reported severe AEs during the clinical development program. The proportion of subjects of any diagnosis treated with somapacitan reporting severe AEs was either comparable to, or smaller than, the proportion of subjects treated with Norditropin

reporting severe AEs. These severe AEs do not represent new safety signals for somapacitan in the proposed populations.

8.3.6.1.1. Phase 3, Trial 4467

SGA

During the 52-week Main Period of the pivotal phase 3 trial, the majority of AEs were either of mild or moderate severity, with a total of 6/141 (4.3%) subjects born SGA reporting 6 AEs graded as severe. Severe AEs were reported in 2/69 (2.9%) subjects the somapacitan group (choking and pneumonia mycoplasma), compared to 2/37 (5.4%) subjects in the 0.035 mg/kg/day Norditropin group (tonsillar hypertrophy and influenza) and 2/36 (5.6%) subjects in the 0.067 mg/kg/day Norditropin group (metapneumovirus infection and tonsillar hypertrophy). Only tonsillar hypertrophy was reported more than once as a severe AE. All severe AEs were also reported as SAEs, and, as discussed in Serious Adverse Events , this reviewer considered that none of the severe AEs were likely to be related to treatment with somapacitan.

During the Extension Period of trial 4467, where all subjects were treated with somapacitan, a total of 1/140 (0.7%) subject born SGA reported 2 severe AEs: adenoidal hypertrophy and tonsillar hypertrophy. Both severe AEs in this period were also SAEs, and, as discussed in Serious Adverse Events , this reviewer considered that a causal association between somapacitan and these events could not be ruled out.

NS

During the 52-week Main Period of the pivotal phase 3 trial, the majority of AEs were either of mild or moderate severity, with a total of 4/77 (5.2%) subjects with NS reporting 7 AEs graded as severe. Severe AEs were reported in 2/49 (4.1%) subjects the somapacitan group compared to 2/28 (7.1%) subjects in the Norditropin group.

One subject in the somapacitan group reported 4 severe, non-serious AEs (pain in extremity, and co-reported events of neck pain, knee arthralgia, and ankle arthralgia), for which the dose of somapacitan was reduced and the AEs all resolved after 1 day. The dose of somapacitan was later resumed at the original dose. The severe AEs of arthralgia may be related to treatment, since arthralgia and arthritis are labeled AEs for hGH products, and also could be due to fluid retention, a labeled warning of hGH products and analogs, including somapacitan. Pain in extremity is not uncommon in this age group and may represent “growing pain” that is the most common cause of musculoskeletal pain in children during this period of growth. Pain in extremity was also reported as a common adverse reaction in the somapacitan label for children with GHD. Neither neck pain, ankle pain, nor pain in extremity recurred. A non-severe, non-serious AE of knee pain was reported about a year later but resolved within a week without changes to somapacitan dosing.

All other subjects reported one severe AE each (all of which were also SAEs), including 1 subject in the somapacitan group (PT: febrile convulsion) and 2 subjects in the Norditropin

group (PTs: adenoidal hypertrophy and OSA syndrome). As discussed in Serious Adverse Events , the severe SAE of OSA syndrome may be related to Norditropin therapy, but the severe SAEs of febrile convulsion and adenoidal hypertrophy were unlikely to related to trial therapies.

During the Extension Period of trial 4467, where all subjects were treated with somapacitan, a total of 1/76 (1.3%) subject reported 1 severe AE: pneumonia. This severe AE was also an SAE, and, as discussed in Serious Adverse Events , this reviewer considered that it was unlikely to be related to treatment with trial drug.

ISS

During the 52-week Main Period of the pivotal phase 3 trial, the majority of AEs were either of mild or moderate severity, with a total of 1/59 (1.7%) subject with ISS in the somapacitan group (1/87 [1.1%] subject in the entire trial) reporting 1 AE graded as severe: inguinal hernia. No subjects in the Norditropin group reported severe AEs during this period. The severe AE of inguinal hernia was also an SAE and deemed by this reviewer as unlikely to have a causal relationship to trial therapy, as discussed in Serious Adverse Events .

During the Extension Period of trial 4467, 1/85 (1.2%) additional subject reported 2 severe AEs: chronic tonsillitis and adenoidal hypertrophy; both of which were SAEs and a causal association between the event of adenoidal hypertrophy and somapacitan could not be ruled out (see Serious Adverse Events).

8.3.6.1.2. Dose Finding Phase 2, Trial 4245

In the Main Period and Extension Period I, from Weeks 0 to 52, all AEs were of mild or moderate severity, as no subjects reported severe AEs.

In the 208-week Extension Period II, where subjects were transitioned to 0.24 mg/kg/week somapacitan, 2/60 (3.3%) subjects reported 2 severe AEs: asthma and blood gonadotropin increased, both unlikely related to study drug. The severe AE of asthma was an SAE (see Serious Adverse Events).

8.3.6.1.3. Phase 3, Trial 4469

To date, only 1/11 (9.1%) subject with ISS reported 1 severe AE in the phase 3 trial 4469: arthralgia. The severe, non-serious AE of arthralgia may be related to treatment, since arthralgia and arthritis are labeled AEs for hGH products, and also could be due to fluid retention, a labeled warning of hGH products and analogs, including somapacitan. However, the severe AE resolved after 192 days without changes or interruption to somapacitan dosing.

No subjects with NS or TS, or born SGA, reported severe AEs.

8.3.6.2. Adverse Events Leading to Dose Reduction/Temporary Interruption

Overall, a small proportion of subjects born SGA, or with NS or ISS, treated with somapacitan and Norditropin reported AEs during the clinical development program that resulted in reduction of dose, or temporary interruption, of either somapacitan or Norditropin. The proportion of subjects of any diagnosis treated with somapacitan reporting AEs resulting in these dose modifications was either comparable to, or smaller than, the proportion of subjects treated with Norditropin reporting AEs requiring dose modifications. These AEs do not represent new safety signals for somapacitan in the proposed populations.

8.3.6.2.1. Phase 3, Trial 4467

SGA

During the 52-week Main Period of the pivotal phase 3 trial, no subject born SGA in the somapacitan group or the 0.067 mg/kg/day Norditropin groups reported AEs in the Main Period that resulted in decrease of trial drug dose. Two of 141 (1.4%) subjects born SGA (both in the 0.035 mg/kg/day Norditropin group: 2/37 [5.4%]) reported 3 AEs that resulted in dose reduction: 1 subject – concurrent AEs of irritability and aggression; 1 subject – product prescribing error.

Additionally, during the Main Period of this trial, 5/141 (3.5%) subjects born SGA reported 14 AEs that resulted in temporary interruption of trial drug, including 1/69 (1.4%) subject in the somapacitan group (melanocytic nevus and pneumonia mycoplasmal, both SAEs), 2/37 (5.4%) subjects in the 0.035 mg/kg/day Norditropin group (1 subject: bronchitis, otitis media acute, tonsillitis streptococcal, upper respiratory tract infection, and viral infection; 1 subject: influenza, nasopharyngitis, pneumonia Hemophilus, and pneumonia streptococcal), and 2/36 (5.6%) subjects in the 0.067 mg/kg/day Norditropin group (1 subject: hand, foot, and mouth disease and upper respiratory tract infection; 1 subject: pyrexia). All AEs resolved and as discussed in Serious Adverse Events , the AEs reported in the somapacitan group are unlikely to be related to trial therapy.

During the Extension Period, no subjects born SGA reported AEs that resulted in temporary interruption, or decreasing the dose, of somapacitan.

NS

During the 52-week Main Period of the pivotal phase 3 trial, 1/49 (2%) subject with NS in the somapacitan group, compared to 0/28 subjects in the Norditropin group, reported 4 severe, non-serious AEs that resulted in reducing the dose of the trial drug (pain in extremity, and co-reported events of neck pain, knee arthralgia, and ankle arthralgia; see discussion under Severe Adverse Events, NS, above).

During the Main Period, 2/49 (4.1%) subjects with NS in the somapacitan arm, compared to 4/28 (14.3%) subjects in the Norditropin arm, reported 3 and 9 AEs, respectively, that

resulted in temporary interruption of trial drug. The AEs resulting in temporary interruption in the somapacitan group included pneumonia and asthma in 1 subject and bronchitis in 1 subject; and in the Norditropin group included 2 AEs of rhinitis and 3 AEs of upper respiratory tract infection in 1 subject, upper respiratory tract infection and rash in 1 subject, cystitis in 1 subject, and OSA syndrome in 1 subject. With the exception of the AE of OSA syndrome, which is ongoing, all AEs resolved.

During the Extension Period, no subjects with NS reported AEs that resulted in dose reduction, and 1/76 (1.3%) subject reported 2 concurrent AEs (pulmonary valve incompetence and aortic valve incompetence) where temporary interruption of trial drug is reported as the action taken. This subject was originally randomized to Norditropin in this trial, and these AEs had an onset 5 months after starting somapacitan therapy, approximately 1 month prior to the database lock date. At this time, these AEs are not resolved, and it is unclear if/when somapacitan dosing restarted. This subject's medical history does include both pulmonary valve incompetence and aortic valve incompetence, and it is unlikely that somapacitan caused these AEs.

ISS

During the 52-week Main Period of the pivotal phase 3 trial, 1/59 (1.7%) subject with ISS in the somapacitan group, compared to 0/28 subjects in the Norditropin group, reported 1 AE that resulted in reducing the dose of the trial drug: insulin-like growth factor (IGF) increased.

In general, it is expected that hGH products and analogs bind the GHR and raise IGFs. Therefore, it is likely that somapacitan therapy is related to the AE of IGF increased. This subject did not have other AEs concurrent with the elevated IGF. The IGF increased AE is not resolved as of the database lock date, despite a reduction in dose (refer to Section 8.3.8, IGF-1, Pivotal Phase 3 Trial 4467).

Additionally, during the Main Period of the trial, 2/59 (3.4%) and 3/28 (10.7%) subjects randomized to somapacitan and Norditropin reported 3 and 7 AEs, respectively, that are listed with action taken being "temporary interruption". All AEs resolved, and none were serious or severe. In the somapacitan group, these AEs include vertigo and hypotension postural in 1 subject and upper respiratory infection in 1 subject and are unlikely to represent new safety signals for somapacitan. In the Norditropin group, these AEs include injection site pain, headache, and 3 AEs of influenza in 1 subject, pain in extremity in 1 subject, and upper respiratory infection in 1 subject.

In the Extension Period, 1/85 (1.2%) subject had 1 AE resulting in reduction of somapacitan dose (conjunctivitis allergic) for which the dose was reduced for a total of 3 doses and then resumed at the original dose and the AE resolved. A total of 2/85 (2.4%) subjects reported 5 AEs resulting in temporary interruption during this period (headache and conjunctivitis allergic in 1 subject and chronic tonsillitis, adenoidal hypertrophy, and rhinitis in 1 subject). Of all these AEs, all resolved, and only chronic tonsillitis and adenoidal hypertrophy were severe or serious and causal association with somapacitan and the AE of adenoidal hypertrophy could not be ruled out (see Serious Adverse Events).

8.3.6.2.2. Dose Finding Phase 2, Trial 4245

In the Main Period and Extension Period I, from Weeks 0 to 52, 1/13 (7.7%) subject in the 0.2 mg/kg/week somapacitan group reported an AE that resulted in reduction of trial drug dose: headache. This AE is non-serious and non-severe, and despite reduction of drug dose, this AE is not resolved.

No AEs reported by any subject in any treatment arm resulted in temporary interruption of trial drug during the first 52 weeks of treatment.

During the 208-week Extension Period II, an additional 3/60 (5%) subjects had 3 AEs that resulted in reduction of somapacitan dose: injection site reaction, headache, and blood creatinine phosphokinase increased (reduced for 2 doses then resumed at original dose). None of these AEs were serious or severe and only the AE of headache has not resolved, and the AE of headache and injection site reaction have not allowed resumption of the original dosing. Also, during this period, 3/60 (5%) subjects reported 3 AEs resulting in temporary interruption of therapy (influenza, COVID19, and periorbital edema) all of which were non-serious, non-severe, and recovered. It is unlikely that the AEs of infectious origin (i.e., influenza and COVID19) were related to therapy. However, the AE of periorbital edema may have causal association with therapy given the known risk of fluid retention included in the warnings and precautions section of the labels of all approved hGH products and analogs, including somapacitan.

8.3.6.2.3. Phase 3, Trial 4469

To date, only 1/11 (9.1%) subject with ISS has reported an AE that resulted dose reduction in the phase 3 trial 4469: IGF increased. This AE is likely related to somapacitan therapy; see the discussion under Phase 3, Trial 4467, ISS, above. This subject also had two AEs of arthralgia concurrent with the elevated IGF, though the arthralgia AEs resolved, while the IGF increased AE is not resolved, despite a reduction in dose, therefore it is unlikely that arthralgia was due to elevated IGF-1 levels.

No subjects with NS or born SGA, reported severe AEs.

No subjects of any diagnosis reported AEs that resulted in temporary interruption of trial drug.

8.3.6.2.4. 120-Day Safety Update

During period of the 120-Day Safety Update, in the pivotal phase 3 trial 4467, 1 subject in the SGA population had a dose reduction due to AE in the Extension Period (a mild, non-serious AE of intraocular pressure increased that subsequently resolved; it is not clear if somapacitan was resumed at previous dosing). With resolution following dose reduction, it is possible this AE may be related to treatment but given the low incidence of reporting in the clinical development program with this AE, it is unlikely to represent a new safety signal.

Additionally, 2 subjects in the SGA population of trial 4467 experienced 4 mild or moderate, non-serious AEs (migraine, vomiting, and blurred vision in 1 subject [none of which are recovered] and pyrexia in 1 subject [recovered]) that resulted in temporary discontinuation of somapacitan. Pyrexia is not uncommon in children of this age group, and there is limited additional information, so a determination of causality is difficult. However, AEs of migraine, vomiting, and blurred vision may represent a constellation of symptoms that are consistent with intracranial hypertension, a known risk of therapy with hGH products and analogs. Thus, it is likely these are related to somapacitan, but do not represent a new safety signal.

No other subject in any other population or in any of the other clinical trials had a dose reduction or temporary interruption of somapacitan due to an AE.

8.3.7. Treatment Emergent Adverse Events and Adverse Reactions

8.3.7.1. Phase 3, Trial 4467

Overall, somapacitan therapy was well tolerated in the SGA, NS, and ISS subject populations. The reporting of the most common AEs in the pivotal phase 3 trial does not reveal new safety signals for somapacitan therapy in the indicated populations. The frequency of TEAEs was comparable between the subgroups of subjects and control group(s).

AEs are analyzed by OCMQ and AEs that occurred in at least > 10% of subjects and more frequently in the somapacitan group(s) than in Norditropin group(s) are reported below for each subpopulation. These results of the most commonly reported AEs are different from the Applicant's analyses due to the fact that the Applicant did not group similar events together and reported AEs that occurred in at least ≥ 5% of subjects (refer to Section 15.4.3 for the reports provided by the Applicant of AEs by PT that occurred with an incidence of ≥ 5%).

SGA

Throughout the Main Period of the pivotal phase 3 trial 4467, 120/141 (85.1%) subjects born SGA experienced at least one AE, with comparable proportions in the somapacitan group (87%) and the 0.035 mg/kg/day Norditropin group (86.5%), while 80% of subjects in the 0.067 mg/kg/day Norditropin group reported at least one AE. The reason for the observed higher proportion reporting AEs in the somapacitan group compared to the 0.067 mg/kg/day Norditropin group, with a risk difference (RD) of 7%, is unclear, but may be attributable to the uneven randomization of subjects (2:1 somapacitan to 0.067 mg/kg/day Norditropin) and a relatively small enrollment, and the 95% confidence interval (CI) of the risk difference includes 0 (95% CI -8.5, 22.4).

AEs that occurred in ≥ 10% of subjects in the somapacitan, 0.035 mg/kg/day Norditropin, or 0.067 mg/kg/day Norditropin groups are listed in Table 32 (in the order of decreasing risk difference between somapacitan and 0.06 mg/kg/day Norditropin). Refer to Table 66, in Section 15.4.3, for a listing of the individual preferred terms included in the most commonly reported, combined OCMQs and GQs present in Table 32.

Table 32. The Most Commonly Reported (≥10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Main Period, Trial 4467, SGA Safety Population

OCMQ/GQ Term	Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)	Risk Difference Somapacitan - 0.035 mg/kg/day Norditropin (%) (95% CI)	Risk Difference Somapacitan - 0.067 mg/kg/day Norditropin (%) (95% CI)	Total (N=141) n (%)
Any AE	32 (86.5)	28 (80.0)	60 (87.0)	0.5 (-13.1, 14.1)	7 (-8.5, 22.4)	120 (85.1)
Cough[1]	6 (16.2)	3 (8.6)	11 (15.9)	-0.3 (-15, 14.4)	7.4 (-5.3, 20)*	20 (14.2)
Respiratory Tract Infection[1]	11 (29.7)	7 (20)	18 (26.1)	-3.6 (-21.7, 14.4)	6.1 (-10.7, 22.9)*	36 (25.5)
Diarrhea[1]	3 (8.1)	2 (5.7)	7 (10.1)	2 (-9.3, 13.4)*	4.4 (-6.1, 14.9)*	12 (8.5)
Pyrexia	6 (16.2)	6 (17.1)	13 (18.8)	2.6 (-12.4, 17.7)*	1.7 (-13.8, 17.2)*	25 (17.7)
Vomiting[1]	4 (10.8)	4 (11.4)	7 (10.1)	-0.7 (-12.9, 11.6)	-1.3 (-14, 11.4)	15 (10.6)
Nasopharyngitis[1]	14 (37.8)	10 (28.6)	18 (26.1)	-11.8 (-30.5, 7)	-2.5 (-20.7, 15.7)	42 (29.8)
Ear Infection[1]	6 (16.2)	6 (17.1)	9 (13.0)	-3.2 (-17.5, 11.1)	-4.1, (-18.9, 10.7)	21 (14.9)
Bronchitis	4 (10.8)	4 (11.4)	5 (7.2)	-3.6 (-15.3, 8.2)	-4.2 (-16.4, 8)	13 (9.2)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool, MAED, and JMP clinical.

* Denotes terms where the risk difference between somapacitan and Norditropin ≥ 1%, and the proportion of subjects reporting that term in either group is ≥ 10%.

[1] Represent preferred terms that were combined OCMQs or GQs. Grouping of several terms in OCMQs and GQs rendered incidence that is different from the Applicant's analysis. Refer to Table 66, in Section 15.4.3, for a listing of the individual preferred terms included in these most commonly reported, combined OCMQs and GQs.

The AEs that occurred in ≥ 10% of subjects born SGA and occurred more frequently in the somapacitan group compared to either Norditropin group (RD ≥ 1%) (by OCMQ analyses) are discussed further below:

Cough

Cough, including PTs of cough and productive cough, occurred in 11 (15.9%) subjects in the somapacitan group (15 AEs), compared to 6 (16.2%) and 3 (8.6%) subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively. None of these AEs were severe or serious. Onset of the AEs ranged from 6 to 348 days after initiation of somapacitan therapy, with a duration ranging from 1 to 32 days. All but 1 AE of cough in the somapacitan group were listed as recovered. Somapacitan dosing was not interrupted or changed for any of these AEs.

Respiratory Tract Infection

The OCMQ term respiratory tract infection included PTs of upper respiratory tract infection, influenza, respiratory syncytial virus infection, mycoplasma infection, pneumonia, pneumonia bacterial, pneumonia mycoplasmal, croup infectious, pneumonia haemophilus, pneumonia streptococcal, respiratory tract infection, and metapneumovirus infection. A total of 18 (26.1%) subjects in the somapacitan group (39 AEs), compared to 11 (29.7%) and 7 (20%) subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively, reported AEs related to respiratory tract infection. The imbalance between the somapacitan group and the 0.067 mg/kg/day Norditropin group in overall AE reporting appears to have been driven by the PTs of upper respiratory tract infection (20.3% vs. 14.3%, respectively) and influenza (10.1% vs. 5.7%, respectively), none of which were severe or serious. One AE reported by a subject in the somapacitan group (pneumonia mycoplasmal) was serious and severe, all others were non-serious and either of mild or moderate severity. All AEs of respiratory tract infection in the somapacitan group had an onset ranging from 23 to 367 days after starting therapy, and most had a duration of 1 to 31 days. All AEs recovered, and, with the exception of the severe SAE of pneumonia mycoplasmal (see discussions in Serious Adverse Events and Section 8.3.6), the dose of somapacitan was not interrupted or changed.

Diarrhea

Diarrhea, including PTs of diarrhea, gastroenteritis, gastrointestinal viral infection, and gastroenteritis viral, was reported in 7 (10.1%) subjects in the somapacitan group (10 AEs), compared to 3 (8.1%) and 2 (5.7%) subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively. The imbalance in reporting of overall PTs between the somapacitan and higher dose Norditropin groups does appear to have been driven by any single PT. All AEs of diarrhea reported in the somapacitan group were mild and non-serious, had an onset ranging from 40 to 368 days after starting therapy, and a duration of 1 to 11 days. All AEs recovered without changing or interrupting somapacitan dosing.

Pyrexia

Pyrexia was reported in 13 (18.8%) subjects in the somapacitan group (17 AEs) and 6 (16.2%) and 6 (17.1%) subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively. In subjects treated with somapacitan, no pyrexia AEs were serious or severe, the onset ranged from Day 5 to Day 371 of the trial, the duration ranged from 1 to 11 days, and all are reported as recovered or recovering without changing or interrupting somapacitan dosing.

Conclusions, SGA Safety Population

These TEAEs reported by ≥ 10% of subjects in any arm of the SGA population in the pivotal phase 3 trial 4467 will be included in Section 6 of the label. The AEs that occurred in ≥ 10% of subjects born SGA and occurred more frequently in the somapacitan group compared to either Norditropin group (RD ≥ 1%) during the Main Period of the trial (i.e., cough, respiratory tract infection, diarrhea, and pyrexia) are not uncommon in this age group, and uneven randomization may have contributed to these imbalances in reporting. Additionally, the AEs of cough and respiratory tract infection only occurred more frequently in the somapacitan group compared to one, but not both, of the Norditropin groups. More importantly, the majority of these AEs were non-serious, not severe, and recovered without interrupting or changing somapacitan dosing. However, because the causal relationship with the drug cannot be ruled out completely because of the observed imbalance, these events will be included in the label for prescriber's awareness.

NS

Throughout the Main Period of the pivotal phase 3 trial, 67/77 (87%) subjects with NS experienced at least one AE. There was a higher proportion of subjects in the somapacitan arm reported at least 1 AE (44/49 [89.8%] subjects) compared to the Norditropin arm (23/28 [82.1%] subjects), with an RD of 7.7%, though the 95% CI includes 0 (95% CI -8.9, 24.2). This observed imbalance may be attributed to uneven randomization of subjects (2:1 somapacitan to Norditropin) and a relatively small overall enrollment.

AEs that occurred in ≥ 10% of subjects in the somapacitan or Norditropin groups are listed in Table 33 (in the order of decreasing RD between somapacitan and Norditropin). Refer to Table 67, in Section 15.4.3, for a listing of the individual preferred terms included in the most commonly reported, combined OCMQs and GQs present in Table 33.

Table 33. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Main Period, Trial 4467, NS Safety Population

OCMQ/GQ term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)	Risk Difference Somapacitan - Norditropin (%) (95% CI)	Total (N=77) n (%)
Any AE	23 (82.1)	44 (89.8)	7.7 (-8.9, 24.2)	67 (87.0)
Respiratory Tract Infection[1]	8 (28.6)	21 (42.9)	14.3 (-7.4, 36.0)*	29 (37.7)
Diarrhea[1]	4 (14.3)	11 (22.4)	8.2 (-9.3, 25.6)*	15 (19.5)
Nasopharyngitis[1]	7 (25.0)	14 (28.6)	3.6 (-16.9, 24)*	21 (27.3)
Headache	2 (7.1)	5 (10.2)	3.1 (-9.7, 15.8)*	7 (9.1)
Ear Infection[1]	4 (14.3)	8 (16.3)	2 (-14.5, 18.6)*	12 (15.6)
Vomiting[1]	3 (10.7)	6 (12.2)	1.5 (-13.1, 16.2)*	9 (11.7)
Cough[1]	4 (14.3)	7 (14.3)	0 (-16.2, 16.2)	11 (14.3)
Injection Site Reaction[1]	4 (14.3)	4 (8.2)	-6.1 (-21.2, 8.9)	8 (10.4)
Abdominal Pain[1]	3 (10.7)	1 (2.0)	-8.7 (-20.8, 3.4)	4 (5.2)
Wound	3 (10.7)	0	-10.7 (-22.2, 0.7)	3 (3.9)
Pyrexia	7 (25.0)	5 (10.2)	-14.8 (-32.9, 3.3)	12 (15.6)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool, MAED, and JMP clinical.
* Denotes terms where the risk difference between somapacitan and Norditropin ≥ 1%, and the proportion of subjects reporting that term in either group is ≥ 10%.
[1] Represent preferred terms that were combined OCMQs or GQs. Grouping of several terms in OCMQs and GQs rendered incidence that is different from the Applicant's analysis. Refer to Table 67, in Section 15.4.3, for a listing of the individual preferred terms included in these most commonly reported, combined OCMQs and GQs.

By OCMQ analysis, the AEs that occurred in ≥ 10% of subjects with NS and occurred more frequently in the somapacitan group compared to the Norditropin group (RD ≥ 1%) in the Main Period of trial 4467 were respiratory tract infection, diarrhea, nasopharyngitis, headache, ear infection, and vomiting, each of which are discussed further below.

Respiratory Tract Infection

The OCMQ term respiratory tract infection included PTs of influenza, influenza like illness, pneumonia, respiratory syncytial virus infection, respiratory tract infection, lower respiratory tract infection, respiratory tract infection viral, tracheitis, upper respiratory tract infection, upper respiratory tract infection bacterial, and viral upper respiratory tract infection. A total of 21 (42.9%) subjects in the somapacitan arm (33 AEs) reported AEs related to respiratory tract infection, compared to 8 (28.6%) subjects in the Norditropin group. Only one subject in the somapacitan group had a respiratory tract infection SAE (PT pneumonia; see Serious Adverse Events). No subjects in the somapacitan group reported severe respiratory tract infection AEs, with onset ranging from Day 4 to Day 341 of the trial and a duration ranging from 1 to 14 days. For all subjects in the somapacitan group, these AEs resolved, and dosing was only changed or interrupted for one subject (PTs of pneumonia and asthma) who had temporary interruption of somapacitan in response to these AEs, as discussed in Section 8.3.6.

Diarrhea

Diarrhea, including PTs of diarrhea, enterocolitis, gastroenteritis, gastroenteritis viral, and parasitic gastroenteritis was reported in 11 (22.4%) subjects in the somapacitan group (13 AEs), compared to 4 (14.3%) subjects in the Norditropin group. All AEs of diarrhea reported in the somapacitan group were mild or moderate, had an onset ranging from 15 to 352 days after starting therapy, and a duration of 1 to 15 days. For only 1 subject, with a PT of gastroenteritis, was the AE serious (see discussion in Serious Adverse Events). All AEs recovered without changing or interrupting somapacitan dosing.

Nasopharyngitis

According to OCMQ analysis, nasopharyngitis, including the PTs of bacterial infection (the reported term for this PT was "common cold, cough bacterial infection"), herpes pharyngitis, nasopharyngitis, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, rhinitis, and sinusitis, was reported by 14 (28.6%) subjects (reporting 28 AEs) and 7 (25%) subjects in the somapacitan and Norditropin arms, respectively. The onset of AEs of nasopharyngitis reported in the somapacitan group ranged from Day 2 to Day 364 of the Main Period of the trial, and 1 AE was not recovered, 1 AE had a duration of 70 days, and all others had a duration ranging from 3 to 34 days. None of the nasopharyngitis AEs reported by subjects in the somapacitan arm were serious or severe, and somapacitan dosing was never interrupted or changed due to these AEs.

Headache

Headache was reported in 5 (10.2%) subjects in the somapacitan group (9 AEs), compared to 2 (7.1%) subjects in the Norditropin group. All headache AEs in the somapacitan group were mild and non-serious. Onset of the AEs ranged from 2 to 370 days after initiation of somapacitan therapy, with a duration ranging from 1 to 14 days. All cases of headache in the somapacitan group were listed as recovered. Somapacitan dosing was not interrupted or changed for any of these AEs.

Ear Infection

Ear infection, including PTs of ear infection, otitis externa, otitis media, otitis media acute, and otitis media chronic, was reported in 8 (16.3%) subjects in the somapacitan group (12 AEs), compared to 4 (14.3%) subjects in the Norditropin group. All AEs of ear infection reported in the somapacitan group were non-serious, mild or moderate, had an onset ranging from 1 to 345 days after starting therapy, and a duration of 3 to 69 days. All but one AE of ear infection in a subject in the somapacitan group has recovered. Somapacitan dosing was neither interrupted nor changed for any of these AEs.

Vomiting

PTs contained in the OCMQ vomiting included gastritis and vomiting. A total of 6 (12.2%) subjects in the somapacitan group reported 10 AEs of vomiting, compared to 3 (10.7%) subjects in the Norditropin group. All AEs of vomiting reported in the somapacitan group were mild or moderate and non-serious, had an onset ranging from 2 to 357 days after starting therapy, and a duration of 1 to 7 days. All cases of vomiting recovered without changing or interrupting somapacitan dosing.

Conclusions, NS Safety Population

The AEs that occurred in ≥ 10% of subjects with NS and occurred more frequently in the somapacitan group compared to the Norditropin group (RD ≥ 1%) during the Main Period of the trial (i.e., respiratory tract infection, diarrhea, nasopharyngitis, headache, ear infection, and vomiting) are not uncommon in this age group, and uneven randomization may have contributed to the imbalances seen. Further, there is an increased risk of intracranial hypertension with hGH therapy. While headache may be a symptom of intracranial hypertension, there were no AEs related to intracranial hypertension reported. More importantly, the majority of these AEs were non-serious, not severe, and recovered without interrupting or changing somapacitan dosing. The majority of these events were also seen in other subgroups and are already included in the label for other hGHs. Overall, the most commonly reported TEAEs do not raise new safety signals for somapacitan use. However, since the causality cannot be ruled out completely due to the imbalance, these TEAEs reported by ≥ 10% of subjects in either treatment will be included in Section 6 of the label for the prescribers' awareness.

ISS

Throughout the Main Period of the pivotal phase 3 trial, 69/87 (79.3%) subjects with ISS experienced at least one AE. There was a slightly higher proportion of subjects in the somapacitan arm reported at least 1 AE (47/59 [79.7%] subjects) compared to the Norditropin arm (22/28 [78.6%] subjects), with a RD of 1.1%, though the 95% CI includes 0 (95% CI -17.3, 19.4). This observed imbalance may be attributed to uneven randomization of subjects (2:1 somapacitan to Norditropin) and a relatively small overall enrollment.

AEs that occurred in ≥ 10% of subjects in the somapacitan or Norditropin groups are listed in Table 34 (in the order of decreasing RD between somapacitan and Norditropin). Refer to Table 68, in Section 15.4.3, for a listing of the individual preferred terms included in the most commonly reported, combined OCMQs and GQs present in Table 34.

Table 34. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Main Period, Trial 4467, ISS Safety Population

Adverse Event	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)	Risk Difference Somapacitan - Norditropin (%) (95% CI)	Total (N=87) n (%)
Any AE	22 (78.6)	47 (79.7)	1.1 (-17.3, 19.4)	69 (79.3)
Ear Infection[1]	2 (7.1)	7 (11.9)	4.7 (-7.9, 17.3)*	9 (10.3)
Injection Site Reaction[1]	2 (7.1)	6 (10.2)	3 (-9.2, 15.3)*	8 (9.2)
Respiratory Tract Infection[1]	8 (28.6)	18 (30.5)	1.9 (-18.5, 22.4)*	26 (29.9)
Nasopharyngitis[1]	6 (21.4)	13 (22.0)	0.6 (-17.9, 19.1)	19 (21.8)
Headache	3 (10.7)	6 (10.2)	-0.5 (-14.4, 13.3)	9 (10.3)
Cough[1]	3 (10.7)	3 (5.1)	-5.6 (-18.4, 7.1)	6 (6.9)
Vomiting[1]	3 (10.7)	3 (5.1)	-5.6 (-18.4, 7.1)	6 (6.9)
Diarrhea[1]	7 (25.0)	6 (10.2)	-14.8 (-32.6, 3)	13 (14.9)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool, MAED, and JMP clinical.
* Denotes terms where the risk difference between somapacitan and Norditropin ≥ 1%, and the proportion of subjects reporting that term in either group is ≥ 10%.
[1] Represent preferred terms that were combined OCMQs or GQs. Grouping of several terms in OCMQs and GQs rendered incidence that is different from the Applicant's analysis. Refer to Table 68, in Section 15.4.3, for a listing of the individual preferred terms included in these most commonly reported, combined OCMQs and GQs.

By OCMQ analysis, the AEs that occurred in ≥ 10% of subjects with NS and occurred more frequently in the somapacitan group compared to the Norditropin group (RD ≥ 1%) in the Main Period of trial 4467 were ear infection, injection site reaction, and respiratory tract infection, each of which are discussed further below.

Ear Infection

Ear infection, including PTs of otitis media, otitis media acute, and ear infection, was reported in 7 (11.9%) subjects in the somapacitan group (7 AEs), compared to 2 (7.1%) subjects in the Norditropin group. All AEs of ear infection reported in the somapacitan group were non-serious, mild or moderate, had an onset ranging from 13 to 225 days after starting therapy, and, while one case had a duration of 198 days and another had a duration of 59 days, most ranged from 4 to 8 days' duration. All AEs of ear infection recovered or are recovering without interrupting or changing somapacitan dosing.

Injection Site Reaction

The OCMQ term injection site reaction included PTs of application site reaction, injection site bruising, injection site hematoma, injection site hemorrhage, injection site urticaria, injection site pruritus, and injection site pain. Injection site reactions were reported by 6 (10.2%) and 2 (7.1%) subjects in the somapacitan (6 AEs) and Norditropin arms, respectively. Injection site reaction AEs reported by subjects in the somapacitan arm had an onset ranging from 22 to 181 days after the start of therapy, and, in 1 case, a duration of 102 days, otherwise duration ranged from 1 to 9 days. All cases of injection site reaction were mild and non-serious, and all recovered/are recovering without interrupting or changing somapacitan dosing.

Respiratory Tract Infection

The OCMQ term respiratory tract infection included PTs of influenza, pneumonia, pneumonia bacterial, respiratory tract infection viral, tracheitis, viral upper respiratory tract infection, upper respiratory tract infection bacterial, respiratory tract infection, and upper respiratory tract infection. A total of 18 (30.5%) subjects in the somapacitan group (25 AEs), compared to 8 (28.6%) subjects Norditropin groups, reported AEs related to respiratory tract infection. The onset of respiratory tract infection AEs in the somapacitan group ranged from 6 to 346 days, with duration mostly ranged from 3 to 15 days, though in one case, the duration was 37 days. No subject in the somapacitan arm experienced a severe respiratory tract infection AE, and in only 1 case (with a PT of influenza; see Serious Adverse Events) was the AE serious. In one case (with a PT of upper respiratory tract infection; see Section 8.3.6) somapacitan dosing was temporarily interrupted, otherwise, none of these AEs resulted in changes to somapacitan dosing.

Conclusions, ISS Safety Population

The AEs that occurred in ≥ 10% of subjects with NS and occurred more frequently in the somapacitan group compared to the Norditropin group (RD ≥ 1%) during the Main Period of the trial (i.e., ear infection, injection site reaction, and respiratory tract infection) are not uncommon in this age group, and uneven randomization may have contributed to these imbalances. While the reporting of injection site reactions in the somapacitan group was higher than in the Norditropin group, examination of these AEs and the individual PTs reported do not yield any significant safety concern for this drug administered via SC injection. In general, the majority of these AEs were non-serious, not severe, and recovered without interrupting or changing somapacitan dosing. The majority of these events were seen in the other subgroups are already included in the other hGH labels. Overall, the most commonly reported TEAEs do not represent new safety signals for somapacitan use. However, since the causality cannot be ruled out completely due to the imbalance, these TEAEs reported by ≥ 10% of subjects in either treatment will be included in Section 6 of the label for the prescribers' awareness.

8.3.7.2. Dose Finding Phase 2, Trial 4245

During the first 52 weeks of treatment of the dose finding phase 2 trial in subjects born SGA, 38/62 (61.3%) subjects reported at least 1 AE, including 7/12 (58.3%) and 6/13 (46.2%) subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively, and 7/12 (58.3%), 9/13 (69.2%), and 9/12 (75%) subjects in the 0.16, 0.2, and 0.24 mg/kg/week somapacitan groups, respectively.

The most commonly reported (≥ 10% in any treatment group) AEs in the first 52 weeks of treatment in the phase 2 trial were nasopharyngitis, ear infection, respiratory tract infection, vomiting, and contusion (see Table 112, in Section 15.4.3). These most commonly reported AEs were similar to what was observed during the 52-Week Main Period of the pivotal phase 3 trial, not only for the SGA population (see Table 32), but also for the NS and ISS populations

(Table 33 and Table 34, respectively), and the reporting and incidences of these AEs did not reveal new safety signals for somapacitan in the indicated populations.

These results of the most commonly reported AEs in the first year of therapy in the dose finding phase 2 trial differ from the Applicant's analyses due to the fact that the Applicant did not group similar events together, and the fact that the Applicant reported AEs that occurred before subjects switched from the treatment to which they were randomized to 0.24 mg/kg/week somapacitan. As discussed in Section 8.1.2.1, subjects could enter Extension Period II (which began after completing 52 weeks of therapy) while still treated with the drug or dose to which they were randomized, and subjects did not all transition to 0.25 mg/kg/week somapacitan on the same trial day. For subjects originally randomized to 0.24 mg/kg/week somapacitan, this meant that the Applicant's analysis included any AE reported in this group through 208 weeks of therapy. In order to assess a period where all subjects were exposed to the drug and dose to which they were randomized for the same period of time, this reviewer specifically evaluated the first 52 weeks of the trial (see Figure 40, in Section 15.4.3, provided by the Applicant, for the report of AEs by PT that occurred with an incidence of ≥ 10%, prior to transitioning from the original randomized treatment).

8.3.7.3. Phase 3, Trial 4469

In general, the reported AEs in trial 4469 were similar to those observed during the 52-Week Main Period of the pivotal phase 3 trial 4467, and review of the AEs reported by subjects in the SGA, NS, and ISS populations of the phase 3 trial 4469 did not reveal any new safety signals.

Throughout the Main (Weeks 0 to 26) and Extension Periods (beginning after Week 26 through the database cutoff date of November 24, 2024) of the phase 3 trial 4469, all enrolled treatment naïve and treatment non-naïve subjects, older than those eligible for enrollment in the pivotal phase 3 trial, born SGA, or with NS or ISS, were treated with 0.24 mg/kg/week somapacitan.

In the SGA, NS, and ISS populations, 9/12 (75%), 10/13 (76.9%), and 10/11 (90.9%) subjects, respectively, reported at least one AE during this trial. The only AEs reported by more than 1 subject in the:

1. SGA population were respiratory tract infections, constipation, and nasopharyngitis (see Table 138);
2. NS population were cough, ear infection, headache, nasopharyngitis, and pyrexia (see Table 139);
3. ISS population were respiratory tract infection, abdominal pain, cough, arthralgia, and pyrexia (see Table 140); and

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8.3.7.4. Extension Periods

Throughout the Extension Periods (beginning after 52 weeks of treatment in the pivotal phase 3 trial 4467 and the dose finding phase 2 trial 4245), no new safety signals were detected based on AE analysis.

In general, the most commonly reported AEs during these extension periods were consistent with those reported during the first 52 weeks of the respective trials. Refer to Section 15.4.3, Table 69, Table 70, and Table 71, for AEs reported by ≥ 10% of subjects in the SGA, NS, and ISS safety populations during the Extension Period of trial 4467, respectively; and refer to Table 113, for AEs reported by ≥ 10% of subjects in Extension Periods II and III of trial 4245.

A review of the 120-Day Safety Update, covering a period From November 24, 2024, through June 02, 2025, also revealed no new safety signals during the ongoing Extension Periods of these trials. The long-term safety profile of somapacitan in these trials as reported in the 120-Day Safety Update was comparable to the safety profiles of these trials reviewed in the original submission of the sBLAs.

8.3.7.5. Conclusions Regarding Observed Adverse Events in the Clinical Development Program

Overall, evaluation of the most commonly reported AEs in the somapacitan clinical development program for short stature associated with the SGA, NS, and ISS populations does not reveal new safety findings compared to the known safety profile of somapacitan or other hGHs.

8.3.8. Laboratory Findings

Hyperglycemia and elevated phosphate and alkaline phosphatase (ALP) are known to be associated with hGH and hGH analog therapy. Chronically elevated IGF-1 levels above the normal range (i.e., IGF-1 > 2 to > 3 SDS) with hGH or hGH analog use may be associated with various AEs, including headache, intracranial hypertension (IH), edema, and tumors. Therefore, this review included an analysis of abnormal values and adverse events related to biochemical changes in glycemic control, phosphate, alkaline phosphatase, and IGF-1. The results of these analyses are briefly summarized in this section.

Analysis of other laboratory values did not identify clinically meaningful differences or patterns between any treatment arms within any of the subject populations (i.e., SGA, NS, or ISS) of the pivotal phase 3 trial 4467 (refer to Table 72 through Table 94, in Section 15.4.3), dose finding phase 2 trial 4245 (refer to Table 114 through Table 121, in Section 15.4.3), or in the phase 3 trial 4469 (refer to Table 141 through Table 169, in Section 15.4.3). Further, and significantly, as per Section 8.3.7, reporting of AEs related to any abnormal laboratory values were not among the most commonly reported AEs for any subject population or treatment arm in any of these three trials.

8.3.8.1. Glycemic Control

Decreased insulin sensitivity and glucose metabolism are known class effects of hGH formulations and their analogs due to IGF-1- and GH-related antagonistic effects of insulin in the liver and other tissues.

The data on glucose metabolism from the clinical development program for somapacitan use in children with short stature associated with being born SGA, NS, or ISS did not raise new clinically significant concerns related to treatment with somapacitan use and impaired glucose tolerance.

8.3.8.1.1. Pivotal Phase 3, Trial 4467

Overall, during the Main Period of the pivotal phase 3 trial, there were only small changes, mostly increases, of unknown clinical significance in mean fasting glucose, hemoglobin A1c (HbA1c), or insulin values across treatment groups in the SGA, NS, and ISS populations (see Table 35, Table 36, and Table 37, respectively).

Table 35. Mean (SD) Fasting Glucose, HbA1c, and Insulin Values, Main Period, Trial 4467, SGA Safety Population

		Norditropin 0.035 mg/kg/day (N=37)		Norditropin 0.067 mg/kg/day (N=35)		Somapacitan 0.24 mg/kg/week (N=69)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Fasting glucose (mg/dL)							
Baseline	Mean (SD)	81.6 (8.6)	-	83.5 (8.5)	-	82.3 (10)	-
	n		37		34		69
Week 26	Mean (SD)	90.5 (8.1)	9 (9.5)	87.1 (8)	3.6 (8.1)	88.4 (10)	6 (11.1)
	n		37		34		68
Week 52	Mean (SD)	85.1 (10.2)	3.6 (9.7)	89.3 (5.3)	5.5 (7.7)	85.2 (6.4)	3 (10.4)
	n		37		34		65
HbA1c (%)							
Baseline	Mean (SD)	5.3 (0.3)	-	5.2 (0.3)	-	5.2 (0.2)	
	n		37		35		68
Week 26	Mean (SD)	5.4 (0.3)	0.1 (0.3)	5.3 (0.3)	0.1 (0.3)	5.4 (0.3)	0.1 (0.2)
	n		37		35		68
Week 52	Mean (SD)	5.3 (0.3)	0 (0.3)	5.3 (0.3)	0.1 (0.3)	5.3 (0.3)	0.1 (0.2)
	n		37		34		66
Fasting insulin (uIU/L)							
Baseline	Mean (SD)	3.9 (2.7)	-	3.7 (2.2)	-	4.4 (3.7)	-
	n		37		35		69
Week 26	Mean (SD)	8.8 (5.5)	5 (5.8)	8.5 (3.9)	4.7 (4.5)	13.1 (12.6)	8.6 (12.9)
	n		36		34		67
Week 52	Mean (SD)	7.6 (5)	3.7 (4.6)	8.9 (5.4)	5.1 (5.1)	7.5 (4.5)	3.2 (4.4)
	n		36		34		67

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided glucose in units of mmol/L. To provide glucose in mg/dL in this table, this reviewer multiplied the mmol/L value by 18.
The Applicant provided insulin in units of pmol/L. To provide insulin in uIU/L in this table, this reviewer divided the pmol/L value by 6.
n = number of subjects with available data.

Table 36. Mean (SD) Fasting Glucose, HbA1c, and Insulin Values, Main Period, Trial 4467, NS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=49)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Fasting glucose (mg/dL)					
Baseline	Mean (SD)	85.2 (9)	-	82.9 (9.8)	-
	n		28		49
Week 26	Mean (SD)	91.1 (10)	5.9 (10.8)	89.4 (9.1)	6.7 (9.6)
	n		28		45
Week 52	Mean (SD)	91.4 (6.3)	5.9 (8.8)	85.3 (6.5)	2.6 (9.9)
	n		27		47
HbA1c (%)					
Baseline	Mean (SD)	5 (0.3)	-	4.9 (0.3)	-
	n		27		48
Week 26	Mean (SD)	5 (0.7)	0 (0.2)	4.9 (0.4)	0.1 (0.2)
	n		28		46
Week 52	Mean (SD)	4.9 (0.7)	0 (0.2)	4.9 (0.4)	0.1 (0.2)
	n		27		47
Fasting insulin (uIU/L)					
Baseline	Mean (SD)	4.4 (2.8)	-	4.8 (3.6)	-
	n		28		49
Week 26	Mean (SD)	9.6 (4.9)	5.1 (4.2)	14.7 (16.6)	9.8 (16.7)
	n		28		46
Week 52	Mean (SD)	9.8 (5.2)	5.4 (4.1)	8.4 (5.7)	3.6 (5.5)
	n		27		48

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided glucose in units of mmol/L. To provide glucose in mg/dL in this table, this reviewer multiplied the mmol/L value by 18.
The Applicant provided insulin in units of pmol/L. To provide insulin in uIU/L in this table, this reviewer divided the pmol/L value by 6.
n = number of subjects with available data.

Table 37. Mean (SD) Fasting Glucose, HbA1c, and Insulin Values, Main Period, Trial 4467, ISS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=59)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Fasting glucose (mg/dL)					
Baseline	Mean (SD)	84.3 (7.9)	-	86 (7.8)	-
	n		27		59
Week 26	Mean (SD)	86.3 (10.2)	2.9 (10)	91 (7.4)	5.2 (8.5)
	n		28		58
Week 52	Mean (SD)	86.6 (7.1)	2.9 (10.2)	88.7 (7.3)	2.6 (7.3)
	n		28		55
HbA1c (%)					
Baseline	Mean (SD)	5.2 (0.3)	-	5.2 (0.3)	-
	n		28		59
Week 26	Mean (SD)	5.2 (0.3)	0.1 (0.2)	5.3 (0.3)	0.1 (0.2)
	n		28		57
Week 52	Mean (SD)	5.3 (0.4)	0.1 (0.2)	5.3 (0.4)	0.1 (0.3)
	n		27		55
Fasting insulin (uIU/L)					
Baseline	Mean (SD)	4.4 (3)	-	4.8 (3.2)	-
	n		28		59
Week 26	Mean (SD)	7.6 (4.5)	3.2 (3.2)	12.6 (6.8)	7.8 (6.4)
	n		28		58
Week 52	Mean (SD)	8.5 (7)	4 (5.3)	9.6 (7.5)	4.8 (7)
	n		27		57

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided glucose in units of mmol/L. To provide glucose in mg/dL in this table, this reviewer multiplied the mmol/L value by 18.
The Applicant provided insulin in units of pmol/L. To provide insulin in uIU/L in this table, this reviewer divided the pmol/L value by 6.
n = number of subjects with available data.

In general, changes in fasting glucose, HbA1c, and insulin values during the Main Period of the pivotal phase 3 trial were comparable across treatment groups for all three populations, with the exception of mean (SD) change from baseline in fasting insulin at the Week 26 visit, which was higher in subjects treated with somapacitan compared to subjects treated with Norditropin (SGA: 8.6 [12.9], 5 [5.8], and 4.7 [4.5] uIU/L in the somapacitan and 0.035 and 0.067 mg/kg/day Norditropin groups, respectively; NS: 9.8 [16.7] and 5.1 [4.2] uIU/L in the somapacitan and Norditropin groups, respectively; ISS: 7.8 [6.4] and 3.2 [3.2] uIU/L in the somapacitan and Norditropin groups, respectively). This difference may be due, in part, to the fact that at the Week 26 visit, the blood draw was 2 to 4 days after dosing in the somapacitan groups, corresponding to peak response, while in the Norditropin groups, labs were drawn pre-dose on the day of visit, corresponding to trough values. At the Week 52 visit, where subjects in the somapacitan groups had blood draws done 4 to 6 days after administration, the mean change from baseline in fasting insulin is comparable across treatment groups in all populations.

While the proportion of subjects in the SGA population with elevated (i.e., above the upper limit of normal; ULN) fasting glucose at least once was higher in the somapacitan group (8.7%) compared to the 0.067 mg/kg/day Norditropin group (2.9%), it was comparable to the 0.035 mg/kg/day Norditropin group (8.1%). Additionally, only 1 subject in the SGA population (in the 0.035 mg/kg/day Norditropin group; 2.7%) reported a decreased glucose value (i.e., below the lower limit of normal; LLN). Finally, ≤ 1 subject in any treatment group in the SGA population reported elevated or decreased HbA1c or insulin values. (See Table 86 in Section 15.4.3).

The proportion of subjects in the NS population with elevated fasting glucose at least once was comparable between the somapacitan group (8.5%) and the Norditropin group (7.1%), 0 subjects in either group reported low glucose, and ≤ 1 subject in either treatment group of the NS population reported decreased or elevated HbA1c or insulin. (See Table 87 in Section 15.4.3).

A comparable proportion of subjects in the ISS population treated with somapacitan and Norditropin reported glucose values > ULN at least once (5.2% vs. 3.6%), and no subjects with ISS had decreased glucose values. A total of 2 (7.1%) and 0 subjects in the Norditropin and somapacitan groups, respectively reported insulin values < LLN at least once, otherwise, no subjects reported elevated insulin, or elevated or decreased HbA1c values. (See Table 88 in Section 15.4.3).

Reporting of glucose parameters outside the normal range during the Extension Period (where all subjects received 0.24 mg/kg/week somapacitan) did not reveal additional safety concerns in the SGA, NS, or ISS populations.

- Of the 65 subjects with available data in the SGA population, 0 and 2 (3.1%) had glucose values < LLN or > ULN, respectively, at least once, and no subjects had decreased or elevated HbA1c or insulin.
- A total of 2 (5.6%) and 1 (2.8%) of the 36 subjects in the NS population with available data reported HbA1c or insulin values < LLN, respectively, at least once. No subjects with NS

reported HbA1c or insulin values > ULN, or glucose values outside the normal range in the extension period.

- None of the 39 subjects with available data in the ISS population had glucose or HbA1c values < LLN or > ULN, respectively, and 2 (5.1%) and 0 subjects reported insulin levels < LLN or > ULN, respectively, at least once.

During the Main Period and Extension period of the pivotal phase 3 trial, no subjects treated with somapacitan in the SGA and ISS population reported AEs related to hypo- or hyperglycemia. During the Main Period of the pivotal phase 3 trial, no subjects in the NS population reported AEs related to hypoglycemia and 2 subjects (both in the somapacitan group; 2/49 [4.1%] subjects) reported non-serious AEs related to hyperglycemia (PTs blood glucose increased). These AEs were both mild and non-serious and resolved without changing or interrupting somapacitan therapy. No subjects with NS reported AEs related to hypo- or hyperglycemia in the Extension Period. All subjects with AEs of hyperglycemia were asymptomatic and did not require dose interruption/change.

8.3.8.1.2. Dose Finding Phase 2, Trial 4245

No clinically relevant changes from baseline in fasting glucose, HbA1c, or insulin levels were noted in any treatment arm (see Table 118 in Section 15.4.3) during the first 52 weeks in subjects born SGA.

The mean increases from baseline in fasting glucose, HbA1c, or insulin levels were slightly higher in the 0.24 mg/kg/week somapacitan group than in the 0.16 and 0.2 mg/kg/week somapacitan groups. However, these differences were small and do not appear to be clinically significant, and the mean increases from baseline in fasting glucose, HbA1c, or insulin levels in the 0.24 mg/kg/week somapacitan group were comparable to, or less than, the mean increases from baseline seen in either one, or both, of the two Norditropin groups (i.e., 0.035 and 0.067 mg/kg/day Norditropin).

With the exception of the 0.16 mg/kg/week somapacitan group, where 0 subjects had elevated glucose values, the proportion of subjects with elevated (i.e., > ULN) fasting glucose at any time in the first 52 weeks of the dose finding phase 2 trial were comparable (2/13 [15.4%] for the 0.067 mg/kg/day Norditropin group and 0.24 mg/kg/week somapacitan group and 2/12 [16.7%] for the 0.035 mg/kg/day Norditropin group and 0.2 mg/kg/week somapacitan group). Additionally, 1 or fewer subjects per treatment group reported low fasting glucose, HbA1c, or insulin, or elevated Hba1c or insulin. (See Table 119, in Section 15.4.3).

During Extension Periods II and III of the phase 2 trial, where all subjects were transitioned to 0.24 mg/kg/week somapacitan, a similar proportion of subjects reported elevated glucose values, while there was an increase in decreased insulin values of unclear clinical significance. Of 60 subjects with available data, 11 (18.3%) subjects reported glucose values > ULN at least once; 6 (10%) subjects reported insulin < LLN at least once; and 1 or fewer subjects reported high insulin values, low glucose values, or low or high HbA1c values.

No AEs related to hypo- or hyperglycemia were reported in subjects treated with somapacitan for 52 weeks. In Extension Periods II and III, where all subjects were transitioned to 0.24 mg/kg/week somapacitan, 4/60 (6.7%) subjects reported 7 AEs of hyperglycemia (PTs of glycosylated hemoglobin increased, hyperglycemia, impaired fasting glucose, and type 1 diabetes mellitus). However, for 1 subject originally randomized to 0.035 mg/kg/day Norditropin, 0.067 mg/kg/day Norditropin, and 0.2 mg/kg/week somapacitan, each, AEs of PTs of hyperglycemia, impaired fasting glucose, and type 1 diabetes mellitus (also an SAE, see Serious Adverse Events), respectively, occurred prior to transition to 0.24 mg/kg/week somapacitan. Thus, 2/60 (3.3%) subjects reported 4 AEs of hyperglycemia after transitioning to 0.24 mg/kg/week somapacitan in trial 4245, none of which were serious or severe, an all recovered without changing or interrupting somapacitan dosing. All subjects were asymptomatic.

8.3.8.1.3. Phase 3, Trial 4469

While interpretation of data from individual populations is limited by the small number of subjects of each population enrolled, overall, during the phase 3 trial 4469, there were limited changes of unknown clinical significance in mean fasting glucose, hemoglobin A1c (HbA1c), or insulin values that were comparable across the SGA, NS, and ISS populations (see Table 155, Table 156, and Table 157, respectively, in Section 15.4.3).

Reporting of glucose parameters outside the normal range was limited to only a few subjects in trial 4469 (see Table 158, Table 159, and Table 160 in Section 15.4.3).

- Only 1/8 (12.5%) treatment non-naïve subject, and no treatment naïve subjects, born SGA reported at least one glucose value > ULN at any point in the phase 3 trial 4469. No subjects born SGA reported low glucose or low or elevated HbA1c or insulin.
- Of subjects in the NS population, 2/7 (28.6%) and 1/7 (14.3%) treatment non-naïve subject reported elevated glucose and insulin, respectively, at least once in the trial. No reports of low glucose or insulin, or low or increased HbA1c occurred in the trial.
- In the ISS population, 1/2 (50%) and 1/9 (11.1%) treatment naïve and treatment non-naïve subjects, respectively, reported elevated glucose at least once in the trial. No subjects reported abnormal HbA1c or insulin.

As of the database lock date, no subjects in the trial 4469 reported AEs of either hypoglycemia or hyperglycemia.

8.3.8.2. Alkaline Phosphatase

Growth hormone therapy can lead to elevated bone alkaline phosphatase (ALP), especially when such therapy is associated with increased skeletal growth, and this risk is included in the Warnings and Precautions section of the labels of hGH products and analogs, including somapacitan. ALP levels were monitored in the somapacitan development program in children born SGA or with NS or ISS.

As expected in growing children, mean ALP increased in subjects of all populations (i.e., SGA, NS, or ISS) in the pivotal phase 3 trial 4467, the dose finding phase 2 trial 4245, and the phase 3 trial 4469, and a significant number of subjects in each treatment group in each population reported ALP levels above the upper limit of normal at least once. However, in general, the mean change in ALP from baseline was comparable between treatment groups within populations. The data on increasing ALP from the clinical development program for somapacitan use in children with short stature associated with being born SGA, NS, or ISS did not raise new clinically significant concerns related to treatment with somapacitan use and increased ALP.

8.3.8.2.1. Pivotal Phase 3, Trial 4467

Overall, during the Main Period of the pivotal phase 3 trial, an increase in mean ALP levels from baseline was observed and a majority of subjects reported elevated ALP levels at least once in all treatment groups of the SGA and ISS populations and approximately 20% of subjects with NS also reported elevated ALP levels at least once. With the exception of subjects born SGA in the 0.067 mg/kg/day Norditropin group, the mean change in ALP from baseline was comparable between treatment groups within populations (see Table 38, Table 39, and Table 40).

In subjects born SGA, those treated with somapacitan had similar or lower changes in ALP compared to the Norditropin group(s).

Table 38. Mean (SD) Alkaline Phosphatase Values, Main Period, Trial 4467, SGA Safety Population

		Norditropin 0.035 mg/kg/day (N=37)		Norditropin 0.067 mg/kg/day (N=35)		Somapacitan 0.24 mg/kg/week (N=69)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Alkaline phosphatase (U/L)							
Baseline	Mean (SD)	244.6 (55.5)	-	232.3 (58.9)	-	234 (92.1)	-
	n		37		35		69
Week 26	Mean (SD)	304 (78.8)	54.3 (46)	299 (77.9)	68.6 (47.4)	284.5 (72.3)	50.5 (93.9)
	n		37		34		66
Week 52	Mean (SD)	291.1 (67.3)	45.4 (49.8)	301.6 (83.3)	70.2 (62)	289.8 (77.6)	55.8 (90.4)
	n		36		34		69

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data.

Table 39. Mean (SD) Alkaline Phosphatase Values, Main Period, Trial 4467, NS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=49)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Alkaline phosphatase (U/L)					
Baseline	Mean (SD)	177.5 (41.3)	-	182.7 (47.4)	-
	n		28		47
Week 26	Mean (SD)	221.3 (46.5)	44.7 (31.5)	239.8 (66.2)	56.2 (36)
	n		26		46
Week 52	Mean (SD)	218 (54.8)	41.8 (29.1)	231.4 (65.6)	50.2 (32.5)
	n		27		48

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data.

Table 40. Mean (SD) Alkaline Phosphatase Values, Main Period, Trial 4467, ISS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=59)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Alkaline phosphatase (U/L)					
Baseline	Mean (SD)	223.3 (70.2)	-	238.9 (104)	-
	n		28		58
Week 26	Mean (SD)	290.4 (113.7)	67 (56)	292.1 (66.4)	46.8 (98.2)
	n		28		58
Week 52	Mean (SD)	280.2 (117.1)	56.9 (56.3)	295.5 (61.2)	48.5 (104.2)
	n		28		56

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data.

There was a higher proportion of subjects with elevated ALP in the NS population treated with somapacitan compared to Norditropin (24.5% vs. 14.3%). However, the proportions of subjects treated with somapacitan reporting elevated ALP were, in general, comparable, or less than, that reported in Norditropin groups within the other populations. The proportion of subjects in the SGA population reporting elevated ALP at least once was 60.9% in the somapacitan group, compared to 68.6% in the 0.067 mg/kg/day Norditropin group, though it was higher in the 0.035 mg/kg/day Norditropin group (81.1%). The ISS population also had a comparable proportion of subjects in the somapacitan and Norditropin group who had ALP > ULN (57.6% vs. 50%, respectively). (See Table 89, Table 90, and Table 91, in Section 15.4.3).

The clinical significance of these elevations is unknown, elevated ALP is a known concern that is included the labels of all hGH products and their analogs, including somapacitan, and, reassuringly, no subject in any population reported AEs related to ALP during the Main or Extension Periods of the pivotal phase 3 trial.

Reporting of ALP outside the normal range during the Extension Period (where all subjects received 0.24 mg/kg/week somapacitan) did not reveal additional safety concerns in the SGA, NS, or ISS populations, as each population reported comparable, or decreased, proportions of subjects reporting elevated ALP at least once, relative to the Main Period:

- SGA population: 45/67 (67.2%) subjects with available data
- NS population: 3/36 (8.3%) subjects with available data
- ISS population: 21/39 (53.8%) subjects with available data

No subjects in any treatment group or population reported ALP < LLN in either the Main or Extension Periods of the trial.

8.3.8.2.2. Dose Finding Phase 2, Trial 4245

Findings of elevated ALP in the dose finding phase 2 trial is consistent with findings in the pivotal phase 3 trial 4467.

Similar to the pivotal phase 3 trial 4467, during the phase 2 trial 4245 in children born SGA, an increase in mean ALP levels from baseline was observed in all treatment groups over the first 39 weeks of therapy (ALP was not checked at the Week 52 visit in this trial). In subjects treated with somapacitan, the mean change in ALP at the end of 39 weeks of therapy was higher in the 0.24 mg/kg/week somapacitan group (77.3 U/L), compared to the 0.16 and 0.2 mg/kg/week somapacitan groups (43.2 and 52.8 U/L, respectively), however, mean values remained within the normal range (see Table 120 in Section 15.4.3).

The proportion of subjects in the dose finding phase 2 trial with elevated ALP at any time during the first 39 weeks of the trial was comparable among the three somapacitan groups (58.3%, 53.8%, and 58.3% in the 0.16, 0.2, and 0.24 mg/kg/week somapacitan groups, respectively), highest in the 0.067 mg/kg/day Norditropin group (76.9%), and lowest in the 0.035 mg/kg/day Norditropin group (33.3%). (See Table 121 in Section 15.4.3).

During Extension Periods II and III of the phase 2 trial, where all subjects were transitioned to 0.24 mg/kg/week somapacitan, no additional significant findings regarding elevated ALP were demonstrated.

No subjects in any period of the phase 2 trial 4245 reported AEs related to ALP levels.

8.3.8.2.3. Phase 3, Trial 4469

Because of the limited number of subjects of each population enrolled, it is difficult to make definitive conclusions regarding the changes in ALP with somapacitan therapy.

Generally, and consistent with trials 4467 and 4245, ALP increased with somapacitan treatment in treatment naïve subjects in each population (i.e., SGA, NS, and ISS) during the phase 3 trial 4469. However, for treatment non-naïve subjects in these populations, ALP had minimal increases, or even decreases, with somapacitan therapy. The reason for these findings is not clear but may be related to the slowed growth with increased duration of therapy and catch-up phenomenon seen with increased growth following initial correction of growth deficits with therapy.

After 26 weeks of somapacitan therapy, mean (SD) change from baseline in ALP in treatment naïve and non-naïve subjects was:

- 131 (37.4) U/L and 50.5 (47.8) U/L, respectively, in the SGA population.
- 72.7 (25.4) U/L and 0 (30.5) U/L, respectively, in the NS population.
- 72 (75) U/L and 5.1 (51.7) U/L, respectively, the ISS population.

(See Table 161, Table 162, and Table 163 in Section 15.4.3).

Further, as with both the pivotal phase 3 trial and the dose finding trial, overall, a significant proportion of treatment naïve and non-naïve subjects in reported ALP > ULN at least once during trial 4469:

- 4/4 (100%) and 5/8 (62.5%) subjects born SGA, respectively
- 4/6 (66.7%) and 0/7 subjects with NS, respectively
- 0/2 and 3/9 (33.3%) subjects with ISS, respectively

(See Table 167, Table 168, and Table 169 in Section 15.4.3).

No subjects of any population in any period of the phase 3 trial 4469 reported AEs related to ALP levels.

8.3.8.3. Phosphate

Growth hormone therapy can lead to elevated phosphate, and this risk is included in the Warnings and Precautions section of the labels of hGH products and analogs, including somapacitan. Phosphate levels were monitored in the somapacitan development program in children born SGA or with NS or ISS.

The data on increasing phosphate from the clinical development program for somapacitan use in children with short stature associated with being born SGA, NS, or ISS did not raise new clinically significant concerns related to treatment with somapacitan use and increased phosphate.

8.3.8.3.1. Pivotal Phase 3, Trial 4467

Overall, during the Main Period of the pivotal phase 3 trial, small increase of unknown clinical significance in mean phosphate levels from baseline was observed in all treatment groups of all populations (i.e., SGA, NS, and ISS). Overall, the mean change in phosphate from baseline was comparable between treatment groups within populations, and mean values were within the normal range (see Table 41, Table 42, and Table 43).

Table 41. Mean (SD) Phosphate Values, Main Period, Trial 4467, SGA Safety Population

		Norditropin 0.035 mg/kg/day (N=37)		Norditropin 0.067 mg/kg/day (N=35)		Somapacitan 0.24 mg/kg/week (N=69)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Phosphate (mg/dL)							
Baseline	Mean (SD)	5 (0.5)	-	5 (0.8)	-	5 (0.5)	-
	n		37		35		68
Week 26	Mean (SD)	5.4 (0.4)	0.4 (0.5)	5.7 (0.7)	0.6 (0.6)	5.6 (0.5)	0.6 (0.5)
	n		37		34		66
Week 52	Mean (SD)	5.4 (0.6)	0.5 (0.6)	5.6 (0.8)	0.6 (0.8)	5.8 (0.5)	0.8 (0.6)
	n		36		34		69

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided phosphate in units of mmol/L. To provide phosphate in mg/dL in this table, this reviewer multiplied the mmol/L value by 3.1.
n = number of subjects with available data.

Table 42. Mean (SD) Phosphate Values, Main Period, Trial 4467, NS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=49)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Phosphate (mg/dL)					
Baseline	Mean (SD)	4.8 (0.5)	-	4.9 (0.5)	-
	n		28		48
Week 26	Mean (SD)	5.3 (0.3)	0.5 (0.6)	5.7 (0.4)	0.8 (0.5)
	n		26		46
Week 52	Mean (SD)	5.3 (0.4)	0.5 (0.5)	5.8 (0.5)	0.9 (0.6)
	n		27		48

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical
The Applicant provided phosphate in units of mmol/L. To provide phosphate in mg/dL in this table, this reviewer multiplied the mmol/L value by 3.1.
n = number of subjects with available data.

Table 43. Mean (SD) Phosphate Values, Main Period, Trial 4467, ISS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=59)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Phosphate (mg/dL)					
Baseline	Mean (SD)	4.8 (0.6)	-	4.9 (0.4)	-
	n		28		58
Week 26	Mean (SD)	5.5 (0.7)	0.6 (0.5)	5.6 (0.5)	0.7 (0.6)
	n		28		58
Week 52	Mean (SD)	5.5 (0.7)	0.7 (0.4)	5.7 (0.4)	0.9 (0.5)
	n		28		56

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided phosphate in units of mmol/L. To provide phosphate in mg/dL in this table, this reviewer multiplied the mmol/L value by 3.1.
n = number of subjects with available data.

In the NS population, there was a higher proportion of subjects with at least 1 phosphate value > ULN in the somapacitan group compared to the Norditropin group (71.4% vs. 39.3%). The proportion of subjects in the SGA population with phosphate > ULN at least once was comparable between the somapacitan (72.5%) and 0.067 mg/kg/day Norditropin groups (71.4%), though lower in the 0.035 mg/kg/day Norditropin group (45.9%). The ISS population also had comparable rates of subjects reporting elevated phosphate between the somapacitan and Norditropin populations (74.6% vs. 71.4%, respectively). (See Table 92, Table 93, and Table 94, in Section 15.4.3).

Reporting of phosphate outside the normal range during the Extension Period (where all subjects received 0.24 mg/kg/week somapacitan) did not reveal additional safety concerns in the SGA, NS, or ISS populations, as each population reported comparable proportions of subjects reporting elevated phosphate at least once, relative to the Main Period:

- SGA population: 34/67 (50.7%) subjects with available data
- NS population: 22/36 (61.1%) subjects with available data
- ISS population: 27/39 (69.2%) subjects with available data

In the Main Period of trial 4467, 1/69 (1.4%) subject born SGA in the somapacitan arm and 2/49 (4.1%) subjects with NS in the somapacitan arm, reported 3 mild, non-serious, asymptomatic AEs of hyperphosphatemia for which dosing was not changed or interrupted, though only 1 of these AEs is reported to have recovered. No other subjects in any treatment arm of any population reported AEs of hyperphosphatemia in the Main Period of trial 4467. During the Extension Period of the trial, the only subject to report an AE hyperphosphatemia was in the ISS sub-trial: 1/85 (1.2%) subject reported a mild, non-serious AE of hyperphosphatemia for which the dose of somapacitan was not changed or interrupted, though the AE has not recovered.

8.3.8.3.2. Dose Finding Phase 2, Trial 4245

Phosphate levels were not monitored in the phase 2 trial.

8.3.8.3.3. Phase 3, Trial 4469

Minimal changes from baseline in phosphate were demonstrated in treatment naïve or treatment non-naïve subjects in the SGA, NS, ISS, or TS populations during the phase 3 trial 4469. Mean (SD) changes from baseline in phosphate in the treatment naïve and non-naïve groups after 26 weeks of somapacitan therapy were:

- 0.4 (0.1) and 0.9 (0.7) mg/dL in the SGA population, respectively
- 1 (0.6) and 0.5 (0.5) mg/dL in the NS population, respectively
- 0.7 (0.4) and 0.4 (0.5) mg/dL in the ISS population, respectively

(See Table 164, Table 165, and Table 166 in Section 15.4.3).

The majority of treatment naïve and non-naïve subjects in all subject populations reported phosphate > ULN at least once during trial 4469:

- 3/4 (75%) and 7/8 (87.5%) subjects in the SGA population, respectively
- 4/6 (66.7%) and 4/7 (57.1%) subjects in the NS population, respectively
- 2/2 (100%) and 8/9 (88.9%) subjects in the ISS population, respectively

(See Table 167, Table 168, and Table 169 in Section 15.4.3).

The clinical significance of these phosphate values is unclear, and no subjects of any population in any period of the phase 3 trial 4469 reported AEs related to phosphate levels.

8.3.8.4. IGF-1

Prolonged exposures to chronic IGF-1 levels are a potential safety concern. Levels of IGF-1 that are clearly associated with adverse reactions (ARs) are not defined. The goal of treatment with hGH or its analogs in children with short stature is improvement in growth and final height while minimizing ARs. IGF-1 is not routinely monitored in clinical practice; there are no data that establish a direct relationship between IGF-1 levels and improvement in growth, the relationship between IGF-1 and growth rate or final adult height is influenced by many factors, such as bone age, birth length, and nutritional status, and as such, has a

limited role as a marker for efficacy.[38] However, levels are measured with AEs potentially related to elevated IGF-1 occur so that the dose can be decreased if appropriate. In general, IGF-1 levels are kept below +2 or +3 SDS.

Therefore, IGF-1 levels were monitored, and dose titration protocols were instituted, throughout the clinical program of somapacitan for children with short stature associated with being born SGA, or with NS or ISS (as described in Sections 8.1.1.1, 8.1.2.1, and 8.1.3.1) to evaluate the proportion of subjects with persistently elevated IGF-1 levels, risk of potential AEs associated with elevated IGF-1 levels, and the magnitude of IGF-1 response to dose adjustment.

IGF-1 levels were drawn at baseline, Week 4, Week 8 (phase 2 trial 4245 and phase trial 4469, only), Week 13, and every 13 weeks until Week 52, then every 26 weeks thereafter during all trials of the clinical development program. During trial 4467, laboratory sampling for subjects receiving somapacitan was as follows:

- Week 4: 12 hours to 2 days after administration.
- Weeks 13, 39, 78: prior to administration on planned dosing day.
- Week 26: 2 to 3 days after administration.
- Weeks 52: 4 to 6 days after administration.
- Weeks 104: up to 4 days after administration.

During trial 4245, laboratory sampling for subjects receiving somapacitan was as follows:

- Weeks 4, 13, 104, 156, 208, 260: on planned day of administration
- Weeks 8, 39, 78, 117, 130, 182, 234: 1 to 4 days after administration.
- Weeks 26, 52: 4 to 6 days after administration.

During trial 4469, laboratory sampling for subjects receiving somapacitan was as follows:

- Week 4: 12 hours to 2 days after administration
- Weeks 8, 20, 39: prior to administration on planned dosing day.
- Week 13: 2 to 4 days after administration.
- Weeks 26, 52: 4 to 6 days after administration.

8.3.8.4.1. Pivotal Phase 3 Trial 4467

8.3.8.4.1.1. Mean IGF-1 Levels

Throughout the Main Period of the trial (i.e., Weeks 0 to 52), the mean (SD) IGF-1 levels were below the target goal of ≤ 2 or ≤ 3 SDS for the SGA, NS, and ISS populations in all treatment arms (see Table 95, Table 96, and Table 97 in Section 15.4.3, Trial NN8640-4467).

[38] Johannsson G, et al. Growth Hormone Research Society. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. *Endocr Connect*. 2018 Mar;7(3):R126-R134.

During the Extension Period of trial 4467, where all subjects received 0.24 mg/kg/week somapacitan, mean (SD) IGF-1 values remained at appropriate levels for all populations at Week 78. However, while mean IGF-1 SDS was seen to increase at the Week 108 visit, there are relatively few subjects with available data at this visit, and the timing of IGF-1 draw at this visit could be up to 4 days after administration of somapacitan and possibly representing peak levels and not corresponding to average weekly IGF-1 levels.

8.3.8.4.1.2. Persistently Elevated IGF-1 Levels

SGA

Throughout the 52 weeks of the Main Period of trial 4467, a comparable proportion of subjects in the SGA population treated with somapacitan (14/69 [20.3%] subjects) or treated with 0.035 mg/kg/day Norditropin (9/37 [24.3%] subjects) had IGF-1 > 2 SDS on at least two consecutive visits; comparatively, a higher proportion of subjects in the 0.067 mg/kg/day Norditropin arm (17/35 [48.6%] subjects) reported IGF-1 > 2 SDS on at least two consecutive visits. Similarly, the proportion of subjects with IGF-1 > 3 SDS on at least two consecutive visits was comparable between the somapacitan (6/69 [8.7%] subjects) and 0.035 mg/kg/day Norditropin groups (3/37 [8.1%] subjects) and higher in the 0.067 mg/kg/day Norditropin group (9/35 [25.7%] subjects).

NS

A total of 5/49 (10.2%) subjects with NS treated with somapacitan, compared to 0 subjects treated with Norditropin, in the Main Period of trial 4467 had IGF-1 > 2 SDS on at least two consecutive visits. The reason for this imbalance is unclear, and may be due to the timing of IGF-1 sampling in each treatment group relative to drug administration, ranging from just before dosing, or 12 hours to 2 days, 2 to 3 days, or 4 to 6 days after administration of somapacitan, depending on the visit, or any time of day after Norditropin administration), though this wasn't seen in the SGA or ISS populations, which had the same timing.

No subjects in the NS population had IGF-1 > 3 SDS on two or more consecutive visits.

ISS

There was a comparable proportion of subjects in the ISS population treated with somatropin (10/59 [16.9%] subjects) compared to those treated with Norditropin (6/28 [21.4%] subjects) during the Main Period of the trial who had IGF-1 > 2 SDS on at least two consecutive visits. There were relatively few subjects in each treatment group who had IGF-1 > 3 SDS on at least two consecutive visits: 4/59 (6.8%) and 1/28 (3.6%) subjects in the somapacitan and Norditropin arms, respectively.

8.3.8.4.1.3. Dose Adjustments Due to Elevated IGF-1

As per protocol, doses of somapacitan and Norditropin could be decreased by 25% in subjects who experience IGF-1 levels > 3 SDS at two consecutive visits or persistent AEs. If the AE or

elevated IGF-1 did not resolve after the first dose reduction, an additional 25% reduction in dose may occur. If IGF-1 remains > 3 SDS despite two dose reductions, the subject should be offered individual medical advice by the Investigator (see Section 8.1.1.1). Notably, the language in the protocol only suggests that dose reductions *could* or *may* occur. As discussed below, as the majority of subjects meeting these criteria did not have dose reductions, it does not appear that investigators were required to reduce dosing in response to elevated IGF-1.

SGA

In the SGA population, of the 3, 9, and 6 subjects in the 0.035 and 0.067 mg/kg/day Norditropin group, or the somapacitan group, respectively, with IGF-1 > 3 SDS on at least two consecutive visits during the Main Period of trial 4467, only 4 subjects, all in the 0.067 mg/kg/day Norditropin group, had a dose reduction due to elevated IGF-1. Of the 6 subjects in the somapacitan group with IGF-1 > 3, none of whom, per the Applicant, had dose reductions, 2 subjects' IGF-1 values decreased to < 3 at the next visit (though for 1 of these subjects the following IGF-1 was again > 3 SDS), and the IGF-1 values for the other 4 subjects remained > 3 at all subsequent visits.

NS

No subjects in the NS population qualified for dose reduction due to elevated IGF-1, as none had IGF-1 > 3 SDS on two or more consecutive visits.

ISS

Of the 1 and 4 subjects in the Norditropin and somapacitan groups, respectively, with IGF-1 > 3 SDS on at least two consecutive visits during the Main Period of trial 4467, only 1 subject, in the somapacitan group, had the dose reduced for elevated IGF-1. As discussed in Section 8.3.6, this subject also had an AE of IGF-1 increased that contributed to the decision to reduce somapacitan dosing. At Weeks 26 and 39 the subject's IGF-1 SDS levels were 4.6 and 3.3, respectively, prompting dose reduction, which occurred 6 weeks prior to the Week 52 visit. At the Week 52 visit (the most recently documented IGF-1 level), IGF-1 SDS remained elevated at 4.5. For the other 3 subjects treated with somapacitan with persistent IGF-1 > 3 SDS, the most recently documented IGF-1 levels were < 3 SDS without dose reductions.

8.3.8.4.1.4. Adverse Events Potentially Associated With Elevated IGF-1

To further evaluate whether persistent elevations in IGF-1 > 3 SDS were associated with AEs, the AEs reported by subjects during the time interval when IGF-1 > 3 SDS on at least two consecutive visits was reviewed in detail.

In the SGA population of trial 4467, a comparable proportion of subjects in the somapacitan group, compared to the 0.035 mg/kg/day Norditropin group, reported an AE while IGF-1 SDS was persistently elevated: 6/69 (8.7%) subjects compared to 3/37 (8.1%) subjects,

respectively. However, the 0.067 mg/kg/day Norditropin group had the highest proportion of subjects with AEs while IGF-1 was elevated: 9/35 (25.7%) subjects. All AEs reported by subjects in the somapacitan arm while IGF-1 was elevated resolved without changing or interrupting somapacitan dosing, and none of these AEs were of any preferred term reported by more than 1 subject in the somapacitan arm and thus are not represented in an increased proportion relative to overall reporting of all AEs reported in the trial. Refer to Table 98, in Section 15.4.3. Therefore, it is unlikely that elevated IGF-1 values occurring with somapacitan therapy are associated any specific adverse reaction reported in this population.

In the ISS population of trial 4467, 4/59 (6.8%) subjects in the somapacitan arm, compared to 1/28 (3.6%) subjects in the Norditropin arm reported an AE while IGF-1 SDS was > 3 on at least two consecutive visits. Of the AEs reported by subjects in the somapacitan arm while IGF-1 was elevated, only the AEs of IGF-1 increased (despite a decrease in somapacitan dosing) and one AE of pain in extremity (in the leg; somapacitan dose not changed) were reported as not recovered. Both these AEs were mild and non-serious. All other AEs resolved without changing or interrupting somapacitan dosing (including another AE of pain in extremity [arm] of the same subject reporting AE of leg pain). None of these AEs were of any preferred term reported by more than 1 subject in the somapacitan arm and thus are not represented in an increased proportion relative to overall reporting of all AEs reported in the trial. Refer to Table 99, in Section 15.4.3.

A causal association between the AE of IGF-1 increased and somapacitan is probable, given that hGH products and analogs are expected to exert their effects through the GH-IGF-1 axis. However, increasing IGF-1 is a known effect of hGH and analog therapy, and can be monitored if concerns of adverse reactions in response to treatment are noted in clinical practice. Additionally, while a causal association between elevated IGF-1 with somapacitan therapy and pain extremity cannot be ruled out, the pain in extremity in the leg persisted despite IGF-1 levels in that subject eventually decreasing below 3 SDS without changes to therapy, and pain in extremity is not uncommon in this age group and may represent “growing pains”.

As such, while prolonged exposures to persistently elevated IGF-1 values are a potential safety concern, the lack of a consistent pattern of any of these AEs with elevated IGF-1 values is reassuring, and any risks related to elevated IGF-1 can be mitigated by monitoring for AEs and dose adjustments.

8.3.8.4.1.5. Extension Period of Trial 4467

78 weeks of treatment, subjects treated with only 0.24 mg/kg/week somapacitan, demonstrated mean IGF-1 SDS remained in the normal range. However, at Week 104, interpretation of mean IGF-1 SDS is more difficult given the relatively small number of

subjects with available data (i.e., 4, 2, and 9 subjects in the SGA, NS, and ISS populations, respectively). For subjects only treated with 0.24 mg/kg/week somapacitan in the:

- SGA cohort:
  - Observed mean (SD) IGF-1 at Week 52 was 1.9 (1.2) SDS, at Week 78 was 1.1 (1.3) SDS, and at Week 104 was 3.3 (2) SDS.
- NS cohort:
  - Observed mean (SD) IGF-1 at Week 52 was 1 (1.3) SDS, at Week 78 was -0.1 (1) SDS, and at Week 104 was 1.7 (1.9) SDS.
- ISS cohort:
  - Observed mean (SD) IGF-1 at Week 52 was 1.6 (1.3) SDS, at Week 78 was 1.1 (1.2) SDS, and at Week 104 was 1.8 (1.3) SDS.

While the mean 104-week IGF-1 SDS remained in the normal range for the NS and ISS populations, in the NS population, this consisted of two subjects with available data, one of whom was in the normal range (IGF-1 of 0.4 SDS) and one who was elevated (IGF-1 of 3 SDS). Further, the mean 104-week IGF-1 SDS for the SGA cohort was elevated but consisted of two subjects with normal values (IGF-1 of 1.8 SDS and 1.6 SDS) and two subjects with elevated values (IGF-1 of 4.1 SDS and 5.8 SDS). Interpretation of these results is limited by the small sample size, the clinical significance of these IGF-1 elevations is unclear, and evaluation of adverse events for the subjects with elevated IGF-1 values at Week 104 did not reveal specific safety concerns. Increase in IGF-1 levels above the normal range is a known risk and can be monitored if concerns of adverse reactions in response to treatment are noted in clinical practice.

8.3.8.4.2. Dose Finding Phase 2, Trial 4245

8.3.8.4.2.1. Mean IGF-1 Levels

Throughout the first 52 weeks of the trial (i.e., the Main Period and Extension Period I), the mean (SD) IGF-1 levels were below the target goal of ≤ 2 or ≤ 3 SDS for the SGA, NS, and ISS populations in all treatment arms (see Table 122 in Section 15.4.3, Trial NN8640-4245). Further, during Extension Periods II and III, as all subjects were transitioned to 0.24 mg/kg/week somapacitan, mean (SD) IGF-1 values up to 260 weeks of treatment remained at appropriate levels.

8.3.8.4.2.2. Persistently Elevated IGF-1 Levels

From the initiation of randomized therapy until subjects were transitioned to 0.24 mg/kg/week somapacitan, a total of 3/12 (25%) and 9/13 (69.2%) subjects in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively, and 5/12 (41.7%) and 7/13 (53.8%) subjects in the 0.16 and 0.2 mg/kg/week somapacitan groups, respectively, had IGF-1 > 2 SDS on at least two consecutive visits. For subjects who were randomized to 0.24 mg/kg/week

somapacitan, 9/12 (75%) subjects had IGF-1 > 2 SDS on at least two consecutive visits in the first 52 weeks of therapy, similar to what was seen in the high dose Norditropin group.

A total of 4/12 (33.3%) subjects in the 0.24 mg/kg/week somapacitan group had IGF-1 > 3 SDS on at least two consecutive visits in the first 52 weeks of therapy, which was a higher number compared to 1/12 (8.3%) subjects in the 0.16 mg/kg/week somapacitan group and 2/13 (15.4%) subjects in the 0.067 mg/kg/day Norditropin group, and 0 subjects in the other groups. During Extension Periods II and III, beginning after 52 weeks of therapy, 4 additional subjects reported IGF-1 SDS > 3 on at least two consecutive visits.

8.3.8.4.2.3. Dose Adjustments Due to Elevated IGF-1

Dose reduction criteria in the first 52 weeks of treatment in the phase 2 trial did not include criteria related to IGF-1 SDS levels, though it was allowed, but not required, for IGF-1 > 3 SDS on two consecutive visits in the subsequent extension periods. No subjects had the dose of treatment reduced due to elevated IGF-1 in trial 4245. However, when including data from treatment beyond 52 weeks, where all subjects were transitioned to 0.24 mg/kg/week somapacitan, the most recently documented IGF-1 value was < 3 SDS for all but 1 of the 11 subjects who had IGF-1 > 3 SDS for at least two consecutive visits at any point in the trial.

8.3.8.4.2.4. Adverse Events Potentially Associated With Elevated IGF-1

The AEs reported by during the time interval when IGF-1 > 3 SDS on at least two consecutive visits was reviewed in detail.

While all subjects were exposed to the treatment to which they were originally randomized, 2/13 (15.4%), 1/12 (8.3%), and 3/12 (25%) subjects reported AEs in the 0.067 mg/kg/day Norditropin group or the 0.16 or 0.24 mg/kg/week somapacitan group, respectively, reported at least 1 AE while IGF-1 > 3 SDS on at least two consecutive visits. No subjects in the 0.035 mg/kg/day Norditropin group or 0.2 mg/kg/week somapacitan group reported IGF-1 > 3 SDS on at least two consecutive visits.

With the exception of an AE of eczema in one subject in the 0.24 mg/kg/week somapacitan group which did not resolve, all AEs reported by subjects while IGF-1 > 3 SDS on at least two consecutive visits during randomized therapy resolved, and none of these cases was the dose of Norditropin or somapacitan adjusted or interrupted. None of these AEs were of any preferred term reported by more than 1 subject in the somapacitan arms and thus are not represented in an increased proportion relative to overall reporting of all AEs reported in the trial. One subject in the 0.24 mg/kg/week somapacitan arm reported AEs of hyperglycemia and glycosylated hemoglobin increased while IGF-1 > 3 SDS, and glucose intolerance is a labeled warning of hGH products and their analogs, however these AEs resolved after IGF-1 normalized, and without changing/interrupting therapy. Refer to Table 123 in Section 15.4.3. Additional evaluation of AEs reported after subjects switched to 0.24 mg/kg/week somapacitan while IGF-1 > 3 SDS did not reveal significant safety signals, and included rhinitis,

otitis media, scarlet fever, blepharospasm, dental caries, respiratory disorder, and enterobiasis, none of which required changes to somapacitan dosing.

As such, while prolonged exposures to persistently elevated IGF-1 values are a potential safety concern, the lack of a consistent pattern of any of these AEs with elevated IGF-1 values is reassuring, and any risks related to elevated IGF-1 can be mitigated by monitoring for AEs and dose adjustments.

8.3.8.4.3. Phase 3, Trial 4469

8.3.8.4.3.1. Mean IGF-1 Levels

The mean IGF-1 SDS was ≤ 2 or ≤ 3 at all visits in the first 52 weeks of treatment in trial 4469 across all treatment populations and regardless of treatment naïve or non-naïve status, with the exception of the two treatment naïve subjects in the ISS population, whose mean IGF-1 SDS at the visits at Weeks 26, 39, and 52, was 3.2 to 3.3. (See Table 170, in Section 15.4.3, Trial NN8640-4469). This elevation is of unclear significance and for all populations and treatment groups, the number of enrolled subjects is small, complicating interpretation.

8.3.8.4.3.2. Persistently Elevated IGF-1 Levels, Dose Adjustments for IGF-1, and Adverse Events Potentially Associated With Elevated IGF-1

Only two subjects (a treatment naïve subject in the ISS population and a treatment non-naïve subject in the SGA population) in trial 4469 had IGF-1 > 3 SDS on at least two consecutive visits. The treatment naïve subject in the ISS population reported AEs of arthralgia, IGF-1 increased, and fungal infection, and the treatment non-naïve subject in the SGA population reported an AE of acne, while IGF-1 was elevated. The AE of acne is not recovered, but dosing of somapacitan was not changed or interrupted for this AE, or for the AEs of fungal infection or arthralgia, both of which were recovered. As discussed in Section 8.3.6, the subject with an AE of IGF-1 increased did have somapacitan dosing decreased in response to the elevated IGF-1. This is the only subject in trial 4469 with somapacitan dose adjustment due to elevated IGF-1. While this AE is not listed as recovered, the subject's next IGF-1 value was < 3 SDS at 2.7.

A causal association between the AE of IGF-1 increased and somapacitan is probable, given that hGH products and analogs are expected to exert their effects through the GH-IGF-1 axis. However, increasing IGF-1 is a known effect of hGH and analog therapy, and can be monitored if concerns of adverse reactions in response to treatment are noted in clinical practice.

8.3.9. Vital Signs

There were no clinically significant changes in blood pressure and pulse, or BMI from baseline to the end of the pivotal phase 3 trial 4467 in any of the SGA, NS, or ISS safety populations, and there were no meaningful differences or patterns between the treatment arms of the

pivotal phase 3 trial within these indicated populations in the Extension Periods or in the phase 2 trial 4245 or in the phase 3 trial 4469.

8.3.10. Electrocardiograms, QT, and Echocardiograms

Electrocardiogram

ECGs were obtained at baseline and every 6 months for subjects with NS, and yearly for subjects born SGA or with ISS, during the pivotal phase 3 trial 4467, the dose finding phase 2 trial 4245, and the phase 3 trial 4469 (in this trial, subjects born SGA or with ISS received an ECG at 6 months and 12 months, and then yearly thereafter, and subjects with TS received ECGs every 6 months).

The review of ECG data did not reveal clinically relevant changes in children born SGA or with NS or ISS as assessments were similar between somapacitan and Norditropin treatment groups in all populations and trials.

A summary of ECG findings are included in Section 15.4.4, Summary of Clinically Significant ECG Findings.

QT

The Applicant did not conduct a dedicated QT study. According to ICH E14, large, targeted proteins (such as somapacitan) and monoclonal antibodies "have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic consideration or data from clinical or non-clinical studies".[39]

During the review cycle for the clinical development program for somapacitan in children with growth failure due to pediatric growth hormone deficiency, the FDA Interdisciplinary review team (IRT) concluded that a dedicated QT study was not required based on known hGH product safety information (no QT prolongation) and absence of QT related safety signals. The IRT team evaluated ECG findings from the phase 3 trial in adults with growth hormone deficiency and confirmed a lack of QT-related safety signals and no risk was labeled. The IRT consultant recommended routine safety monitoring of ECG in the pediatric trials (refer to IRT consult in DARRTS from September 05, 2019).

The submitted ECG data in the current sBLA did not indicate any new effects of somapacitan on the QTc interval at the proposed therapeutic dose.

[39] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic

Echocardiogram

Only subjects with NS and TS had routine evaluations of echocardiograms in the clinical development program, as congenital cardiac findings are not uncommon in these syndromes. As noted above, the findings in TS population are not discussed in this review. In general, echocardiogram findings did not raise safety concerns.

Pivotal Phase 3, Trial 4467

During the 52-week Main Period of this trial, a total of 7/49 (14.3%) subjects with NS in the somapacitan arm, compared to 3/28 (10.7%) subjects in the Norditropin arm, had abnormal echocardiogram findings in trial 4467. Of these subjects, two subjects in the somapacitan group had new findings on echocardiogram: mildly dilated right ventricle and mild right and left ventricular hypertrophy in one subject and "stenosis a. pulmonalis valvularis, supravalvularis et rami bil a. pulmonalis s/p operation, ASD" in one subject (who did have pulmonary artery stenosis on screening echocardiogram). During the Extension Period, an additional 5/76 (6.6%) subjects had echocardiogram findings that were not present on screening echocardiogram: mildly dilated right ventricle, pulmonary insufficiency, aortic regurgitation, tricuspid regurgitation, mild mitral regurgitation, small patent foramen ovale, and mild aortic shunt.

One subject in somapacitan arm had an AE of aortic valve incompetence during the Main Period; this subject also had the abnormal echocardiogram finding of 'mild aortic shunt' in the Extension Period (not reported as AE). The AE was mild, non-serious, and did not result in changing or interrupting somapacitan dosing, though the AE has not recovered. One subject in the Extension Period reported AEs of aortic and pulmonary valve incompetence (both non-serious and not severe, though somapacitan dosing was briefly interrupted without resolution; see Section 8.3.6). This subject was noted to have the abnormal echocardiogram findings of pulmonary insufficiency and aortic regurgitation in the Extension Period.

Phase 3, Trial 4469

Only one treatment naïve subject with NS had an abnormal echocardiogram finding: moderate aortic regurgitation. This finding was first noted at the Week 26 visit, and no further echocardiograms have been documented.

This same subject had an AE of aortic valve incompetence. This AE was non-serious, of moderate severity, and did not require changing or interrupting somapacitan dosing, though it has not recovered. Causal assessment regarding somapacitan and this AE is difficult to establish given that NS is known to be associated with congenital heart defects, this subject had a known diagnosis of second-degree aortic valve regurgitation prior to starting the trial, and though it was reported as an AE because it was seen to be worsening, the subject has not had a follow up echocardiogram by the time of the database lock date to determine if it persists with continued somapacitan dosing.

8.3.11. Immunogenicity

Pharmacotherapy with biological agents can induce the development and anti-drug antibodies (ADAs). The main concern with anti-GH antibodies is their potential to interfere with GH by changing GH PK or by directly blocking binding of GH to the GH receptor, thereby impacting drug effectiveness. There are also ADA-related safety concerns, including immunogenicity related adverse reactions (such as injection site reactions or hypersensitivity reactions) or effects on the frequency or severity of already known drug class adverse reactions, such as hyperglycemia, tumors, or intracranial hypertension.

ADA (including anti-somapacitan antibodies, anti-hGH antibodies, and anti-hGH cross-reacting antibodies) were monitored at pre-specified timepoints, and antibody persistence was defined as the presence of antibodies at two or more consecutive visits. If subjects were positive for ADA, they were evaluated for anti-hGH neutralizing antibodies (NAbs) positivity.

- During the phase 3 trials 4467 and 4469, ADAs were monitored at baseline, then every 13 weeks until Week 78, after which they were monitored every 26 to 52 weeks.
- During the phase 2 trial 4245, ADAs were monitored at baseline, Week 4, at the end of every year of treatment, and, for subjects switching from a previous dose of somapacitan or Norditropin, to 0.24 mg/kg/week somapacitan, at the time of switch.

The immunogenicity results obtained in clinical studies were evaluated as follows:

- Anti-somapacitan antibodies
  - incidence of anti-somapacitan antibodies
  - levels and persistence over time
  - further characterization of anti-somapacitan antibodies for cross-reactivity with endogenous hGH
  - In vitro neutralizing effect of anti-somapacitan antibodies against somapacitan
  - In vitro neutralizing effect of anti-somapacitan antibodies (with cross-reactivity to endogenous hGH) against endogenous hGH
- Impact of anti-somapacitan antibodies on PK (by somapacitan PK concentrations)
- Impact of anti-somapacitan antibodies on PD and efficacy (by IGF-1, IGFBP-3 and Height Velocity)
- Impact of anti-somapacitan antibodies on safety (by general AEs and immunogenicity related AEs)

Immunogenicity Results Summary

The immunogenicity profile varied across the different patient populations and studies (see Table 44). In the SGA population, Trial 4467 demonstrated that 10 out of 69 children (14.5%) developed at least one positive anti-somapacitan antibody sample. Notably, 7 children (10.1%) had persistent anti-somapacitan antibodies defined as two or more consecutive positive antibody samples, while 3 children (4.3%) had transient antibodies with only one

positive sample. In contrast, both studies 4469 and 4245 in the SGA population showed no children testing positive for anti-somapacitan antibodies.

For the NS population, Study 4467 showed that 2 out of 49 children (4.1%) developed at least one positive anti-somapacitan antibody sample, with one subject having transient antibodies and one subject with antibodies present on two consecutive visits. Study 4469 demonstrated a higher percentage but smaller absolute number, with 1 out of 6 GH treatment-naïve children (16.7%) developing transient anti-somapacitan antibodies.

The ISS population in Study 4467 showed 7 out of 59 children (11.9%) developing at least one positive anti-somapacitan antibody sample. Among these, 4 children (6.8%) had persistent antibodies while 3 children (5.1%) had transient antibodies. Study 4469 in the ISS population showed no children testing positive for anti-somapacitan antibodies.

Table 44. Anti-Somapacitan Antibody Incidence by Population and Study

Population	Study	Total Participants (Somapacitan Arm)	ADA Positive Participants	Incidence (%)	Persistent ADA*	Transient ADA**
SGA	4467	69	10	14.5%	7 (10.1%)	3 (4.3%)
	4469	12	0	0%	0	0
	4245	60	0	0%	0	0
NS	4467	49	2	4.1%	1 (2%)	1 (2%)
	4469	6*	1	16.7%	0	1 (16.7%)
ISS	4467	59	7	11.9%	4 (6.8%)	3 (5.1%)
	4469	11	0	0%	0	0

Persistent ADA: ≥2 consecutive positive antibody samples
*Transient ADA: Only 1 positive antibody sample
*GH treatment-naïve children only
Source: Reviewer generated.

Comparison With Norditropin

The anti-hGH antibody incidence in the Norditropin® comparator arms was generally lower than the anti-somapacitan antibody incidence. In the SGA population, 2 out of 48 children (4.2%) across Studies 4467 and 4245 developed anti-hGH antibodies. For the NS population, 1 out of 28 children (3.6%) in Study 4467 developed anti-hGH antibodies, and similarly, 1 out of 28 children (3.6%) in the ISS population developed anti-hGH antibodies. The Applicant notes that all anti-somapacitan antibody positive samples were cross-reactive to hGH.

Timing of Anti-Somapacitan Antibodies Detection

In children with SGA, Study 4467 showed antibody detection beginning at Week 13, with the highest incidence at Week 52 where 13.0% of children tested positive. Among the 10 positive children (14.5% of 69 total), 3 children (4.3%) developed transient antibodies while 7 children (10.1%) had persistent antibodies. Notably, no anti-somapacitan antibodies were detected in SGA children in Studies 4469 or 4245.

Children with NS demonstrated lower antibody incidence, with 2 of 49 children (4.1%) testing positive at Week 52 in Study 4467 (one of whom was also positive at Week 78), and 1 of 6 children (16.7%) testing positive at Week 39 in Study 4469.

The ISS population showed antibody detection from Week 13 onwards in 7 of 59 children (11.9 %) from Study 4467, with peak detection at Weeks 39 and 52 (8.8-8.9%). Among ISS patients, 3 children (5.1%) had transient antibodies and 4 children (6.8%) had persistent antibodies, while no antibodies were detected in Study 4469.

Antibody Titer Characteristics

All detected anti-somapacitan antibodies were classified as low titer, defined as samples below 1056 with minimum required dilution (MRD = 33) or below 32 without MRD adjustment. The observed titer ranges varied by population: SGA children showed titers of 1-8 (33-264 with MRD), NS children demonstrated the lowest ranges of 1-2 (33-66 with MRD) in Study 4467 and a titer of 16 (528 with MRD) in Study 4469, while ISS children had titers ranging from 2-16 (66-528 with MRD). Despite these population differences, all antibody responses remained within the low titer category, indicating a consistent pattern of mild immunogenic response to somapacitan treatment across all pediatric indications.

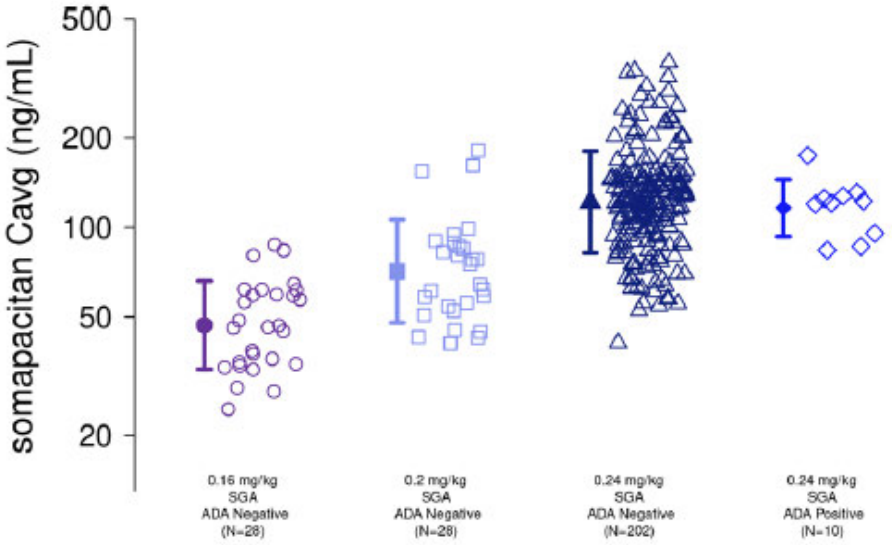
Neutralizing Antibody Incidence

Across all studies and populations there were no neutralizing antibodies detected.

Impact on Pharmacokinetics

The analysis of somapacitan PK revealed no meaningful impact from anti-somapacitan antibody formation. Figure 13 demonstrates that in the SGA population, there were similar exposure levels between ADA-negative (N=202) and ADA-positive (N=10) participants in the SGA population.

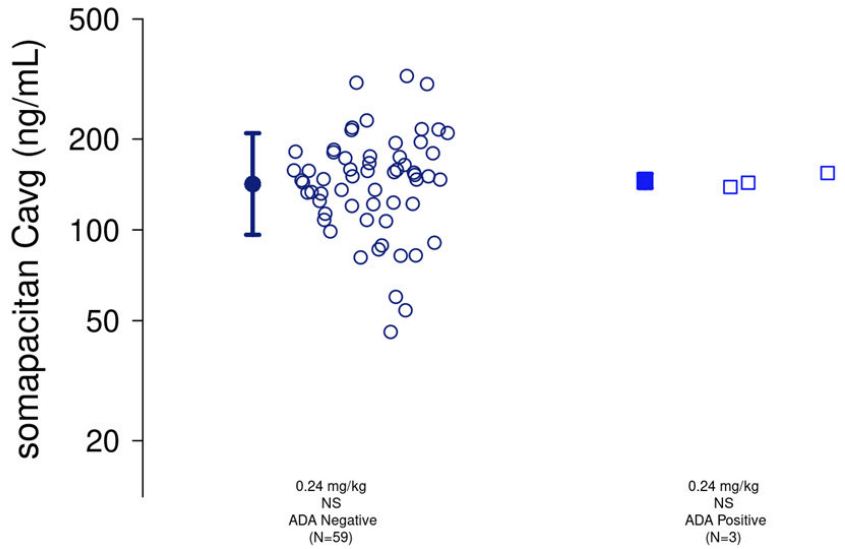
Figure 13. Exposure in Participants With and Without Anti-Drug Antibodies – SGA



Source: SGA-NS-ISS Modelling report (M 5.3.3.5), Figure 6-6. Notes: Open symbols are individual exposure estimates by anti-drug antibodies. Closed symbols and bars indicate geometric means and standard deviations. Data are from study 4245, 4467 and 4469 for the 0.24 mg/kg/week dose level.
Abbreviations: ADA: anti-drug antibodies; Cavg: average steady-state concentration in a dosing interval; SGA: short for gestational age.

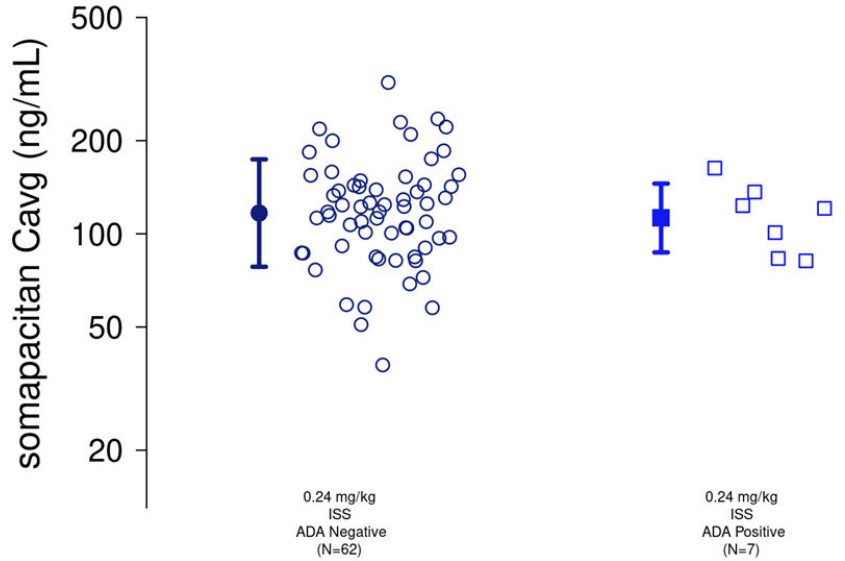
Similar patterns were observed in the NS and ISS populations. Figure 14 shows that modeling derived somapacitan exposure in NS children was comparable between antibody-positive and antibody-negative participants. For the ISS population, Figure 15 demonstrated consistent findings, showing no difference in somapacitan exposure between ADA-negative (N=62) and ADA-positive (N=7) participants.

Figure 14. Exposure in Participants With and Without Anti-Drug Antibodies – NS



Source: SGA-NS-ISS Modelling report (M 5.3.3.5), Figure 8-6. Notes: Open symbols are individual exposure estimates by anti-drug antibodies. Closed symbols and bars indicate geometric means and standard deviations. Data are from study 4467 and 4469 for the 0.24 mg/kg/week dose level.
Abbreviations: ADA: anti-drug antibodies; Cavg: average steady-state concentration in a dosing interval; NS: Noonan syndrome.

Figure 15. Exposure in Participants With and Without Anti-Drug Antibodies – ISS

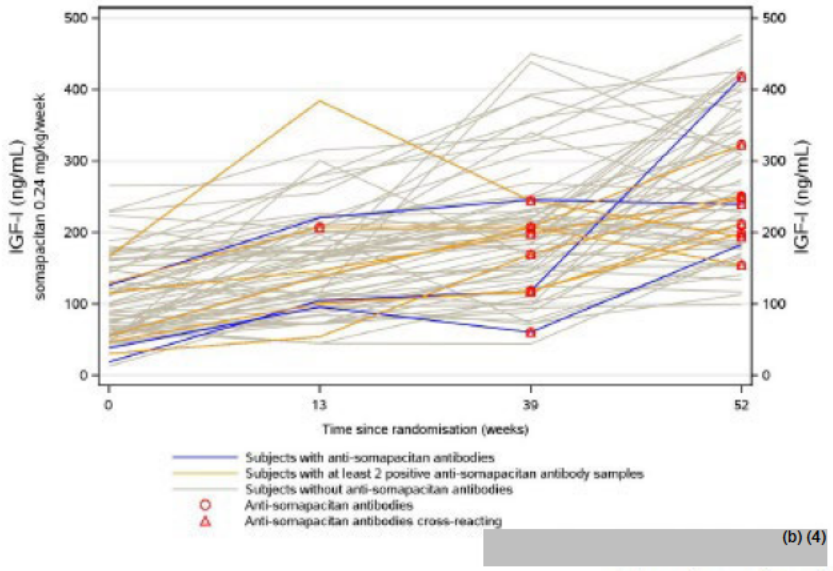


Source: SGA-NS-ISS Modelling report (M 5.3.3.5), Figure 7-6. Notes: Open symbols are individual exposure estimates by anti-drug antibodies. Closed symbols and bars indicate geometric means and standard deviations. Data are from studies 4467 and 4469 for the 0.24 mg/kg/week dose level.
Abbreviations: ADA: anti-drug antibodies; Cavg: average steady-state concentration in a dosing interval; ISS: idiopathic short stature

Impact on Pharmacodynamics

The pharmacodynamic assessment focused on IGF-I and IGFBP-3 levels, which are key biomarkers of growth hormone activity. In the SGA population, Figure 16 and Figure 17 demonstrate that children positive for anti-somapacitan antibodies had IGF-I and IGFBP-3 levels within the same range as antibody-negative children, with no apparent trend toward higher or lower values in antibody-positive participants.

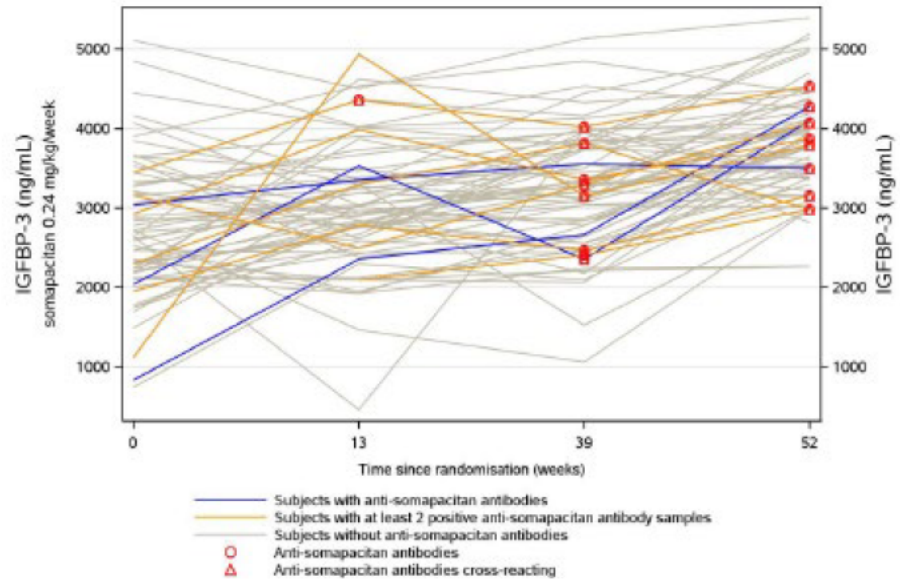
Figure 16. IGF-I (Ng/Ml) and Occurrence of ADA in Study 4467 (Week 52)- SGA



Cross-reference: Appendix 7.3, Figure 9

Source: 5.3.5.3 Integrated summary of immunogenicity, Figure 4-7

Figure 17. IGFBP-3 (Ng/Ml) and Occurrence of ADA in Study 4467 (Week 52)- SGA



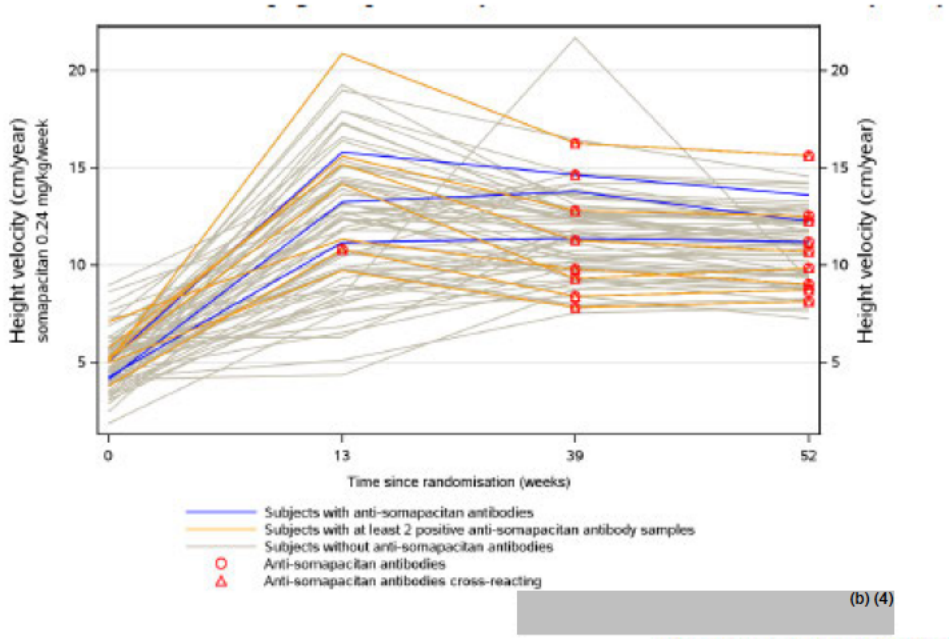
Source: 5.3.5.3 Integrated summary of immunogenicity, Figure 4-8

The NS and ISS populations showed similar results that antibody-positive children maintained comparable IGF-I and IGFBP-3 levels to antibody-negative children throughout the study period.

Impact on Efficacy

Height velocity, the primary efficacy endpoint, was not adversely affected by anti-somapacitan antibody formation across all populations. In trial 4467, in the SGA population, children with anti-somapacitan antibodies maintained height velocity measurements comparable to antibody-negative children (Figure 18 and Table 45).

Figure 18. Height Velocity (Cm/Year) and Occurrence of Antibodies Study 4467 (52 Weeks) - SGA



Cross-reference: Appendix 7.3, Figure 13

Source: 5.3.5.3 Integrated summary of immunogenicity, Figure 4-9

Table 45. Mean (SD) Annualized Height Velocity (Cm/Year) in Subjects Who Were Antibody Positive or Negative, Main Period, Trial 4467, SGA Population

	Norditropin 0.035 mg/kg/day (N=37)	Norditropin 0.067 mg/kg/day (N=35)	Somapacitan 0.24 mg/kg/week (N=69)	
Antibody Status	Subjects With Negative Anti-hGH Antibody n = 37 (100%)	Subjects With Negative Anti-hGH Antibody n = 35 (100%)	Subjects With Negative ADA n = 59 (85.5%)	Subjects With ≥ 1 Positive ADA n = 10 (14.5%)
Baseline	5.1 (1.4)	5 (1.6)	5 (1.4)	5 (0.9)
Week 13	11.1 (3.2)	13 (4.1)	11.9 (3.5)	13.8 (3.3)
Week 26	10.5 (2)	12.1 (2.8)	11.8 (2.2)	12.3 (3.1)
Week 39	10 (1.8)	11.6 (2)	11.6 (2.3)	11.5 (2.8)
Week 52	9.5 (1.5)	11.1 (1.8)	11 (1.8)	11.2 (2.4)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

Similar efficacy preservation was observed in the NS population and ISS population, where height velocity remained consistent between antibody-positive and antibody-negative children (refer to Table 46 and Table 47).

Table 46. Mean (SD) Annualized Height Velocity (Cm/Year) in Subjects Who Were Antibody Positive or Negative, Main Period, Trial 4467, NS Population

	Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=49)	
Antibody Status	Subjects With Negative Anti-hGH Antibodies n = 27 (96.4%)	Subjects With ≥ 1 Positive Anti-hGH Antibodies n = 1 (3.6%)	Subjects With Negative ADA n = 47 (95.9%)	Subjects With ≥ 1 Positive ADA n = 2 (4.1%)
Baseline	4.6 (1.9)	6.4 (-)	5 (2.9)	7.3 (3.3)
Week 13	10.2 (4)	8.1 (-)	11.2 (4)	10.9 (3.4)
Week 26	10 (2.6)	7.1 (-)	11.3 (2.4)	11.6 (0.6)
Week 39	9.5 (2.3)	6.4 (-)	10.6 (2)	11.7 (0.2)
Week 52	9.3 (2.3)	7 (-)	10.4 (1.7)	10.4 (0.1)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

Table 47. Mean (SD) Annualized Height Velocity (Cm/Year) in Subjects Who Were Antibody Positive or Negative, Main Period, Trial 4467, ISS Population

	Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=59)	
Antibody Status	Subjects With Negative Anti-hGH Antibodies n = 27 (96.4%)	Subjects With ≥ 1 Positive Anti-hGH Antibodies n = 1 (3.6%)	Subjects With Negative ADA n = 52 (88.1%)	Subjects With ≥ 1 Positive ADA n = 7 (11.9%)
Baseline	4.7 (1.6)	2.2 (-)	5 (1.7)	5.3 (2.3)
Week 13	11.8 (3)	11.2 (-)	10.9 (3.3)	11.9 (3.1)
Week 26	11.7 (2.2)	10 (-)	11 (2.3)	12 (2.3)
Week 39	11.1 (1.8)	9.3 (-)	10.2 (1.9)	11 (1.8)
Week 52	10.7 (1.6)	9.5 (-)	10.1 (1.7)	10.7 (1.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

Available data from the Extension period suggest the presence of ADA did not impact growth with up to 2 years of treatment with somapacitan:

- In SGA population, mean (SD) AHV at 78 weeks was 8.8 (0.8) cm/year (n = 4) vs. 8.9 (2) cm/year (n = 63), and at 104 weeks was 8.3 cm/year (n = 1) vs. 9 (1.3) cm/year (n = 7), between subjects who had at least one ADA positive result and subjects who never tested positive for ADAs, respectively
- In NS and ISS populations, mean (SD) AHV at the 78-week time point was 10.1 (0.8) cm/year in subjects who tested positive at least once to somapacitan ADA (n = 2), compared to 8.4 (1.6) cm/year in subject who never tested positive for somapacitan ADA (n =34).1 subject, each, had positive ADA without impact on growth.
- In ISS population, mean (SD) AHV at 78 weeks was 9.2 (1.1) cm/year (n = 4) vs. 8.4 (1.6) cm/year (n = 35), and at 104 weeks was 8.8 (2.1) cm/year (n = 2) vs. 7.8 (1.5) cm/year (n = 9), in subjects who had at least one ADA positive result and subjects who never tested positive for ADAs, respectively.

However, overall interpretation of growth is complicated by the limited number of subjects with anti-hGH antibodies.

Safety

Analysis of AEs in ADA-positive subjects in trial 4467 (see Severe Hypersensitivity and Anaphylaxis) did not reveal new safety signals related to immunogenicity and somapacitan therapy. No subject with positive antibodies reported AEs related to hypersensitivity at any point in the trial.

The immunogenicity findings from other clinical trial conducted in the intended populations did not raise safety or efficacy concerns. No subjects treated with somapacitan had positive ADA in phase 2 trial, 4245. In phase 3 trial 4469, no ADA were detected in SGA or ISS populations. In the NS population of trial 4469, 1/6 (16.7%) treatment naïve subject had positive ADAs to somapacitan at Week 39 and did not have any impact on efficacy or safety of the drug.

Conclusions on Immunogenicity

No immunogenicity concerns were raised in the clinical program. Overall, the number of subjects who developed positive ADAs during the treatment was small, and comparable or smaller to Norditropin. The proportion of subjects with positive ADAs was also comparable between treatment subgroups. There were no neutralizing antibodies, only few subjects had tested positive for ADA more than once and titer of ADAs was generally low. More importantly, there was no effect of ADA on safety or efficacy of somapacitan observed. Subjects with positive ADAs demonstrated similar growth as ADA-negative subjects and there were no hypersensitivity reactions or other AEs associated with ADA.

8.3.12. Analysis of Submission-Specific Safety Issues

Tumorigenesis, intracranial hypertension (IH), slipped capital femoral epiphysis (SCFE; including risk for osteonecrosis), glucose intolerance and diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism, progression of scoliosis, hypersensitivity, lipoatrophy (related to injection site), and fluid retention are class specific AEs included in all approved hGH labels. As such, these are considered to be adverse events of special interest (AESIs). As such, this reviewer also evaluated AEs possibly related to pain in extremity (e.g., pain in extremity, growing pains, arthralgia, myalgia) as submission-specific safety issues, while evaluation of headaches is included in the assessment of intracranial hypertension.

These AESIs are briefly summarized below, except for AEs related to hyperglycemia/diabetes mellitus, which are discussed in Section 8.3.8.1.

Unless otherwise noted the few cases specified, the AEs reported by subjects treated with somapacitan in the following subsections of Section 8.3.12, occurred in a few subjects only, were non-serious, not severe, and did not require changes in somapacitan dosing, or temporary interruption or permanent discontinuation of somapacitan therapy.

Increased Risk of Neoplasm

IGF-1 is a growth promoting factor, and chronically elevated IGF-1 levels may play a role in tumorigenesis. There is no conclusive evidence regarding an increased risk of neoplasm in patients with GHD treated with hGH products or analogs. However, based on the putative biological mechanism, all hGH and analog formulations are contraindicated in patients with active malignancies and the risk of neoplasm is included in Section 5 Warnings and Precautions of all hGH and analog labels.

There was a low incidence of neoplasm reported with somapacitan therapy in the clinical development program, with no imbalance seen between treatment groups or populations evaluated. All but one AE of neoplasm were reported in one subject each; melanocytic nevi were reported in 2 subjects (1 subject each in the SGA and NS populations). The clinical trial data do not suggest an increased risk of malignant tumor with somapacitan therapy or suggest that the neoplasms reported were related to somapacitan therapy. The somapacitan label already includes the risk of malignancies in Section 5.

Pivotal Phase 3, Trial 4467

SGA

During the Main Period of trial 4467, 1/69 (1.4%) and 1/37 (2.7%) subject in the somapacitan and 0.035 mg/kg/day Norditropin groups, respectively, reported AEs related to neoplasms. In the somapacitan group, the reported neoplasm was melanocytic nevus, an SAE, and, as discussed in Serious Adverse Events , unlikely to be related to somapacitan therapy.

No subjects in the SGA population reported AEs related to neoplasms in the Extension Period of the pivotal phase 3 trial.

NS

A total of 2/49 (4.1%) and 2/28 (7.1%) subjects in the NS population treated with somapacitan and Norditropin, respectively, reported AEs related to neoplasms during the Main Period of trial 4467. The AEs reported in the somapacitan group were melanocytic nevus (which was not serious, mild in severity, and recovered without changing or interrupting somapacitan therapy) and cholesteatoma, which was an SAE, and, discussed in Serious Adverse Events , unlikely to be related to somapacitan therapy.

During the Extension Period of the pivotal phase 3 trial, 1 additional subject, originally randomized to Norditropin and since transitioned to somapacitan, reported an AE of bone giant cell tumor, which was also an SAE that was unlikely to be related to somapacitan therapy, as discussed in Serious Adverse Events .

ISS

No subject with ISS reported AEs related to neoplasms during any period of the pivotal phase 3 trial 4467.

Dose Finding Phase 2, Trial 4245

During the first 52 weeks of randomized treatment in trial 4245, only 1 subject, in the 0.16 mg/kg/week somapacitan arm (1/12 [8.3%] subject) reported an AE related to neoplasms, with the PT skin papilloma (reported term: wart on toe). During Extension Periods II and III, where all subjects transitioned to 0.24 mg/kg/week somapacitan, 1 additional subject reported a neoplasm-related AE, with the PT of fibrous cortical defect.

Phase 3, Trial 4469

No subject of any population (i.e., SGA, NS, ISS, or TS), reported an AE related to neoplasm during this trial.

Intracranial Hypertension and Headache

Due to an increased risk of IH with hGH therapy, fundoscopic examinations were conducted in all trials at baseline in the U.S. It was also performed in the case of severe headache, visual symptoms, and nausea/vomiting, at the discretion of the investigator at all sites.

No evidence of IH was reported in any trial (i.e., trials 4467, 4245, or 4469).

Since headache may be a symptom of IH, this reviewer also evaluated AEs of headache. Headache occurred in few subjects only, were not serious and resolved without dose interruption in the majority of patients. The rate of headache was comparable between the subgroups of patients. Overall, these findings did not raise any safety concerns, and headache

is not uncommon in general pediatric population. However, since funduscopic examination was not performed in any of subjects with headache, the conclusion regarding whether the events were related to IH is complicated.

These findings are briefly summarized below.

Pivotal Phase 3, Trial 4467

SGA

In the Main Period of the pivotal phase 3 trial, the rate of headaches in the SGA population was similar between treatment groups and were reported in 2 (5.4%), 2 (5.7%), and 4 (5.8%) subjects in the 0.035 and 0.067 mg/kg/day Norditropin, and somapacitan arms, respectively. During the Extension Period, only 1 (0.7%) subject reported an AE of headache.

NS

Headache was reported in 5 (10.2%) subjects in the somapacitan group, compared to 2 (7.1%) subjects in the Norditropin group of the NS population in the Main Period of the pivotal phase 3 trial. During the Extension Period, 1 (1.3%) subject reported an AE of headache. Despite a risk difference ≥ 1% between the somapacitan and Norditropin groups, all headache AEs reported by subjects receiving somapacitan were mild and non-serious and recovered without stopping, interrupting, or changing dosing.

ISS

In the ISS population, during the Main Period of trial 4467, a comparable proportion of subjects treated with Norditropin (3 [10.7%] subjects) and somapacitan (6 [10.2%] subjects) reported AEs related to headaches. During the Extension Period, 3 (3.5%) subjects reported AEs of headache, one of whom required both interruption, and later discontinuation, of study drug in response to the AE of headache, as discussed in Section 8.3.5, Extension Period.

Dose Finding Phase 2, Trial 4245

During the first 52 weeks of treatment in the dosing finding phase 2 trial, relatively few subjects reported AEs related to headaches, including 1 (7.7%) subject in the 0.067 mg/kg/day Norditropin group, 1 (8.3%) subject in the 0.16 mg/kg/week somapacitan group, and 1 (7.7%) subject in the 0.2 mg/kg/week somapacitan group. During Extension Periods following 52 weeks of treatment, 2 (3.2%) subjects reported AEs related to headaches. As discussed in Section 8.3.6, Adverse Events Leading to Dose Reduction/Temporary Interruption, Dose Finding Phase 2, Trial 4245, only 2 AEs of headache required dose reduction, though the AEs did not resolve in response.

Phase 3, Trial 4469

A total of 1 (11.1%) treatment non-naïve subject with ISS, 1 (12.5%) treatment non-naïve subject in the SGA population, and 1 (14.3%) treatment non-naïve subject and 1 (16.7%) treatment naïve subject with NS reported AEs related to headaches.

Slipped Capital Femoral Epiphysis and Osteonecrosis

SCFE was not reported by any subject in the clinical development program for short stature associated with being born SGA, or with NS, ISS.

During the dose finding phase 2 trial 4245, 1 (1.6%) subject in Extension Period II, after transition from 0.035 mg/kg/day Norditropin to 0.24 mg/kg/week somapacitan, reported an AE of osteochondrosis of the right ankle. During the phase 3 trial 4469, 1 (50%) treatment naïve subject with ISS reported an AE of osteitis (described as calcaneal apophysitis). These are the only AEs across trials 4467, 4245, and 4469 that may represent possible findings related to osteonecrosis. However, a causal association with somapacitan treatment is unclear. Both SCFE and osteonecrosis are labeled warnings in all hGH products and analogs.

Pancreatitis

Pancreatitis was not reported as an AE by any subject in trials 4467, 4245, or 4469.

Adrenal Insufficiency and Fatigue

The clinical trial data do not suggest a significant new safety information related to adrenal insufficiency as no subject in any treatment arm (Norditropin or somapacitan), in any population (SGA, NS, ISS, or TS) of any trial (trials 4467, 4245, or 4469) reported AEs related to adrenal insufficiency.

Hypothyroidism

Growth hormone therapy has been associated with an increased risk of worsening, or unmasking, hypothyroidism, and hypothyroidism is listed in the Warnings and Precautions section of the labels of all approved hGH products and analogs. Monitoring for new onset or worsening hypothyroidism can be done with routine labs, and replacement thyroid hormone can be prescribed, or dose adjusted as needed.

There were only a few subjects in each subgroup (≤ 2) who developed hypothyroidism, all cases were nonserious, and did not require dose adjustment. The clinical development program did not suggest significant new safety information related to hypothyroidism.

Pivotal Phase 3 Trial 4467

SGA

During the Main Period of trial 4467, relatively few subjects in the SGA population reported AEs related to hypothyroidism: 2 (7.1%) and 1 (1.4%) subject in the 0.035 mg/kg/day Norditropin and the somapacitan arms, respectively. These AEs included PTs of hypothyroidism and blood thyroid stimulating hormone increased. No subjects in the SGA population reported AEs of hypothyroidism in the Extension Period of the trial.

NS

Only 1 (2%) subject in the somapacitan arm, and no subjects in the Norditropin arm reported an AE related to hypothyroidism in the Main Period of trial 4467. No subjects in the NS population reported AEs of hypothyroidism in the Extension Period of the trial.

ISS

No subjects treated with Norditropin, and only 1 (1.7%) subject treated with somapacitan, in the ISS population, reported AEs of hypothyroidism during the Main Period of the pivotal phase 3 trial 4467. No subjects in the ISS population reported AEs of hypothyroidism in the Extension Period of the trial.

Dose Finding Phase 2 Trial 4245

No subjects in any period of the dose finding phase 2 trial reported AEs related hypothyroidism.

Phase 3 Trial 4469

Throughout the entire phase 3 trial 4469, 1 (16.7%) treatment naïve subject in the NS population reported an AE related to hypothyroidism was.

Progression of Scoliosis

Progression of preexisting scoliosis in patients undergoing rapid growth is labeled in the Warnings and Precautions section of all approved hGH products and analogs, including somapacitan.

Overall, only a few subjects across the clinical development program reported AEs related to scoliosis. All cases of scoliosis were non-serious and not severe, and none resulted in changing or interrupting study drug therapy. No new safety signal was identified in clinical program.

Pivotal Phase 3 Trial 4467

No subjects in the Main Period of the pivotal phase 3 trial 4467 reported AEs of scoliosis.

During the Extension Period, 1 (1.3%) subject with NS and 1 (1.2%) subject with ISS reported an AE of scoliosis. These subjects' medical history did not include a diagnosis of scoliosis.

Dose Finding Phase 2 Trial 4245

In the Extension Periods, 2 (3.2%) subjects reported AEs of scoliosis, including 1 subject who was found to have thoracic scoliosis while still on 0.067 mg/kg/day Norditropin therapy and lumbar scoliosis after transitioning to 0.24 mg/kg/week somapacitan.

Phase 3 Trial 4469

No subjects with SGA, NS, or ISS reported scoliosis.

Severe Hypersensitivity and Anaphylaxis

Serious systemic hypersensitivity reactions, including anaphylactic reactions and angioedema have been reported with other hGH therapies.

The clinical trial data do not suggest significant new safety information related to hypersensitivity or that treatment with somapacitan resulted in anaphylactic reactions or severe hypersensitivity reactions. Hypersensitivity reactions occurred in small number of subjects in each subgroup, and there was no imbalance in types of these reactions between groups. The majority of hypersensitivity reactions were non-serious, resolved, and did not require treatment discontinuation. No anaphylactic reactions were reported. None of hypersensitivity reactions were associated with positive ADA. The causality assessment is further confounded by past medical history of various hyperreactivity reactions in these subjects and the fact that hypersensitivity reactions are not uncommon in general pediatric population.

The brief summary of hypersensitivity reactions is discussed below.

Pivotal Phase 3 Trial 4467

SGA

The frequency of hypersensitivity-related AEs during the Main Period of the pivotal phase 3 trial was comparable across treatment groups: 6 (16.2%), 3 (8.5%), and 7 (10.1%) subjects reported hypersensitivity-related AEs in the 0.035 and 0.067 mg/kg/day Norditropin, and somapacitan arms, respectively. These AEs were allergic cough, allergic sinusitis, bronchial hyperreactivity, bronchospasm, conjunctivitis allergic, drug hypersensitivity (in a subject in the 0.035 mg/kg/day Norditropin arm; the specific drug causing hypersensitivity is not clarified), eczema, eye swelling, rash, rash erythematous, rhinitis allergic, and urticaria. In the Extension Period, 7 (5%) subjects reported hypersensitivity-related AEs, including allergic

respiratory disease, conjunctivitis allergic, dermatitis allergic, rash, rhinitis allergic, and urticaria. None of these AEs were serious.

NS

During the Main Period of trial 4467 3 (10.7%) vs. 6 (10.2%) subjects in Norditropin and somapacitan groups, respectively, reported AEs related to hypersensitivity. These hypersensitivity-related AEs included allergic cough, conjunctivitis allergic, dermatitis, eczema, lip swelling, rash, rhinitis allergic, urticaria, and urticaria papular. In the Extension Period, 2 (2.6%) reported related AEs, including PTs of eczema and asthma. Hypersensitivity-related AEs in somapacitan group did not require changing or interrupting study drug, and none were serious or severe.

ISS

A higher proportion of subjects with ISS in the somapacitan arm, compared to the Norditropin arm, reported hypersensitivity-related AEs in the Main Period of the pivotal phase 3 trial: 9 (15.3%) vs. 2 (7.1%) subjects, respectively. These AEs included PTs of asthma, conjunctivitis, dermatitis, dermatitis atopic, erythema, neurodermatitis, rash, rhinitis allergic, and urticaria. In the Extension Period, 6 (7.1%) subjects reported hypersensitivity AEs, including angioedema, asthma, conjunctivitis allergic, dermatitis atopic, rhinitis allergic, and urticaria. One AE of conjunctivitis allergic reported during the Extension Period required temporary interruption of somapacitan (as discussed in more detail in Section 8.3.6, Adverse Events Leading to Dose Reduction/Temporary Interruption, ISS).

Dose Finding Phase 2 Trial 4245

One subject each in the 0.035 and 0.067 mg/kg/day Norditropin groups and 0.16 and 0.2 mg/kg/week somapacitan groups (8.3%, 7.7%, 8.3%, and 7.7%, respectively) and 2 (16.7%) subjects in the 0.24 mg/kg/week somapacitan group reported AEs related to hypersensitivity in the 52-week randomized treatment portion of trial 4245. In the following Extension Periods, after 52 weeks of treatment, 13 (21%) of subjects reported AEs related to hypersensitivity. The AEs included in the hypersensitivity analyses included PTs of asthma, conjunctivitis allergic, dermatitis allergic, eczema, erythema, hand dermatitis, perioral dermatitis, periorbital edema, rash, rash pustular, rhinitis allergic, and urticaria.

One subject originally randomized to 0.067 mg/kg/day Norditropin reported an AE of periorbital edema after transitioning to 0.24 mg/kg/week somapacitan, which resulted in temporary interruption of study drug (see Section 8.3.6, Adverse Events Leading to Dose Reduction/Temporary Interruption, Dose Finding Phase 2, Trial 4245).

Phase 3 Trial 4469

None of the adolescent subjects in the phase 3 trial 4469 reported AEs related to hypersensitivity.

Injection Site Reactions and Lipoatrophy

Injection site reactions are expected events with injectable drugs, and lipoatrophy is a labeled warning for hGH products and analogs, including somapacitan.

Overall, the number of subjects within injection site reactions was small, the proportion of subjects with AEs related to injection site reactions and lipoatrophy demonstrated no imbalance in the rate of these reactions across the treatment groups. All reactions in subjects treated with somapacitan were non serious and the majority resolved without treatment. Only 2 somapacitan-treated subjects in clinical program (1 subject in the phase 2 trial and 1 non-treatment naïve subject with NS in the phase 3 trial 4469) developed non-serious AE of lipoatrophy. The somapacitan label recommends appropriately rotating the injection site to minimize risk of lipoatrophy. No new safety signals were identified.

Pivotal Phase 3 Trial 4467

SGA

During the Main Period of trial 4467, no subjects in the 0.035 mg/kg/day Norditropin group and 2 (5.7%) vs. 4 (5.8%) subjects in the 0.067 mg/kg/day Norditropin arm and the somapacitan arm respectively, reported injection site reactions. During the Extension Period, only 3 (2.1%) subjects reported injection site reactions. The injection site reactions included injection site bruising, injection site erythema, injection site hematoma, injection site hemorrhage, and injection site pain.

NS

An equal number of subjects, 4 (14.3%) and 4 (8.2%) subjects in the Norditropin and somapacitan groups, respectively, reported injection site reactions during the Main Period of the pivotal phase 3 trial. The imbalance between the proportions of subjects reporting these AEs may be due to uneven randomization. During the Extension Period, 4 (5.3%) subjects reported injection site reactions. These reactions included injection site bruising, injection site erythema, injection site hematoma, injection site hemorrhage, and injection site induration.

ISS

During the Main Period of trial 4467, a slightly higher number of subjects treated with somapacitan (6 [10.2%] subjects) compared to those treated with Norditropin (2 [7.1%] subjects), reported injection site reactions. The imbalance between the proportions of subjects reporting these AEs may be due to uneven randomization. During the Extension Period, 2 (2.4%) subjects reported injection site reactions. These AEs included application site pain, application site reaction, injection site bruising, injection site hematoma, injection site hemorrhage, injection site pain, injection site pruritus, and injection site urticaria.

Dose Finding Phase 2 Trial 4245

During the Extension Periods, when all subjects transitioned to 0.24 mg/kg/week somapacitan, 2 (3.2%) subjects reported injection site reactions, with AEs of injection site pain and injection site reaction. As discussed in Section 8.3.6, Adverse Events Leading to Dose Reduction/Temporary Interruption, Dose Finding Phase 2, Trial 4245, one AE of injection site reaction recovered after the dose of somapacitan was reduced.

Phase 3 Trial 4469

Throughout the phase 3 trial 4469, one treatment non-naïve subject in the NS population reported injection site reaction. Additionally, 1 (14.3%) treatment non-naïve subject with NS reported an AE of lipoatrophy that did not require changes or interruption of somapacitan dosing.

Fluid Retention/Edema

Growth hormone therapy has been associated with an increased risk of fluid retention, which listed in the Warnings and Precautions section of all hGH labels and analogs, including somapacitan. Thus, the safety data were analyzed for evidence of edema or fluid retention.

Review of AEs related to fluid retention/edema in the clinical development program revealed that few subjects reported related AEs.

The only subject across the three clinical trials who reported an AE related to fluid retention was 1 subject (1 [2%] subject in the somapacitan arm) in the NS population of the Main Period of the pivotal phase 3 trial 4467. This subject reported a non-serious, non-severe, AE related to edema, with a PT of peripheral leg swelling that did not require reducing, stopping, or interrupting somapacitan therapy.

8.3.13. Safety Analyses by Demographic Subgroups

The Applicant reported safety analyses by demographic subgroups in the pivotal phase 3 trial 4467 to include sex (male or female) and age (< 6 years of age or ≥ 6 years of age). In addition, this reviewer also reviewed safety by race (Asian, Black or African American, American Indian or Alaska Native, White, Multiple, and Not Reported).

Overall, there were no significant safety concerns in the AE profile of somapacitan by age, sex, or race for subjects with SGA, NS, or ISS. Refer to Table 100 through Table 108, in Section 15.4.3.

Specific Safety Studies/Clinical Trials

No specific safety studies/clinical trials were conducted for somapacitan.

8.3.14. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not provide new non-clinical data in these supplements. In the original submission for BLA 761156 for the indication of adult growth hormone deficiency, the nonclinical team determined that the carcinogenic risk for somapacitan is expected to be similar to that of currently marketed hGH products, and, as such, standard 2-year carcinogenicity studies in rodents were not performed. Refer to the review of the original BLA submission, submitted to DARRTS on July 23, 2020.

A low incidence of AEs related to neoplasms was noted during the clinical development program of somapacitan for short stature associated with the SGA, NS, and ISS populations, with no significant differences between treatment groups (see Increased Risk of Neoplasm). All but melanocytic nevi occurred in one subject, each. Malignant changes related to preexisting nevi are already labeled in Section 5 of all hGH products, including somapacitan.

Human Reproduction and Pregnancy

There were no exposures in pregnant or lactating women during the development program.

According to the Division of Pediatrics and Maternal Health (DPMH) review for the original submission of BLA 761156 for the indication of adult growth hormone deficiency (see DARRTS review dated April 21, 2020), data published over several decades regarding the use of short-acting hGH products in pregnant women was sufficient in evaluating the safety of somapacitan in pregnant women. No adverse developmental outcomes have been described in animal reproduction studies for either short- or long-acting hGH products. Therefore, it was recommended that labeling should convey that although there is no pregnancy outcome information with the use of somapacitan in pregnant women, no safety concerns or adverse pregnancy outcomes have been reported with several decades of hGH use in pregnant women.

DPMH also noted in the above mentioned review that although there are no data on the presence of somapacitan in human milk, limited published literature with short-acting hGH indicates that, due to the large molecular weight and long peptide structure of hGH, it is unlikely that there is any significant drug transfer into breast milk or oral absorption by a breast fed infant. However, animal data do show the presence of somapacitan in rat milk at up to 50% plasma levels. Therefore, DPMH recommended that the lactation labeling include information regarding limited published lactation data with short-acting hGH, a statement regarding the presence of somapacitan in animal milk, and the required Pregnancy and Lactation Labeling Resources (PLLR) lactation benefit/risk statement. DPMH considered the available data were sufficient to inform the use of somapacitan during lactation, and, as such, a requirement for a post marketing lactation study for somapacitan was not recommended.

No new information was included in this submission.

No additional labeling edits were required at the time of the current review.

Pediatrics and Assessment of Effects on Growth

BLA 761156 for Sogroya (somapacitan) was approved on April 28, 2023, (BLA 761156/S-005) for the indication of treatment of pediatric patients aged 2.5 years and older with growth failure due to inadequate secretion of endogenous GH.

The proposed indication for the current supplements (BLA 761156/S-012, S-014, and S-015) are:

- S-012: Treatment of pediatric patients with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age.
- S-014: Treatment of pediatric patients with growth failure associated with Noonan syndrome (NS).
- S-015: Treatment of pediatric patients with idiopathic short stature (ISS).

The Applicant conducted a pivotal phase 3 efficacy and safety trial (trial 4467) in subjects 2.5 to 11 years of age of each of the above proposed populations, a phase 2 dose-finding trial (trial 4245) in subjects 2.5 to 11 years of age born SGA, and a phase 3 safety and efficacy trial (trial 4469) in subjects who would otherwise be eligible for trial 4467, but who were older, 10 to 18 years of age. These three trials included long-term safety extension periods to provide additional, long-term data on safety and efficacy, and the clinical development program provided data supporting the safe use and efficacy of somapacitan to improve growth in children 2.5 years of age and older in the SGA, NS, and ISS populations.

The phase 3 trial 4469 included safety data for a limited number of subjects as old as 15 years of age. The mechanism of action of GH is expected to be the same in all children (i.e., GH binds to and activates GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, and as GH and IGF-1 stimulate epiphyseal growth plates and the formation of new bone, resulting in increased linear growth). Thus, it is expected that older children will respond with improved growth after exposure to somapacitan.

However, there are no data for subjects younger than 2.5 years of age for any of these populations. Additionally, for children born SGA, initiation of GH therapy is not recommended before 2 years of age as many of these children have appropriate catch-up growth by this time, and to allow for evaluation of underlying growth-limiting conditions if they do not have appropriate growth by this time. For children with ISS, this is a diagnosis of exclusion and an appropriate duration of time to evaluate for growth failure and evaluation of underlying growth-limiting conditions must also be conducted; it is also unlikely that there will be a major benefit to treatment before the age of 2.5 years. For children with NS, treatment of short stature with GH therapy during early childhood, including < 2.5 years of age, is controversial, in part due to safety concerns such as cardiac comorbidity and increased risk of certain malignancies.

Therefore, data from the clinical development program support approval of somapacitan for:

- S-012: Treatment of pediatric patients 2.5 years of age and older with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age.
- S-014: Treatment of pediatric patients 2.5 years of age and older with growth failure associated with Noonan syndrome (NS).
- S-015: Treatment of pediatric patients 2.5 years of age and older with idiopathic short stature (ISS).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

During the Main Period of the pivotal phase 3 trial, 3 (6.1%) subjects with NS treated with somapacitan reported AEs related to overdose. In the Extension Period of trial 4467, 1 subject in the NS population (a subject who also had an AE of overdose in the Main Period) and 1 subject in the ISS population reported AEs of overdose. Specific information related to the dose level received, the length of exposure to the overdose, or the reason for overdose, was not available.

During the phase 3 trial 4469 in adolescents, 1 (11.1%) treatment non-naïve subject with ISS reported 3 AEs of overdose; in total, this subject received 3 doses of somapacitan at a 25% increase over the prescribed dose, and each of these doses was reported as an AE.

All AEs related to overdose of somapacitan, across the entire clinical development program, were mild and non-serious. In none of these AEs was the prescribed dose of somapacitan interrupted or was the prescribed dose changed, and no other AEs were co-reported with the AEs of overdose.

The proposed label adequately indicates that inappropriate use of somapacitan may result in significant negative health consequences, which is consistent with other hGH products and analogs.

No subject in any clinical trial reported AEs related to abuse or misuse.

The potential for withdrawal and rebound effects are not known GH therapy class effects and have not been studied.

Suspected Transmission of an Infectious Agent via Trial Product

There were no reports of suspected transmission of an infectious agent *via* trial product in the clinical development program.

8.3.15. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Sogroya was approved on August 28, 2020, for the replacement of endogenous GH in adult GHD. On April 28, 2023, Sogroya was approved for the additional indication of treatment of pediatric patients aged 2.5 years and older with growth failure due to inadequate secretion of

endogenous GH. As per periodic adverse experience reports submitted to the Agency to date, no increase in frequency of the labeled AEs, and no new safety signals, have been identified in the postmarketing period.

Expectations on Safety in the Postmarket Setting

Overall, the safety profile of somapacitan in children with short stature associated with being born SGA, or with NS or ISS was well characterized in the clinical program and is expected to be similar to the known safety profile of somapacitan and other hGH and analog formulations. The expected AEs in the postmarketing settings are mechanistically anticipated IGF-1-related pharmacodynamic effects of the drug and the known safety profile of hGH (e.g., blood glucose abnormalities, edema, IH, hypersensitivity, scoliosis, SCFE, tumors, and immunogenicity).

8.4. Integrated Assessment of Safety

The safety profile of somapacitan in pediatric subjects with short stature born SGA, associated with NS, or with ISS was adequately characterized. The risks associated with the use of somapacitan are consistent with risks expected for the hGH class of drugs and their analogs and are monitorable. Adverse reactions associated with the use of hGH products and analogs include the risks of headache, tumorigenesis, IH, SCFE, glucose intolerance and diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism, progression of scoliosis, hypersensitivity, lipoatrophy (related to injection site), fluid retention, and elevations in ALP and phosphate.

Since somapacitan is already approved for the treatment of adult GHD and short stature associated pediatric GHD, its label already includes these risks, as well as mitigation strategies.

Hyperglycemia

Glucose intolerance is a known risk with the use of hGH products and analogs due to IGF-1 related insulin antagonistic effects in the liver and other tissues. This risk is included in Section 5 Warnings and Precautions of all hGH products and analogs, including somapacitan.

Across all 3 clinical trials there were no clinically significant changes from baseline in mean fasting glucose, HbA1c, or insulin values for subjects in the SGA, NS, or ISS populations treated with somapacitan or Norditropin. All changes were small and of unknown clinical significance. The only SAE related to hyperglycemia (new onset type 1 diabetes mellitus) occurred in the phase 2 dose finding trial 4245 in children born SGA. As discussed in Serious Adverse Events , Dose Finding Phase 2, Trial 4245, somapacitan therapy may have precipitated the onset of type 1 diabetes mellitus, but it is unlikely to have been the cause of the new onset diabetes as type 1 diabetes mellitus is an autoimmune disorder.

Increased Risk of Neoplasm

The risk of neoplasms is a known effect of hGH and is included in all hGH labels, including the somapacitan label.

There was a low incidence of neoplasm reported with somapacitan therapy in the clinical development program, with no imbalance seen between treatment groups (i.e., Norditropin and somapacitan) or populations evaluated (i.e., SGA, NS, or ISS).

Hypothyroidism

Worsening or unmasking of hypothyroidism is a well-known AE of therapy with hGH products and analogs, and hypothyroidism is listed in the Warnings and Precautions section of the labels of all approved hGH products and analogs, including somapacitan.

The number of subjects with AEs related to hypothyroidism was small, all events were non-serious and did not require dose adjustment/interruption.

Progression of Scoliosis

Progression of preexisting scoliosis in patients undergoing rapid growth is labeled in the Warnings and Precautions section of all approved hGH products and analogs, including somapacitan, which also instruct providers to monitor patients with a history of scoliosis for disease progression. hGH products have not been shown to increase the occurrence of scoliosis.

No subjects of any population reported AEs of scoliosis during the Main Period of the pivotal phase 3 trial 4467, or in the first 52 weeks of the dose finding phase 2 trial. Very few subjects in the Extension Periods of these trials, or in the phase 3 trial 4469 in adolescents, reported AEs of scoliosis, all of which were non-serious and not severe, and none resulted in changing or interrupting study drug therapy.

Hypersensitivity

Systemic hypersensitivity reactions, including anaphylactic reactions and angioedema have been reported with other hGH therapies. Hypersensitivity reactions are labeled events in hGH and analog labels, including somapacitan.

A small number of subjects reported hypersensitivity reactions in clinical programs. A review of all reactions related to hypersensitivity during the clinical development program revealed that the majority were not serious or severe, and did not require stopping, interrupting, or changing somapacitan dosing. No anaphylactic reactions were reported in any of trials. No subjects were positive for somapacitan antibodies when reporting these AEs.

No changes to the label are recommended at this time.

Immunogenicity

Pharmacotherapy with biological agents can induce the development of ADAs that may decrease efficacy of the drug and/or induce hypersensitivity reactions. The immunogenicity data from the somapacitan clinical development program in the pediatric SGA, NS, and ISS populations did not raise particular concerns.

In the Main Period of the pivotal phase 3 trial 4467 the proportion of subjects in the SGA and ISS populations (14.5% and 11.9%, respectively) treated with somapacitan who generated ADAs was higher compared to 0 and 3.6% of subjects treated with Norditropin in the SGA and ISS populations, respectively, who generated anti-hGH antibodies. In the NS population, the proportion of subjects with antibodies were comparable between the somapacitan and Norditropin groups. The observed imbalances might be due to uneven randomization in treatment groups and overall small sample size. More importantly, the frequency of antidrug antibodies in somapacitan-treated patients was low and within the expected range for hGH products and there was no effect of ADA on safety or efficacy of the drug. The majority of ADA had low titers. There were no neutralizing antibodies in the clinical program.

However, the rate of antibodies observed in pediatric population with SGA, ISS, and NS should be included in Section 12 of the label under Immunogenicity.

Injection Site Reactions and Lipoatrophy

Injection site reactions are expected events with injectable drugs.

The proportion of subjects with AEs related to injection site reactions demonstrated no imbalance in the rate of these reactions across the treatment groups or subject populations, and the majority were not severe, non-serious, and did not require any changes or interruption in somapacitan therapy. Only 2 subjects across all three trials developed lipoatrophy; the events were non-serious.

The risk of injection site reactions and recommendations to rotate the site of the injections to minimize the risk of lipodystrophy is already appropriately included in the Warnings and Precautions section of the somapacitan label.

Fluid Retention and Edema

Edema is a well-known and labeled adverse reaction for all hGH labels and analogs. The risk of fluid retention is already included in the somapacitan label.

During the pediatric clinical development program for the SGA, NS, and ISS populations, only 1 subject reported AEs related to edema. This AE was non-serious and not severe and recovered without changing or interrupting somapacitan dosing and likely does not represent a new safety signal.

Other Adverse Events Related to hGH and Analog Class

No pediatric subjects reported AEs related to SCFE, pancreatitis, adrenal insufficiency, or intracranial hypertension in the SGA, NS, and ISS clinical development programs. These events are already included in the somapacitan label.

Elevations in Alkaline Phosphatase and Phosphate

Growth hormone therapy can lead to elevated phosphate and alkaline phosphatase, especially when such therapy is associated with increased skeletal growth. This risk is included in the Warnings and Precautions section of the labels of hGH products and analogs, including somapacitan.

There was an observed increase in mean alkaline phosphatase and phosphate values of unknown clinical significance in all populations. The changes were comparable between treatment groups (i.e., Norditropin or somapacitan) within populations (i.e., SGA, NS, or ISS). The data on increasing alkaline phosphatase and phosphate from this program did not raise new safety concerns. No changes to the label are required at this time.

IGF-1

The goal of treatment with hGH products and analogs in children of the SGA, NS, and ISS populations is the improvement of growth and final adult height while avoiding adverse reactions. In the Main Period of the pivotal phase 3 trial, a higher percentage of subjects with NS treated with somapacitan (10.2%), compared to subjects treated with Norditropin (0), had IGF-1 > 2 SDS (pre-specified level) on at least two consecutive visits, while no subject with NS had IGF-1 > 3 SDS on at least two consecutive visits. In the SGA and ISS populations of this trial, the proportion of subjects treated with somapacitan who had IGF-1 > 2 or 3 SDS on at least two consecutive visits was either comparable to, or lower than, the proportion of subjects treated with Norditropin who had IGF-1 > 2 or 3 SDS on at least two consecutive visits. Majority of subjects had decrease in IGF-1 on the subsequent visits without dose reduction. Only one subject in the pivotal phase 3 trial 4467, in the ISS population, treated with somapacitan had the dose of somapacitan reduced in response to elevated IGF-1 > 3 SDS during the Main Period of trial 4467.

Prolonged exposure to chronically elevated IGF-1 levels is a potential safety concern and may be associated with various AEs, including headache, IH, edema, and tumors. No such safety signals were noted in clinical program. (see Section 8.3.8, IGF-1). Target IGF-1 levels that optimize the balance between height gain and potential risks are not established to date. The Growth Hormone Research society advises that in non-GHD conditions, dosing should be guided on an individual basis based on auxological measurements and IGF-1 is used as a long-

term safety marker during GH treatment.[40,41] During GH treatment of non-GHD conditions, in order to achieve an acceptable growth response, IGF-1 may transiently be above the normal range, however the safety implications are unknown and the potential risk can be mitigated by monitoring for AEs and dose adjustments.

Common AEs

During the Main Period of the pivotal phase 3 trial 4467, the most commonly reported AEs (≥ 10% of subjects in any treatment arm of the SGA, NS, or ISS populations) were:

- Cough
  - SGA: 16.2%, 8.6%, and 15.9% in the low and high dose Norditropin, and somapacitan arms, respectively
  - NS: 14.3% in both the Norditropin and somapacitan arms
  - ISS: 10.7% and 5.1% in the Norditropin and somapacitan arms, respectively
- Respiratory tract infection
  - SGA: 29.7%, 20%, and 26.1% in the low and high dose Norditropin, and somapacitan arms, respectively
  - NS: 28.6% and 42.9%, in the Norditropin and somapacitan arms, respectively
  - ISS: 28.6% and 30.5%, in the Norditropin and somapacitan arms, respectively
- Diarrhea
  - SGA: 8.1%, 5.7%, and 10.1% in the low and high dose Norditropin, and somapacitan arms, respectively
  - NS: 14.3% and 22.4% in the Norditropin and somapacitan arms, respectively
  - ISS: 25% and 10.2% in the Norditropin and somapacitan arms, respectively
- Pyrexia:
  - SGA: 16.2%, 17.1%, and 18.8% in the low and high dose Norditropin, and somapacitan arms, respectively
  - NS: 25% and 10.2% in the Norditropin and somapacitan arms, respectively

[40] Johannsson G, et al. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. *Endocr Connect*. 2018 Mar;7(3):R126-R134. doi: 10.1530/EC-18-0047. Epub 2018 Feb 26. PMID: 29483159; PMCID: PMC5868631.

[41] Collett-Solberg PF, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. *Horm Res Paediatr*. 2019;92(1):1-14. doi: 10.1159/000502231. Epub 2019 Sep 12. PMID: 31514194; PMCID: PMC6979443.

- Vomiting
  - SGA: 10.8%, 11.4%, and 10.1% in the low and high dose Norditropin, and somapacitan arms, respectively
  - NS: 10.7% and 12.2% in the Norditropin and somapacitan arms, respectively
  - ISS: 10.7% and 5.1% in the Norditropin and somapacitan arms, respectively
- Nasopharyngitis
  - SGA: 37.8%, 28.6%, and 26.1% in the low and high dose Norditropin, and somapacitan arms, respectively
  - NS: 25% and 28.6% in the Norditropin and somapacitan arms, respectively
  - ISS: 21.4% and 22%, in the Norditropin and somapacitan arms, respectively
- Ear infection
  - SGA: 16.2%, 17.1%, and 13% in the low and high dose Norditropin, and somapacitan arms, respectively
  - NS: 14.3% and 16.3% in the Norditropin and somapacitan arms, respectively
  - ISS: 7.1% and 11.9% in the Norditropin and somapacitan arms, respectively
- Bronchitis
  - SGA: 10.8%, 11.4%, and 7.2% in the low and high dose Norditropin, and somapacitan arms, respectively
- Headache
  - NS: 7.1% and 10.2% in the Norditropin and somapacitan arms, respectively
  - ISS: 10.7% and 10.2% in the Norditropin and somapacitan arms, respectively
- Injection site reaction
  - NS: 14.3% and 8.2% in the Norditropin and somapacitan arms, respectively
  - ISS: 7.1% and 10.2% in the Norditropin and somapacitan arms, respectively
- Abdominal pain
  - NS: 10.7% and 2% in the Norditropin and somapacitan arms, respectively
- Wound
  - NS: 10.7% and 0 in the Norditropin and somapacitan arms, respectively

The pattern of these AEs was similar to AEs associated with the use of somapacitan in children with short stature due to GHD. Some of these AEs occurred more frequently in the somapacitan group compared to Norditropin group(s) (RD ≥ 1%) within the SGA, NS, or ISS populations during the Main Period of trial 4467: cough, respiratory tract infection, diarrhea, pyrexia, nasopharyngitis, headache, ear infection, vomiting, and injection site reactions. The further analyses of these AEs revealed that the vast majority were non-serious, not severe, and recovered without interrupting, stopping, or changing somapacitan dosing; an uneven randomization may have contributed to these imbalances in reporting. Moreover, all these

events are not uncommon in general pediatric population. No new safety signals were identified with a longer duration of treatment with 0.24 mg/kg/week somapacitan (up to 279, 109, and 116 weeks in the pediatric SGA, NS, and ISS populations, respectively). Overall, these data do not represent new safety signals.

To avoid artificially focusing on adverse events attributed to somapacitan and minimizing adverse events attributed to the active control, the adverse events reported in the 52-week main period of the phase 3 trial experienced by ≥ 10% of subjects in either the somapacitan or Norditropin group should be included in the label.

Serious Adverse Events

Two subjects in the Main Period of the pivotal phase 3 trial 4467 reported SAEs where a causal association between treatment with somapacitan and the events could not be ruled out: 1 (1.4%) subject in the SGA population and 1 (2%) subject in the NS population treated with somapacitan both reported SAEs of adenoidal and tonsillar hypertrophy that resulted in surgical procedures to resolve the events. In addition, 3 additional subjects in either the Extension Period of trial 4467 or in the other trials also reported the SAEs of tonsillar/adenoidal hypertrophy. While adenoidal and tonsillar hypertrophy are not uncommon findings in pediatric patients, and there was evidence of preexisting complications of these events in some of these of subjects prior to starting therapy, given worsening of these complications, the need for surgical procedures within the relatively short period of treatment, and the known tissue growth-stimulating effect of IGF-1 (adenoidal/tonsillar hypertrophy is already a labeled AE for recombinant human IGF-1; Increlex), this reviewer cannot rule out a possible causal association between somapacitan use and these events.

To provide awareness to providers, these relevant events will be reported in the somapacitan label.

Children Younger Than 2.5 Years of Age

There are no safety data on the use of somapacitan for subjects younger than 2.5 years of age for any of these populations. There is no predictive model that may evaluate PK/PD profile of somapacitan in subjects <2.5 years of age. It is therefore unknown if subjects < 2.5 years of age have a similar, greater, or lower IGF-1 response to somapacitan compared to subjects ≥ 2.5 years of age. Additionally, the duration and reversibility of potential AEs related to IGF-1 also remains unknown in this younger population. Further, children born SGA and with ISS, are not diagnosed with short stature associated with these conditions before age 2. For children with NS, treatment of short stature with GH therapy during early childhood, including < 2.5 years of age, is controversial, in part due to safety concerns such as cardiac comorbidity and increased risk of certain malignancies. Because of these concerns, somapacitan should not be indicated for patients born SGA, or with NS or ISS, who are < 2.5 years of age.

Conclusions

The safety profile of somapacitan in children ≥ 2.5 years of age with ISS, or short stature associated with NS or with being born SGA, is acceptable given its potential benefits of treatment in these pediatric populations.

The safety profile of somapacitan in children ≥ 2.5 years of age with ISS, or short stature associated with NS or with being born SGA, was well characterized in the clinical development program, and overall consistent with approved use of somapacitan and with the hGH and analog class. The AEs observed are monitorable and can be identified and managed by health care providers, and their risk can be adequately addressed through the label.

8.5. Statistical Issues

There were no major statistical issues identified during this review.

8.6. Conclusions and Recommendations

The primary source of evidence and safety of somapacitan for the each of the proposed indications was provided from the adequate and well controlled sub-trials included in the basket phase 3 trial 4467 conducted in each of the intended populations, i.e., in subjects with short stature associated with the other non-GHD condition (ISS, born SGA, or NS). Trial 4467 was conducted in pediatric subjects with proportional short stature associated with non-GHD conditions. Each sub-trial was designed to demonstrate that somapacitan was non-inferior to AHV after 52 weeks of therapy with Norditropin independently in each subpopulation of subjects with short stature associated with non-GHD syndromes (i.e., born SGA, ISS, and NS). Each sub-trial included an active comparator group(s), i.e., Norditropin. The primary endpoint in all sub-trials were the same, i.e., AHV at the end of 52 weeks of treatment, and was conducted in subjects with proportional short stature associated with a non-GHD condition. Each sub-trial included prespecified independent primary efficacy analyses to establish the efficacy of the drug in each of the proposed indications. Providing substantial evidence of effectiveness from the adequate and well-controlled sub-trials in each of these proposed indications of proportional short stature associated with a non-GHD condition is acceptable. While each condition results in short stature as a result of different etiologies, there is a strong mechanistic understanding of how hGH exerts its effect in children with short stature born SGA, associated with NS, or with ISS. Exogenous hGH therapy improve growth by acting along a similar mechanism of action in all three conditions. The structure-function relationship of endogenous GH is well-understood. The wide variety of GH biological effects is mediated by one mechanism of action, i.e., GH binding to and activating GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, which stimulates the proliferation of chondrocytes and results in bone growth. No alternative receptors mediating GH activity have been identified. It has been already demonstrated that treatment with approved hGH products improve linear growth in all three conditions (as per Section 2). Clinical trials evaluating the use hGH to improve growth in these indications use

similar efficacy endpoints (i.e., AHV and/or height SDS at 52 or 104 weeks; as per Section 7.2), The active moiety of somapacitan has the same primary amino acid sequence as native hGH and thus is expected to have the same action at the target receptor as native hGH.

The phase 3 trial met the prespecified endpoints for each of the three populations (i.e., SGA, NS, and ISS):

- The effect of 0.24 mg/kg/week somapacitan on AHV (11 cm/year) was non-inferior to the effect of 0.035 mg/kg/day Norditropin (9.4 cm/year) and 0.067 mg/kg/day Norditropin (11.1 cm/year) after 52 weeks of treatment in pediatric subjects with short stature born SGA.
  - Estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.035 and 0.067 mg/kg/day Norditropin was 1.6 cm/year (95% CI 0.91, 2.23; p-value < 0.001) and -0.1 cm/year (95% CI -0.75, 0.6; p-value = 0.823), respectively and the lower limits of the 95% CI (0.91 and -0.75, respectively), were above the prespecified non-inferiority margin of -1.6 cm/year.
- The effect of 0.24 mg/kg/week somapacitan on AHV (10.4 cm/year) was non-inferior to the effect of 0.05 mg/kg/day Norditropin (9.4 cm/year) after 52 weeks of treatment in pediatric subjects with growth failure associated with NS.
  - Estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.05 mg/kg/day Norditropin was 1.2 cm/year (95% CI 0.32, 2.03; p-value = 0.0071), and the lower limits of the 95% CI (0.32), were above the prespecified non-inferiority margin of -1.6 cm/year.
- The effect of 0.24 mg/kg/week somapacitan on AHV (10.2 cm/year) was non-inferior to the effect of 0.05 mg/kg/day Norditropin (10.5 cm/year) after 52 weeks of treatment in pediatric subjects with ISS.
  - Estimated treatment difference in mean AHV at 52 weeks between somapacitan and 0.05 mg/kg/day Norditropin was -0.3 cm/year (95% CI -1, 0.42; p-value = 0.4107), and the lower limits of the 95% CI (-1), were above the prespecified non-inferiority margin of -1.6 cm/year.

However, somapacitan-induced AHV in subjects with ISS and NS was not compared to the maximum approved dose of Norditropin; doses of Norditropin for the ISS and NS populations in the trial were 0.05 mg/kg/day, and the maximum approved doses of Norditropin are 0.066 mg/kg/day for NS and 0.067 mg/kg/day for ISS. Therefore, language should be added to Section 14 of the label to clarify that the comparisons of somapacitan to Norditropin in the ISS and NS population were to less than maximum approved dosing of the comparator in order to inform the prescriber when selecting the product for the treatment.

The results of the secondary analyses of the pivotal phase 3 trial 4467 were supportive. Treatment with somapacitan improved the other growth parameters (AHV SDS and height SDS after 52 weeks of treatment) and these changes were either increased in the somapacitan group compared to the Norditropin group(s) or comparable between treatment groups. Over 52 weeks of treatment, the change in mean height SDS from baseline was 1) in

the SGA population: 1.17 in the somapacitan group and 0.85 and 1.22 in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively; 2) in the NS population: 1.07 in the somapacitan group and 0.75 in the 0.05 mg/kg/day Norditropin group; and 3) in the ISS population: 0.99 in the somapacitan group and 1.09 in the 0.05 mg/kg/day Norditropin group. Mean change in AHV SDS over 52 weeks of treatment for children 1) in the SGA population: 7.06 in the somapacitan group and 5.23 and 7.16 in the 0.035 and 0.067 mg/kg/day Norditropin groups, respectively; 2) in the NS population: 6.3 in the somapacitan group and 5.24 in the 0.05 mg/kg/day Norditropin group; and 3) in the ISS population: 5.98 in the somapacitan group and 6.51 in the 0.05 mg/kg/day Norditropin group. Finally, mean changes in bone age were small and did not demonstrate rapid advancement of bone age with treatment. Height SDS is widely used in clinical practice to evaluate the appropriate growth of children at various stages of development and change in height SDS is traditionally accepted and used as a supportive growth endpoint in trials evaluating the effect of hGH on growth in pediatric patients with short stature. Therefore, change in height SDS should be included in the label, but without statistical claims, since there was no hierarchical testing, and no adjustment for multiplicity was performed for any of secondary endpoints.

The open label extension period of the pivotal phase 3 trial 4467, the phase 2 trial 4245 in subjects born SGA, and the phase 3 trial 4469 in children older than 10 years of age provided additional evidence of effectiveness. The results demonstrated long-term improvement in growth parameters in children 2.5 years of age and older with short stature born SGA and no catch-up growth by 2 years of age, with growth failure associated with NS, or with ISS, and open epiphyses. In the extension period of the pivotal phase 3 trial, data with continued treatment with somapacitan showed continued growth in all populations, though AHV decreased with continued treatment. This trend is expected and a similar trend is observed during therapy with approved hGH products: in children exposed to only 0.24 mg/kg/week somapacitan 1) in the SGA population, the observed mean AHV was 8.8 and 8.7 cm/year after 78 and 104 weeks, respectively; 2) in the NS population, the observed mean AHV was 8.4 and 7.4 cm/year after 78 and 104 weeks, respectively; and 3) in the ISS population, the observed mean AHV was 8.6 and 7.6 cm/year after 78 and 104 weeks, respectively.

The safety of somapacitan was evaluated in 212 pediatric subjects with short stature born SGA, 88 pediatric subjects with short stature associated with NS, and 97 pediatric subjects with ISS, who received at least 1 dose of 0.24 mg/kg/week somapacitan in either the pivotal phase 3 trial 4467, the dose finding phase 2 trial 4245, or the phase 3 trial in adolescents, trial 4469. A total of 93, 62, and 70 pediatric subjects in the SGA, NS, and ISS populations, respectively, were assigned 0.24 mg/kg/week somapacitan from the onset of treatment; all other subjects initially received either Norditropin or lower doses of somapacitan and were switched to 0.24 mg/kg/week somapacitan after at least 52 weeks of treatment. As of the database cutoff of November 24, 2024, for the original applications, out of the 212 pediatric subjects in the SGA population, a total of 132 (62.3%) subjects were exposed to 0.24 mg/kg/week somapacitan for ≥ 1 year, 46 (21.7%) subjects for ≥ 2 years, 12 (5.7%) subjects for ≥ 3 years, 12 (5.7%) subjects for ≥ 4 years, and 1 (0.5%) subject for ≥ 5 years; out of 88 pediatric subjects in the NS population, a total of 52 (59.1%) subjects were exposed to 0.24

mg/kg/week somapacitan for ≥ 1 year and 2 (2.3%) subjects for ≥ 2 years; and out of 97 pediatric subjects in the ISS population, a total of 68 (70.1%) subjects were exposed to 0.24 mg/kg/week somapacitan for ≥ 1 year and 7 (7.1%) subjects for ≥ 2 years.

Overall, the safety profile of somapacitan in pediatric subjects ≥ 2.5 years of age with short stature born SGA, short stature associated with NS, and with ISS was well characterized. The risks associated with the use of somapacitan are consistent with the risks expected for the hGH and analog class of drugs and with risk of somapacitan use for the approved indications that already labeled (GHD in adult and pediatric populations). These adverse reactions include the risk of hyperglycemia, development of new tumors, intracranial hypertension, SCFE, pancreatitis, adrenal insufficiency, hypothyroidism, progression of preexisting scoliosis, severe hypersensitivity, injection site reactions, edema, and elevations in alkaline phosphatase and phosphate.

There were no deaths in the clinical program, and only 3 subjects in the clinical development program permanently discontinued somapacitan treatment due to AEs. Two subjects in the Main Period of the pivotal phase 3 trial 4467 reported SAEs where a causal association between treatment with somapacitan and the events could not be ruled out, 2 subjects (1 each in the SGA and ISS populations) reported SAEs of adenoidal and tonsillar hypertrophy that resulted in surgical procedures to resolve the events. While adenoidal and tonsillar hypertrophy are not uncommon findings in pediatric patients, there were no imbalance in the frequency of the event between somapacitan and Norditropin groups, and there was evidence of preexisting complications of these events for both subjects prior to starting therapy in this trial, given worsening of these complications and the need for surgical procedures within the 52-week treatment Main Period of the trial, this reviewer cannot rule out a possible causal association between somapacitan use and these events. In addition, 3 additional subjects in the somapacitan clinical program also reported AE of adenoid/tonsillar hypertrophy, and there is a known tissue growth-stimulating effect of IGF-1. Therefore, to provide awareness to providers, these events will be reported in the somapacitan label. However, due to the uncertainties and multiple confounding factors, the event will be included in Section 6. This risk will be also monitored through routine pharmacovigilance.

The most commonly reported AEs by subjects in the Main Period of the pivotal phase 3 trial across the SGA, NS, and ISS populations (≥ 10% of subjects in any treatment arm) included cough, respiratory tract infection, diarrhea, pyrexia, vomiting, nasopharyngitis, ear infection, bronchitis, headache, injection site reaction, abdominal pain, and wound). These events are also not uncommon in the general pediatric population. These most commonly reported AEs will be reported in Section 6 of the label. Of the most commonly reported AEs, those that occurred more frequently in the somapacitan group compared to either Norditropin group (RD ≥ 1%) within the SGA, NS, or ISS populations during the Main Period of trial 4467 included AEs related to cough, respiratory tract infection, diarrhea, pyrexia, nasopharyngitis, headache, ear infection, vomiting, and injection site reactions; and analyses of these AEs revealed that the vast majority were non-serious, not severe, and recovered without interrupting, stopping, or changing somapacitan dosing, and further, uneven randomization may have contributed to these imbalances.

Other adverse events that are hGH class adverse reactions were observed with low frequency in subjects treated with somapacitan. In the pivotal phase 3 trial 4467, the following AEs were observed in subjects in the SGA, NS, and ISS populations: hyperglycemia (0%, 4.1%, and 0%, respectively), headache (5.8%, 10.2%, and 10.2%, respectively), fatigue (1.4%, 2%, and 0%, respectively), hypothyroidism (1.4%, 2%, and 1.7%, respectively), injection site reactions (5.8%, 8.2%, and 10.2%, respectively), edema (0, 2%, and 0%, respectively), and hyperphosphatemia (1.4%, 4.1%, and 0%, respectively). No SCFE, adrenal insufficiency, pancreatitis were reported in subjects treated with somapacitan.

Chronically elevated IGF-1 levels (i.e., IGF-1 > 2 or > 3 SDS) are associated with a potential risk for various AEs, including headache, intracranial hypertension, edema, and tumors. In the pivotal phase 3 trial 4467, a higher percentage of subjects with NS treated with somapacitan (10.2%), compared to subjects treated with Norditropin (0), had IGF-1 > 2 SDS on at least two consecutive visits, while no subject with NS had IGF-1 > 3 SDS on at least two consecutive visits. In the SGA and ISS populations of this trial, the proportion of subjects treated with somapacitan who had IGF-1 > 2 (20.3% and 16.9%, respectively) or 3 SDS (8.7% and 6.8%, respectively) on at least two consecutive visits was either comparable to, or lower than, the proportion of subjects treated with Norditropin who had IGF-1 > 2 (SGA: 24.3% and 48.6%; ISS: 21.4%) or 3 SDS (SGA: 8.1% and 25.7%; ISS: 3.6%) on at least two consecutive visits. IGF-1 levels > 3 SDS on more than two consecutive visits decreased in the majority of subjects without dose reduction. Only one subject, in the ISS population, had the dose of somapacitan reduced in response to elevated IGF-1 >3 SDS. None of the elevated IGF-1 levels were associated with AEs. Target IGF-1 levels that optimize the balance between height gain and potential risks are not established to date, and the lack of a direct correlation between IGF-1 levels and clinical outcome limits the use of IGF-1 to guide dosing. The risk of elevated IGF-1 can be mitigated by monitoring for AEs and dose adjustments. In pediatric patients treated with hGH for ISS or short stature associated with NS or SGA at birth, goal IGF-1 levels are typically below 2 or 3 SDS. During 52 weeks of treatment with somapacitan and Norditropin, mean IGF-1 levels remained within these ranges. The mean 52-week IGF-1 SDS for children 1) born SGA was 1.9, 1.1, and 2 in the somapacitan and 0.035 and 0.067 mg/kg/day Norditropin groups, respectively; 2) with NS was 1 and 0.2 in the somapacitan and 0.05 mg/kg/day Norditropin groups respectively; and 3) with ISS was 1.6 and 1.3 in the somapacitan and 0.05 mg/kg/day Norditropin groups respectively.

The immunogenicity data did not raise particular concerns. The reporting of positive ADA in subjects treated with somapacitan in the pivotal phase 3 trial in the SGA, NS, and ISS populations was 14.5%, 4.1%, and 11.9%, respectively. In all subjects who generated ADA following initiation of somapacitan therapy in the pivotal phase 3 trial, there were no neutralizing antibodies, and the presence of ADAs did not have an impact on safety or efficacy of somapacitan.

Analysis of safety data from the ongoing Extension Period of the pivotal phase 3 trial, from the dose finding phase 2 trial 4245 in children with short stature born SGA and from the phase 3 trial 4469 in adolescents was generally consistent with the safety data from the Main Period of the pivotal phase 3 trial 4467. No new safety signals were identified with a longer

duration of therapy (at least 4 years in the phase 2 trial) or in the limited number of subjects otherwise eligible for trial 4467, but older than 10 years of age for whom data were available.

The Applicant proposes this drug for all pediatric subjects with short stature born SGA and no catch-up growth by 2 years of age, and for pediatric subjects of all ages with growth failure associated with NS or with ISS, and open epiphyses. However, no subjects < 2.5 years of age were included. Further, for children born SGA, initiation of GH therapy is not recommended before 2 years of age as many of these children have appropriate catch-up growth by this time, and to allow for evaluation of underlying growth-limiting conditions if they do not have appropriate growth by this time. For children with ISS, this is a diagnosis of exclusion and an appropriate duration of time to evaluate for growth failure and evaluation of underlying growth-limiting conditions must also be conducted; it is also unlikely that there will be a major benefit to treatment before the age of 2.5 years. For children with NS, treatment of short stature with GH therapy during early childhood, including < 2.5 years of age, is controversial, in part due to safety concerns such as cardiac comorbidity and increased risk of certain malignancies. In addition, it is unknown if subjects < 2.5 years of age have a similar, greater, or lower IGF-1 response to somapacitan compared to subjects ≥ 2.5 years of age. Further, if subjects < 2.5 years of age were to have persistently elevated IGF-1 after treatment with somapacitan, given its longer half-life relative to currently available, daily hGH therapies, any AEs observed may not be as easily reversible upon discontinuation of the drug. Lastly, the magnitude of somapacitan-induced growth in this young population also unknown. Because of these concerns, somapacitan should not be indicated for patients born SGA, or with NS or ISS, who are < 2.5 years of age.

While the pivotal phase 3 trial 4467 did not include subjects older than 11 years of age, the phase 3 trial 4469 did include data safety and efficacy data from a limited number of children as old as 15 years of age. Given that the mechanism of action of GH is expected to be the same in all children (i.e., GH binds to and activates GH receptors with subsequent transcription of genes encoding a variety of proteins, including IGF-1, and as GH and IGF-1 stimulate epiphyseal growth plates and the formation of new bone, resulting in increased linear growth), it is expected that these older subjects will respond with improved growth after exposure to somapacitan.

In conclusion, based on the evidence, the benefits outweigh the risks for somapacitan therapy in pediatric patients ≥ 2.5 years of age with 1) short stature born SGA and with no catch-up growth by 2 years of age; 2) growth failure associated with NS; and 3) ISS. The effect of somapacitan on AHV after 52 weeks of therapy is 1) non-inferior and superior to low dose Norditropin, and non-inferior to the maximum approved dosing of Norditropin, for the SGA indication; 2) non-inferior and superior to less than maximum approved dosing of Norditropin for the NS indication; and 3) non-inferior to less than maximum approved dosing of Norditropin for the ISS indication, and it is expected that this benefit will translate into improved final adult height. The safety profile of somapacitan is acceptable in view of the potential benefit. The AEs observed are predictable, can be adequately identified and managed by health care providers, many are well-known class effects of therapy with

approved hGH products and analogs, and will be adequately described in labeling. Therefore, the review team recommends APPROVAL for somapacitan for the following indications:

- Treatment of pediatric patients 2.5 years of age and older with short stature born small for gestational age (SGA) and with no catch-up growth by 2 years of age.
- Treatment of pediatric patients 2.5 years of age and older with growth failure associated with Noonan syndrome (NS).
- Treatment of pediatric patients 2.5 years of age and older with idiopathic short stature (ISS).

9 Advisory Committee Meeting and Other External Consultations

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

10 Pediatrics

On April 28, 2023, Sogroya (somapacitan; BLA 761156/S-005) was approved for the indication of treatment of pediatric patients aged 2.5 years and older with growth failure due to inadequate secretion of endogenous GH. The proposed indication for somapacitan is treatment of pediatric patients with 1) short stature born SGA and with no catch-up growth by 2 years of age; 2) growth failure associated with NS; and 3) ISS. A pivotal phase 3 efficacy and safety trial was conducted in patients 2.5 to 11 years of age in each of the proposed populations. A phase 2 dose finding trial was conducted in subjects aged 2.5 to 11 years of age in subjects with short stature born SGA. A phase 3 trial was conducted in subjects of each of the proposed populations who would otherwise be eligible for the pivotal phase 3 trial but were older than 11 years of age, and included subjects as old as 15 years of age.

11 Labeling Recommendations

11.1. Prescription Information

The Prescription Information (PI) review includes a summary of the rationale for major changes incorporated into the finalized PI as compared to the Applicant's draft submitted on May 6, 2025 (Table 48). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare provider.

Table 48. Key Labeling Changes and Considerations

Full PI Sections	Rationale for Major Changes to Finalized PI Compared to Applicant's Draft PI
1 INDICATIONS AND USAGE	For the pediatric population, redundant text (e.g., (b) (4) was removed after each new indication to improve readability. For the adult population, (b) (4) was removed and sentence restructured to start with the drug name (e.g., SOGROYA is indicated...) and to align with the pediatric indication and usage statement.
2 DOSAGE AND ADMINISTRATION	2.3 Recommended Dosage and Monitoring for Pediatric Patients To reduce redundancy, the recommended dosage for SGA, NS, and ISS were combined because they are the same for the three new indications.
6 ADVERSE REACTIONS	6.1 Clinical Trials Experience Per 21 CFR210.57(c)(7), the Adverse Reactions/ Clinical Trials experience section of labeling must list the adverse reactions identified in the clinical trials that occurred at or above a specified rate. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. Additionally, description of the overall clinical trial database(s) must precede the adverse reactions in order to interpret the adverse reactions. Created Table 3 Adverse Reactions Occurring ≥10% in SOGROYA or Somatropin-Treated Pediatric Patients with SGA at Week 52 to summarize the most common adverse reactions in the SGA population. Created Table 4 Adverse Reactions Occurring ≥10% in SOGROYA or Somatropin-Treated Pediatric Patients with NS at Week 52 to summarize the most common adverse reactions in the NS population. Created Table 5 Adverse Reactions Occurring ≥10% in SOGROYA or Somatropin-Treated Pediatric Patients with ISS at Week 52 to summarize the most common adverse reactions in the ISS population. Added adenoidal and tonsillar hypertrophy adverse reaction in text after common adverse reactions tables.
8 USE IN SPECIFIC POPULATIONS (e.g. Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.4 Pediatric Use The pediatric use subsection requires a regulatory statement, commonly referred to as the pediatric use statement, if there is evidence that supports safety and effectiveness of a drug for an indication in pediatric patients. The SGA, NS, and ISS indications were grouped with existing GHD indication for a concise summary of the studies in the approved population. The limitation of use statement "The safety and effectiveness of SOGROYA for the treatment of growth failure...have not been established in pediatric patients less than 2.5 years of age" was updated to include the SGA, NS, and ISS indications.
12 CLINICAL PHARMACOLOGY	12.2 Pharmacodynamics The pharmacodynamic subsection must include a description of any biochemical or physiologic effects of the drug related to the drug's clinical effect. IGF-1 level is considered a PD marker for growth. For each patient population, change in IGF-1 SDS levels was reported. (b) (4) were deleted. 12.3 Pharmacokinetics

Full PI Sections	Rationale for Major Changes to Finalized PI Compared to Applicant's Draft PI
	The recommended dosage of SOGROYA for patients with SGA, NS, and ISS is 0.24 mg/kg/week. Tmax, time to SS, and terminal half-life are reported as a range, rather than repeating the nearly identical values. 12.6 Immunogenicity For the SGA population (b) (4)
14 CLINICAL STUDIES	14.2 Pediatric Patients Born Small for Gestational Age, 14.3 Pediatric Patients with Noonan Syndrome, and 14.4 Pediatric Patients with Idiopathic Short Stature Added baseline characteristics (e.g., age, race, sex, baseline height SDS) of the patient population. Added text stating somatropin dose evaluated in the trial was not the maximum approved dose. Table with primary efficacy endpoint of annualized height velocity was retained. (b) (4) was deleted; mean increase in height SDS was retained in text.

Source: compiled by reviewer

12 Risk Evaluation and Mitigation Strategies (REMS)

No safety issues rising to the level of requiring a risk evaluation and mitigation strategy was identified in the application. Safety issues will be handled through appropriate labeling.

13 Postmarketing Requirements and Commitment

None

14 Deputy Division Director (Clinical) Comments

No additional comments.

15 Appendices

15.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): Trial NN8640-4467

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 537		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 9		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Trial NN8640-4245

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 220		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Trial NN8640-4469

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 48		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.2. Nonclinical Pharmacology/Toxicology

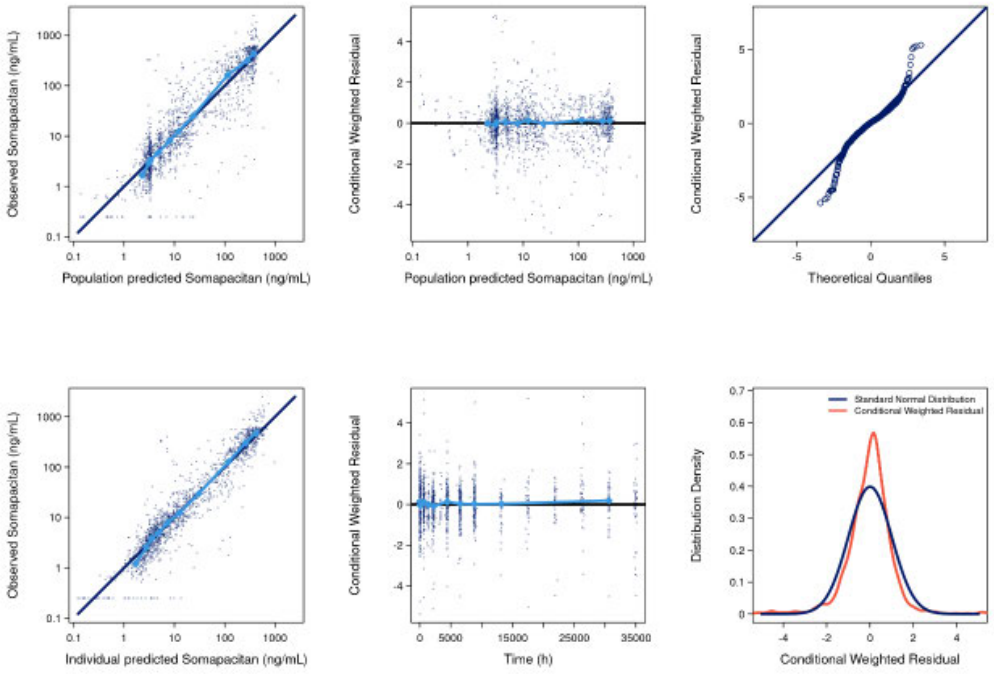
None.

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Pharmacometrics Review

The Applicant's population PK and PD analysis was reviewed and found to be acceptable for descriptive labeling of both somapacitan PK and IGF-I pharmacodynamics. The final model was found to capture the central tendency of the data as shown in Figure 19 through Figure 24. Covariate effects on both somapacitan PK and IGF-I pharmacodynamics are shown in Figure 25 through Figure 30 for each of the populations (SGA, ISS, and NS). While these effects were quantified in the population PK/PD assessment, the review team determined the extent of these covariate effects (other than body weight) did not warrant dose adjustment. In the case of body weight, the proposed dose is weight based.

Figure 19. Goodness-of-Fit Plots for Somapacitan PK for the Final Population PK/PD Model

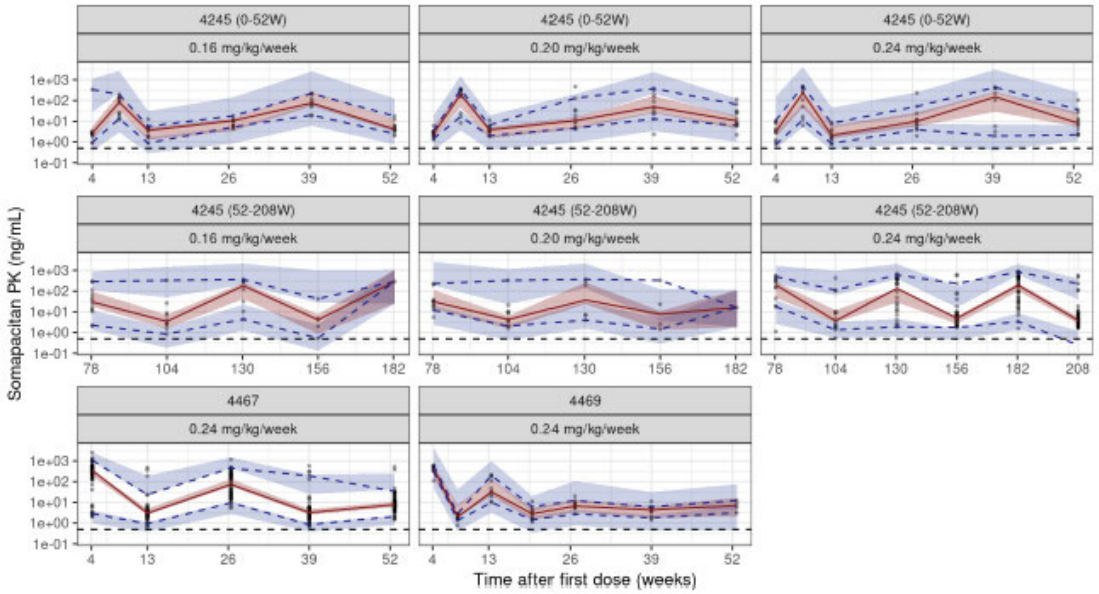


Notes: Plots show standard goodness of fit plots for the base PK/PD model (A) and final PK/PD model (B). Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Light blue lines are median values for quantiles of concentration or time.

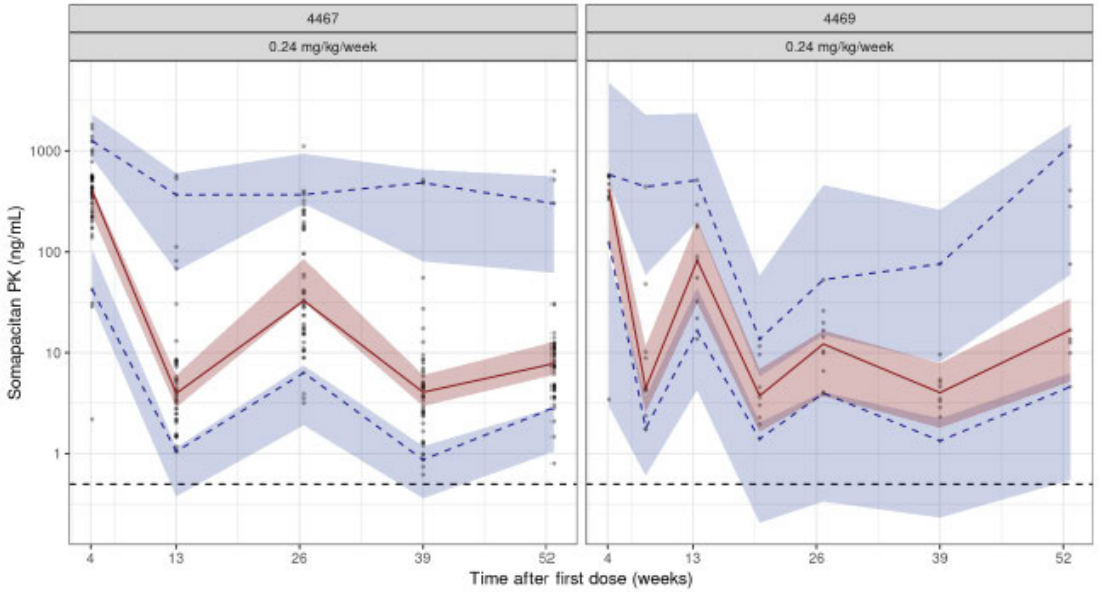
Source: Applicant's Population PK/PD Report, Figure 13-35b

Figure 20. Visual Predictive Check of Somapacitan PK From Study 4245, 4467 and 4469 for the Final PK/PD Model for SGA (Panel A) and ISS (Panel B)

A



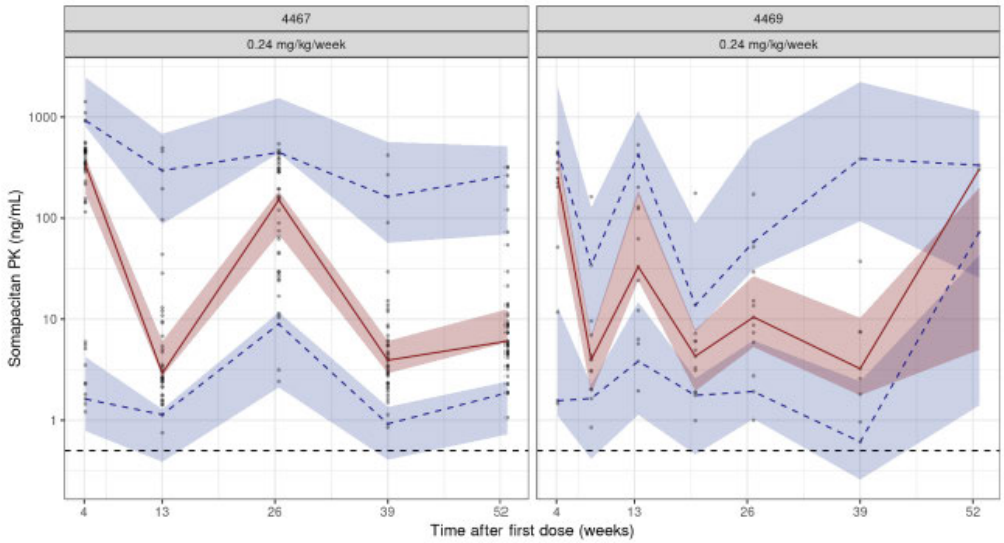
B



Notes: Data are medians with 5th and 95th percentiles (red and blue lines) of somapacitan concentrations after first dose. Shaded areas are 95% CIs around the medians and 5th and 95th percentiles based on 1000 simulations with the final PK/PD model.

Source: Applicant's Population PK/PD Report, Figure 13-40

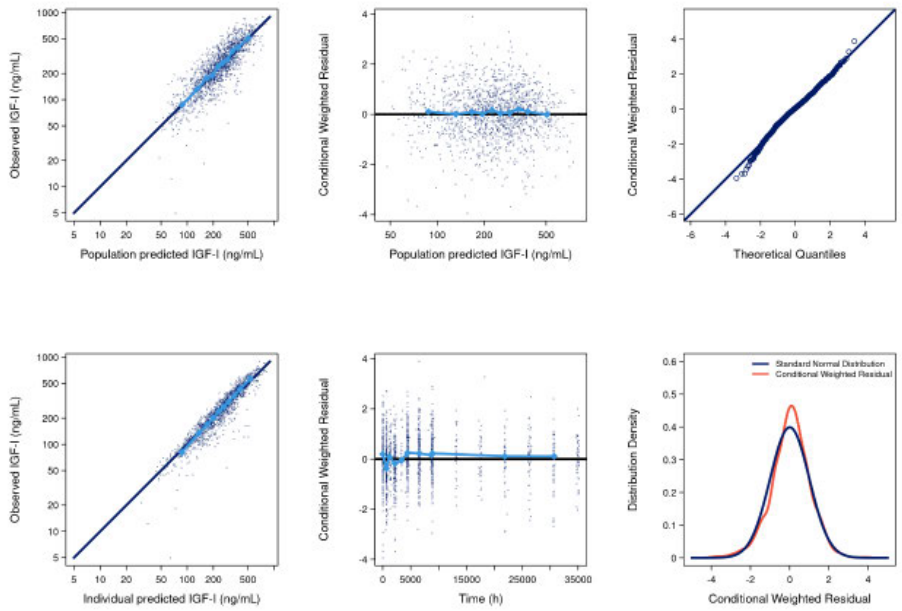
Figure 21. Visual Predictive Check of Somapacitan PK From Study 4245, 4467 and 4469 for the Final PK/PD Model for the NS Population



Notes: Data are medians with 5th and 95th percentiles (red and blue lines) of somapacitan concentrations after first dose. Shaded areas are 95% CIs around the medians and 5th and 95th percentiles based on 1000 simulations with the final PK/PD model.

Source: Applicant's Population PK/PD Report, Figure 13-52B

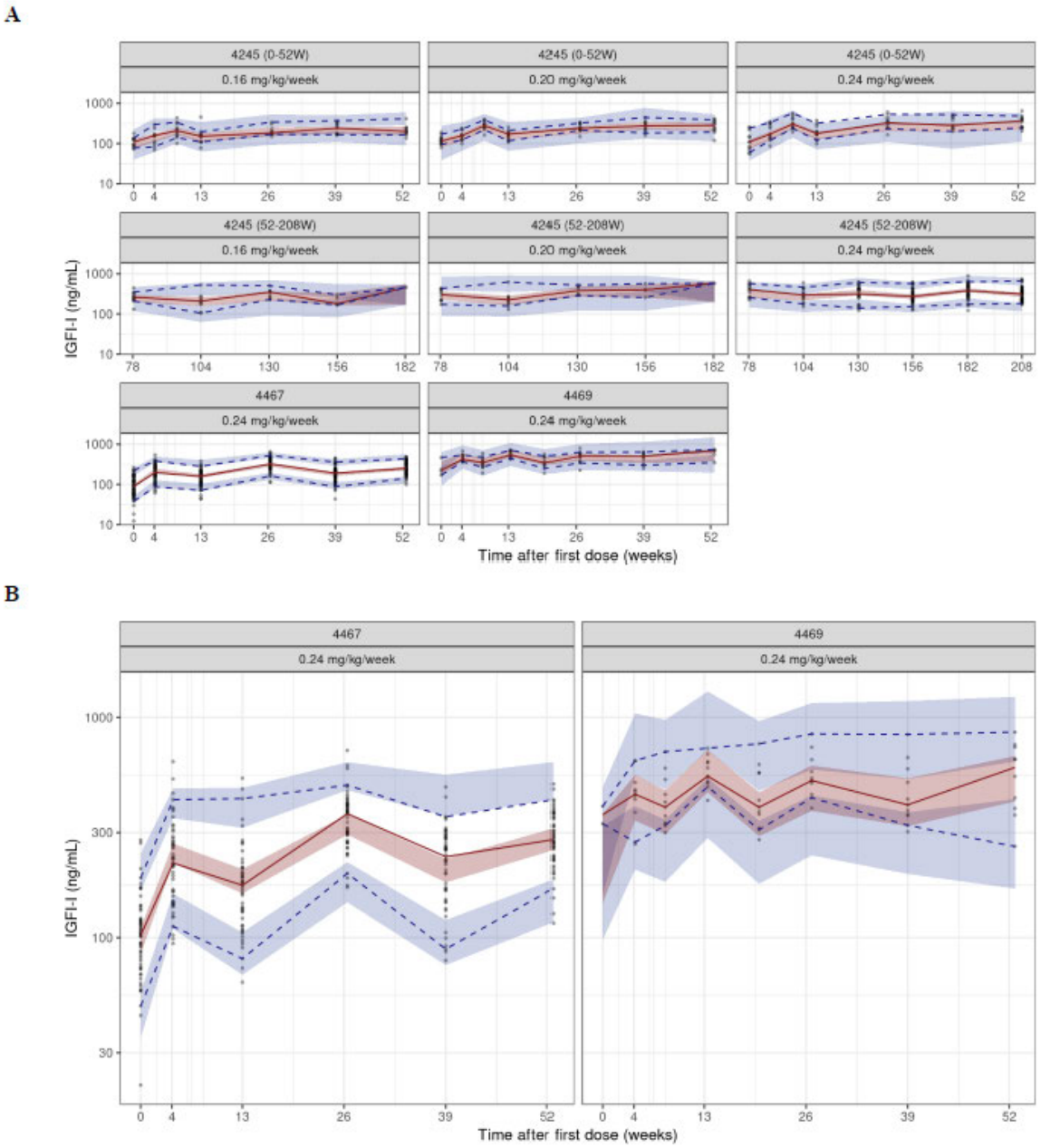
Figure 22. Goodness-of-Fit Plots for IGF-I for the Final PK/PD Model



Notes: Plots show standard goodness of fit plots for the base PK/PD model (A) and final PK/PD model (B). Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Light blue lines are median values for quantiles of concentration or time.

Source: Applicant's Population PK/PD Report, Figure 13-36B

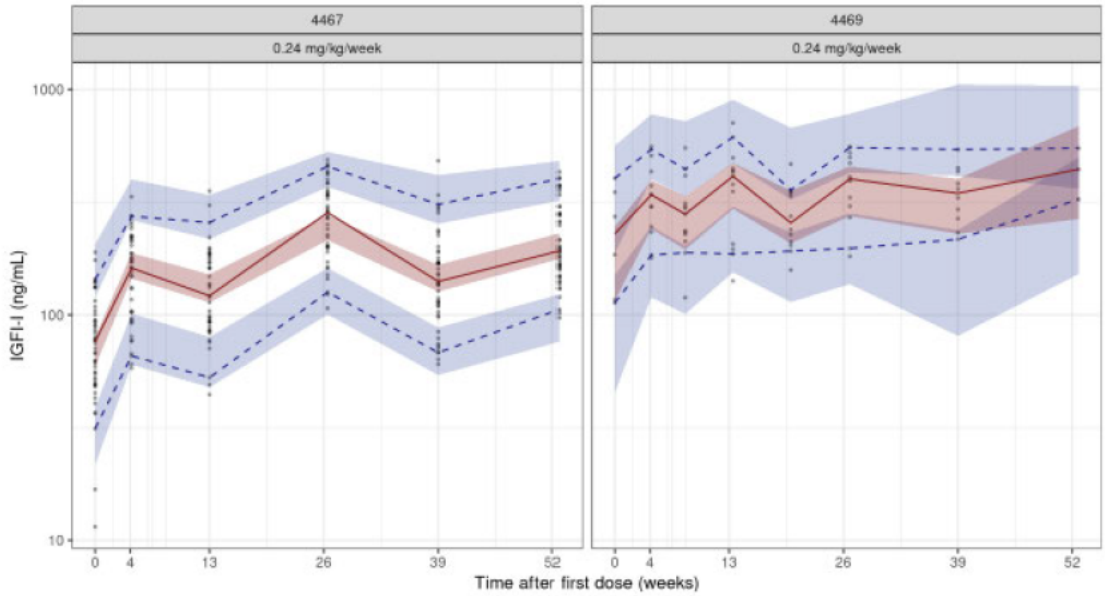
Figure 23. Visual Predictive Check of IGF-I From Study 4245, 4467 and 4469 for the Final PK/PD Model for SGA (Panel A) and ISS (Panel B)



Notes: Data are medians with 5th and 95th percentiles (red and blue lines) of somapacitan concentrations after first dose. Shaded areas are 95% CIs around the medians and 5th and 95th percentiles based on 1000 simulations with the final PK/PD model.

Source: Applicant's Population PK/PD Report, Figure 13-41

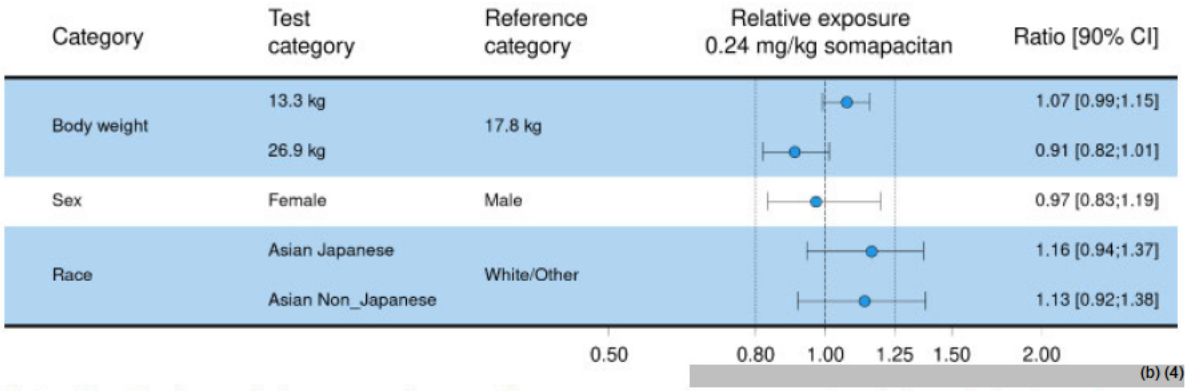
Figure 24. Visual Predictive Check of IGF-I From Study 4245, 4467, and 4469 for the Final PK/PD Model for the NS Population



Notes: Data are medians with 5th and 95th percentiles (red and blue lines) of somapacitan concentrations after first dose. Shaded areas are 95% CIs around the medians and 5th and 95th percentiles based on 1000 simulations with the final PK/PD model.

Source: Applicant's Population PK/PD Report, Figure 13-53

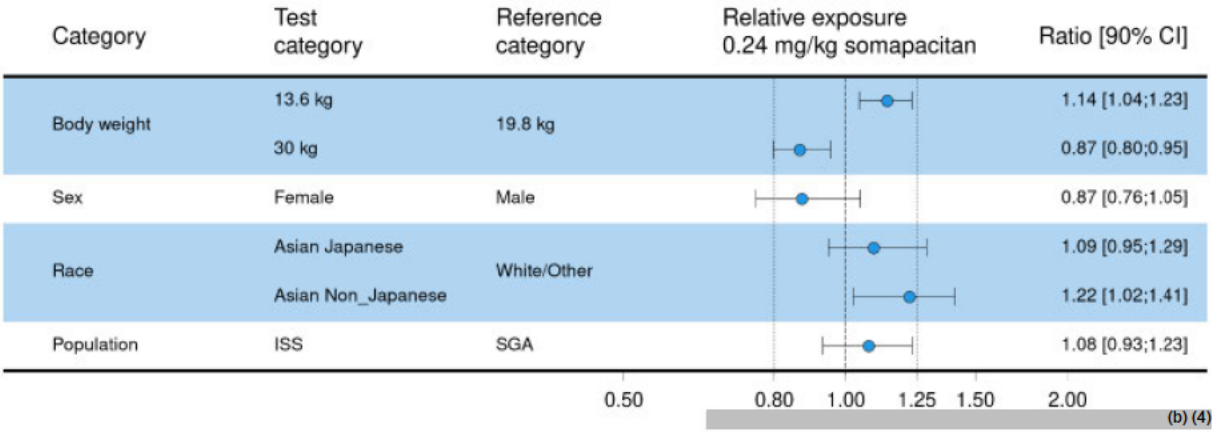
Figure 25. Forest Plot for Demographic Covariates on Relative Exposure in the SGA Patients



Notes: The plot shows relative exposure in terms of average somapacitan concentrations during a dosing interval at steady state for somapacitan 0.24 mg/kg/week. The points and bars show estimated means and 90% confidence intervals based on bootstrap relative to the reference subject (white male with a body weight of 17.8 kg). Body weight categories (13.3 and 26.9 kg) represent the approximate 5% and 95% percentiles at week 52 in study 4467. Vertical dotted lines indicate the [0.80; 1.25] interval.

Source: Applicant's Population PK/PD Report, Figure 6-3

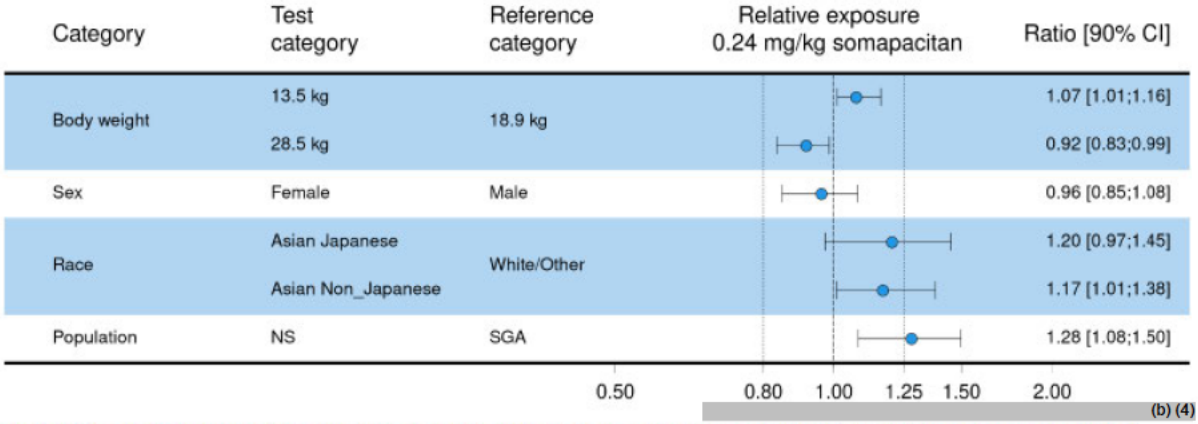
Figure 26. Forest Plot for Demographic Covariates on Relative Exposure in ISS Patients



Notes: The plot shows relative exposure in terms of average somapacitan concentrations during a dosing interval at steady state for somapacitan 0.24 mg/kg/week. The points and bars show estimated means and 90% confidence intervals based on bootstrap relative to the reference subject (white male with a body weight of 19.8 kg). Body weight categories (13.6 and 30.0 kg) represent the approximate 5% and 95% percentiles at week 52 in study 4467. Vertical dotted lines indicate the [0.80; 1.25] interval.

Source: Applicant's Population PK/PD Report, Figure 7-3

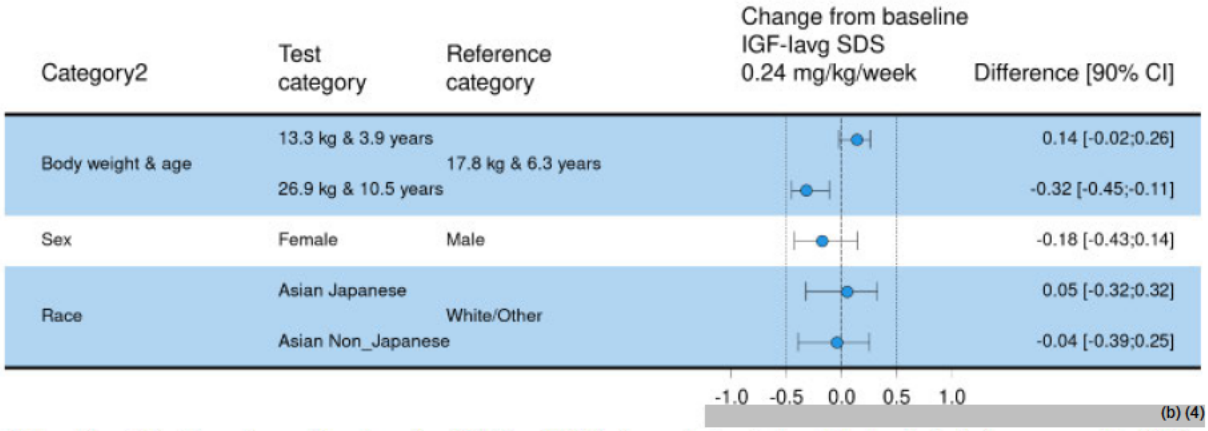
Figure 27. Forest Plot for Demographic Covariates on Relative Exposure in NS Patients



Notes: The plot shows relative exposure in terms of average somapacitan concentrations during a dosing interval at steady state for somapacitan 0.24 mg/kg/week. The points and bars show estimated means and 90% confidence intervals based on bootstrap relative to the reference subject (white male with a body weight of 18.9 kg). Body weight categories (13.5 and 28.5 kg) represent the approximate 5% and 95% percentiles at week 52 in study 4467. Vertical dotted lines indicate the [0.80; 1.25] interval.

Source: Applicant's Population PK/PD Report, Figure 8-3

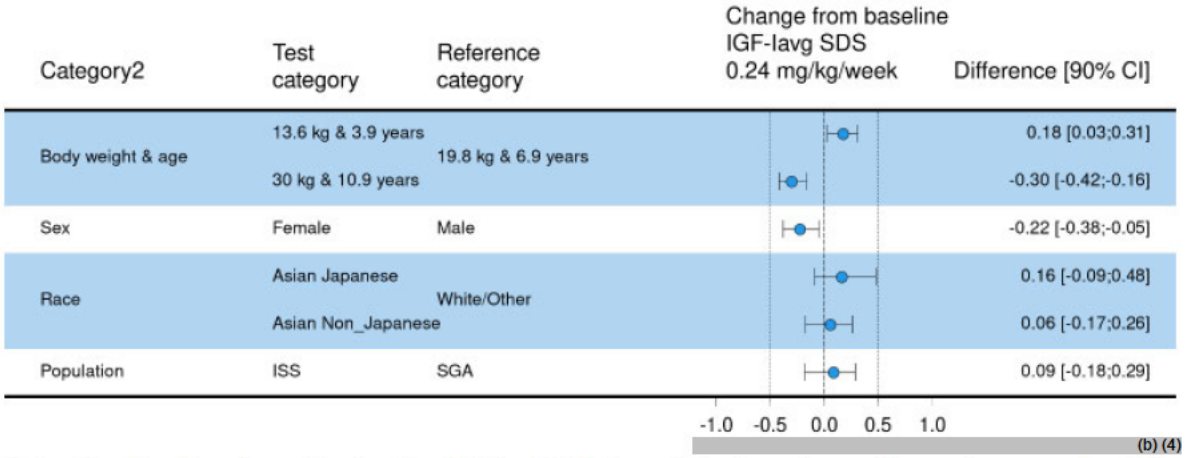
Figure 28. Forest Plots of Demographic Difference in Change From Baseline IGF-I_{avg} in SGA Patients



Notes: The plots show change from baseline IGF-I_{avg} SDS during a dosing interval at steady state for somapacitan 0.24 mg/kg/week. The points and bars show estimated means and 90% confidence intervals for difference to the reference subject (white male of 6.3 years with a body weight of 17.8 kg). Confidence intervals were obtained by bootstrap. For the test categories of low body weight (5th percentile) and high body weight (95th percentile) in study 4467, age was adjusted for appropriate SDS calculation based on the observed correlation between body weight and age. Vertical dotted lines indicate the [-0.5; 0.5] interval.

Source: Applicant's Population PK/PD Report, Figure 6-5

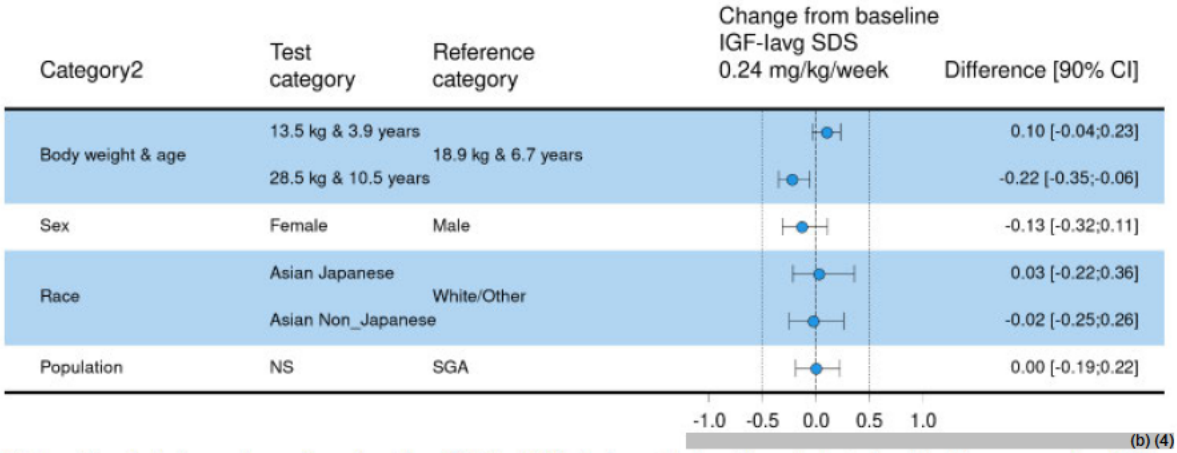
Figure 29. Forest Plots on Demographic Differences in Change From Baseline IGF-I_{avg} in ISS Patients



Notes: The plots show change from baseline IGF-I_{avg} SDS during a dosing interval at steady state for somapacitan 0.24 mg/kg/week. The points and bars show estimated means and 90% confidence intervals for difference to the reference subject (white male of 6.9 years with a body weight of 19.8 kg). Confidence intervals were obtained by bootstrap. For the test categories of low body weight (5th percentile) and high body weight (95th percentile) in study 4467, age was adjusted for appropriate SDS calculation based on the observed correlation between body weight and age. Vertical dotted lines indicate the [-0.5; 0.5] interval.

Source: Applicant's Population PK/PD Report, Figure 7-5

Figure 30. Forest Plots on Demographic Differences in Change From Baseline IGF-I_{avg} in NS Patients



Notes: The plots show change from baseline IGF-I_{avg} SDS during a dosing interval at steady state for somapacitan 0.24 mg/kg/week. The points and bars show estimated means and 90% confidence intervals for difference to the reference subject (white male of 6.7 years with a body weight of 18.9 kg). Confidence intervals were obtained by bootstrap. For the test categories of low body weight (5th percentile) and high body weight (95th percentile), age was adjusted for appropriate SDS calculation based on the observed correlation between body weight and age. Vertical dotted lines indicate the [-0.5; 0.5] interval.

Source: Applicant's Population PK/PD Report, Figure 8-5

15.3.2. Bioanalytical Methods Report

The bioanalytical methods employed four validated methods: ELISA-based quantification of Norditropin (TM.1305, LLOQ 0.3125 ng/mL), LOCI-based quantification of somapacitan (TM.1976, LLOQ 0.500 ng/mL), and bridging ELISA methods for anti-somapacitan (TM.1782) and anti-somatropin (TM.1781) antibody detection (see Table 49). These methods were identical to those used in the original AGHD application and have been deemed acceptable in the BLA review. The methods demonstrated robust performance with acceptable calibration accuracy ($R^2 > 0.99$, bias within ±4%), quality control precision (CV < 10%), and incurred sample reproducibility (ISR) pass rates.

Table 49. Bioanalytical Methods Overview

Method	Analyte	Technique	Matrix	Range/LLOQ	Validation Report	Status
TM.1305	Norditropin (hGH)	Sandwich ELISA (Quantikine Kit)	Human serum	0.3125-20.0 ng/mL	7910.103113.1 (2017)	Validated
TM.1976	Somapacitan (NNC0195-0092)	LOCI (Proximity-based dual bead)	Human serum	0.500-650 ng/mL	11929.091418 (2018)	Validated
TM.1782	Anti-Somapacitan Antibodies	Bridging ELISA (Acid dissociation)	Human serum	MRD 1:33	11232.023017.1 (2020)	Validated
TM.1781	Anti-Somatropin Antibodies	Bridging ELISA	Human serum	MRD 1:33	11233.031517 (2018)	Validated

Source: Summary of Clinical pharmacology Review

15.4. Clinical Appendices

15.4.1. Eligibility Criteria

15.4.1.1. Trial NN8640-4467

Figure 31. Inclusion Criteria, Trial NN8640-4467

5.1 Inclusion criteria

Participants are eligible to be included in the study only if the following criteria apply:

1. Informed consent of parent or legally acceptable representative of participant and child assent, as age appropriate must be obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. No prior exposure to growth promoting therapy, including but not limited to growth hormone, IGF-I and ghrelin analogues.

Applicable to children with SGA:

3. Born small for gestational age (birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards). **Japan:** Please see local requirements in Appendix 11 (Section 10.11)
4. Prepubertal children:
    a) Boys:
        - Age above or equal to 2 years and 26 weeks and below 11.0 years at screening.
        - Testis volume below 4 mL[2]
    b) Girls:
        - Age above or equal to 2 years and 26 weeks and below 10.0 years at screening.
        - Tanner stage 1 for breast development: No palpable glandular breast tissue)[2]
5. Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention[3]. **India:** Please see local requirements in Appendix 11 (Section 10.11).
6. Impaired height velocity defined as annualised height velocity below the 50th percentile for chronological age and sex according to the standards of Prader[4] calculated over a time span of minimum 6 months and maximum 18 months prior to screening.
7. Body Mass Index below the 95th percentile according to Centers for Disease Control and Prevention, Body Mass Index-for-age growth charts[3]. **India:** Please see local requirements in Appendix 11 (Section 10.11).

Applicable to girls with TS:

8. Confirmed diagnosis of TS by 30-cell (or more) lymphocyte chromosomal analysis.* **United Kingdom:** Please see local requirements in Appendix 11 (Section 10.11).
9. Prepubertal girls:
    - Age above or equal to 2 years and 26 weeks and below 10.0 years at screening.
    - Tanner stage 1 for breast development: No palpable glandular breast tissue)[2]
10. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention[3]. **India:** Please see local requirements in Appendix 11 (Section 10.11).
11. Historical height measured 6–18 months prior to screening.
12. Thyroid hormone replacement therapy should be adequate and stable for at least 90 days prior to randomisation, if applicable.

Applicable to children with NS:

13. Clinical diagnosis of NS according to van der Burgt score list (see Table 8-2)[5] **Japan:** Please see local requirements in Appendix 11 (Section 10.11).
14. Prepubertal children:
    a) Boys:
        - Age above or equal to 2 years and 26 weeks and below 11.0 years at screening.
        - Testis volume below 4 mL[2]
    b) Girls:
        - Age above or equal to 2 years and 26 weeks and below 10.0 years at screening.
        - Tanner stage 1 for breast development: No palpable glandular breast tissue)[2]
15. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention[3]. **India:** Please see local requirements in Appendix 11 (Section 10.11).
16. Historical height measured 6–18 months prior to screening.
17. Thyroid hormone replacement therapy should be adequate and stable for at least 90 days prior to randomisation, if applicable.

Applicable to children with ISS:

18. Prepubertal children:
    a) Boys:
        - Age above or equal to 2 years and 26 weeks and below 11.0 years at screening.
        - Testis volume below 4 mL[2]
    b) Girls:
        - Age above or equal to 2 years and 26 weeks and below 10.0 years at screening.
        - Tanner stage 1 for breast development: No palpable glandular breast tissue)[2]
19. Bone age:
    a) Boys:
        - Bone age below or equal to 12 years.
        - Bone age not delayed or advanced more than 2 years compared to chronological age.
    b) Girls:
        - Bone age below or equal to 11 years.
        - Bone age not delayed or advanced more than 2 years compared to chronological age.
20. Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention[3]. **India:** Please see local requirements in Appendix 11 (Section 10.11).
21. Historical height measured 6–18 months prior to screening.
22. One normal GH secretion (GH peak above 7 ng/mL) during GH stimulation test performed within 18 months prior to screening or if such a test is not available for children with ISS, a test should be performed as part of the screening assessments and the result must be available prior to randomisation. **China mainland, India, Israel, Japan and Korea:** Please see local requirements in Appendix 11 (Section 10.11).

*If a 30-cell count is not available for patients with TS, a test should be done, and results must be available prior to randomisation.

Source: Protocol for trial 4467, Section 5.1 Inclusion Criteria, pages 54 to 56.

Figure 32. Exclusion Criteria, Trial NN8640-4467

Participants are excluded from the study if any of the following criteria apply:

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous randomisation into same sub-study in this study.
3. Receipt of any investigational medicinal product within 3 months before screening or participation in another clinical study at the time of randomisation. **Brazil:** Please see local requirement in Appendix 11 (Section 10.11).
4. Children with suspected or confirmed growth hormone deficiency according to local practice.
5. Children diagnosed with diabetes mellitus or screening values from the central laboratory of
    a. fasting plasma glucose above or equal to 126 mg/dL (7.0 mmol/L) or
    b. HbA_{1c} above or equal to 6.5%.

6. Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.
7. Children requiring inhaled glucocorticoid therapy at a dose greater than 400 µg/day of inhaled budesonide or equivalent (i.e., 250 µg/day for fluticasone propionate) for longer than 4 consecutive weeks within the last 12 months prior to screening.
8. Concomitant administration of other treatments that may have an effect on growth, e.g., but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).
9. Diagnosis of attention deficit hyperactivity disorder (ADHD).
10. History or known presence of any malignancy, intracranial tumour, or intracranial cyst.
11. History or known presence of active Hepatitis B or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B).
12. Any disorder, which in the investigator's opinion, might jeopardise participant's safety or compliance with the protocol.
13. The participant or the parent/legally acceptable representative is likely to be non-compliant in respect to study conduct, as judged by the investigator.
14. Current treatment with sex hormones or aromatase inhibitors.

Applicable to children with SGA:

15. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements, such as, but not limited to: **India:** Please see local requirements in Appendix 11 (Section 10.11).
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder/condition that can cause short stature such as, but not limited to, psychosocial deprivation, nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism). **India:** Please see local requirements in Appendix 11 (Section 10.11).
    e. NS.
    f. Hormonal deficiencies.
    g. Children who are small due to malnutrition defined as -2 standard deviations according to standards. **0–5 years:** weight for height on World Health Organisation Multicentre Growth Reference Study 2006. **Above 5 years:** World Health Organisation 2007 Body Mass Index. **India:** Please see local requirements in Appendix 11 (Section 10.11).
    h. Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.

Applicable to children with TS:

16. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements, such as, but not limited to:
India: Please see local requirements in Appendix 11 (Section 10.11).
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder/condition that can cause short stature such as, but not limited to, psychosocial deprivation, nutritional disorders, chronic systemic illness and chronic renal disease.
    d. NS.
    e. Mosaicism below 10%.
    f. TS with Y-chromosome mosaicism where gonadectomy has not been performed.
    g. NYHA class II or above or requiring medication for any heart condition.
    h. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.

Applicable to children with NS:

17. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements, such as, but not limited to:
India: Please see local requirements in Appendix 11 (Section 10.11).
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder/condition that can cause short stature such as, but not limited to, psychosocial deprivation, nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism). **India:** Please see local requirements in Appendix 11 (Section 10.11).
    e. Noonan-related disorders: Noonan syndrome with multiple lentigines (formerly called 'LEOPARD' syndrome), Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome (CFC), Costello syndrome, neurofibromatosis type 1 (NF1) and Legius syndrome. Genetic testing results must be available prior to randomisation to exclude these.
    f. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.

Applicable to children with ISS:

18. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements, such as, but not limited to:
India: Please see local requirements in Appendix 11 (Section 10.11).
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.

c. Any other disorder/condition that can cause short stature such as, but not limited to, psychosocial deprivation, nutritional disorders, chronic systemic illness and chronic renal disease.
d. TS (including mosaicism). **India:** Please see local requirements in Appendix 11 (Section 10.11).
e. NS.
f. Hormonal deficiencies.
g. Born small for gestational age (defined as birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards).
h. Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.

Source: Protocol for trial 4467, Section 5.2 Exclusion Criteria, pages 56 to 59.

Table 50. Diagnostic Criteria for Noonan Syndrome*, Van Der Burgt Score List

Feature	A = major	B = minor
1 Facial	• Typical face[a]	• Suggestive face
2 Cardiac	• Pulmonary valve stenosis and/or typical ECG[b]	• Other defect
3 Height	• <3rd centile (-1.88 SDS)	• <10th centile (-1.28 SDS)
4 Chest wall	• Pectus carinatus/excavatum	• Broad thorax
5 Family history	• First degree relative definite Noonan syndrome	• First degree relative suggest Noonan syndrome
6 Other	• All 3 (males): mental retardation, cryptorchidism, lymphatic dysplasia	• One of mental retardation, cryptorchidism, lymphatic dysplasia

*Definite Noonan syndrome: 1A plus one of 2A-6A or two of 2B-6B; 1B plus two of 2A-6A or three of 2B-6B.
[a]The typical face anomalies consists of a broad forehead, hypertelorism, ptosis, down-slanting palpebral fissures, micrognathia, apparently lowset, posteriorly angulated ears with a thick helix and a broad short neck.
[b]The typical ECG is characterised by an abnormal R/S ratio over the left precordial leads, wide QRS complexes, left-axis deviation and a giant Q wave.

Source: Protocol for trial 4467, table 8-2, page 80

15.4.1.2. Trial NN8640-4245

Figure 33. Inclusion Criteria, Trial NN8640-4245

Subjects are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent of parent or legally acceptable representative of subject and child assent, as age-appropriate must be obtained before any trial-related activities.
   a) The parent or legally acceptable representative of the child must sign and date the Informed Consent Form (according to local requirements).

   b) The child must sign and date the Child Assent Form or provide oral assent (if required according to local requirements).

2. Pre-pubertal children:
   a) Boys:
      - Age ≥ 2 years and 26 weeks and < 11.0 years at screening.
      - Testes volume < 4 ml.

   b) Girls:
      - Age ≥ 2 years and 26 weeks and < 10.0 years at screening.
      - Tanner stage 1 for breast development (no palpable glandular breast tissue).

3. Born small for gestational age (birth length and/or weight < -2 SDS) (according to national standards).
   For Israel and Japan: see Appendix 9

4. Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and gender at screening according to the standards of Centers for Disease Control and Prevention.
   For India: see Appendix 9

5. Impaired height velocity defined as annualised height velocity below the 50th percentile for chronological age and gender according to the standards of Prader calculated over a time span of minimum 6 months and maximum 18 months prior to screening.

6. No prior exposure to growth hormone therapy or IGF-I treatment.

7. Gestational age at birth ≥ 32 weeks.

8. Body Mass Index <95th percentile according to Centers for Disease Control and Prevention, Body Mass Index-for-age growth charts.
   For India: see Appendix 9

Source: Protocol for trial 4245, Section 6.1 Inclusion Criteria, page 28.

Figure 34. Exclusion Criteria, Trial NN8640-4245

Subjects are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as randomisation.
3. Receipt of any investigational medicinal product within 3 months before screening or participation in another clinical trial at time of randomisation.
4. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements:
    a) Turner Syndrome (including mosaicisms)
    b) Chromosomal aneuploidy and significant gene mutations causing medical "syndromes" with short stature, including but not limited to Laron syndrome, Noonan syndrome, Prader-Willi Syndrome, abnormal SHOX-1 gene analysis or absence of GH receptors
    c) Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants
    d) Congenital abnormalities (causing skeletal abnormalities), including but not limited to Russell-Silver Syndrome or skeletal dysplasias
    e) Family history of skeletal dysplasia

    For India: see Appendix 9
5. Children with hormonal deficiencies including suspected or confirmed growth hormone deficiency according to local practise.
6. Children diagnosed with diabetes mellitus or screening values from central laboratory of
    a) Fasting plasma glucose ≥126 mg/dl (7.0 mmol/L) or
    b) HbA1c ≥ 6.5 %
7. Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.
8. Children requiring inhaled glucocorticoid therapy at a dose of greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks within the last 12 months prior to screening.
9. Concomitant administration of other treatments that may have an effect on growth, e.g. but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).
10. Diagnosis of attention deficit hyperactivity disorder.

11. Prior history or known presence of malignancy including intracranial tumours.

12. Prior history or known presence of active Hepatitis B or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B).

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

    For France, Spain, and UK: see Appendix 9

14. The subject or the parent/legally acceptable representative is likely to be non-compliant in respect to trial conduct, as judged by the investigator.

15. Children who are small due to malnutrition defined as -2 SD according to standards: 0-5 years: weight for height on World Health Organisation Multicentre Growth Reference Study 2006 and >5 years: World Health Organisation 2007 Body Mass Index.
    For India: see Appendix 9

Source: Protocol for trial 4245, Section 6.2 Exclusion Criteria, pages 29 and 30.

15.4.1.3. Trial NN8640-4469

Figure 35. Inclusion Criteria, Trial NN8640-4469

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Pre-screening is defined as review of the patient medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent of parent or legally acceptable representative of participant and child assent, as age appropriate must be obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Thyroid hormone replacement therapy should be adequate and stable for at least 90 days prior to allocation, if applicable.
3. Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.
4. Historical height measured 6-18 months prior to screening.

Applicable to children with SGA:

5. Born small for gestational age (birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards).
6. Age:
    a. Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
    b. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
7. *For GH treatment naïve participants:* Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]

Applicable to children with TS:

8. Diagnosis of TS according to local clinical practice.
9. Age:
    a. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
10. *For GH treatment naïve participants:* Impaired height defined as at least 2.0 standard deviation below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]
11. *For GH treatment naïve participants:* Confirmed diagnosis of TS by 30-cell (or more) lymphocyte chromosomal analysis *or* confirmation of TS and TS mosaicism using CGH-array.

Applicable to children with NS:

12. Diagnosis of NS according to local clinical practice.

13. Age:
    a. Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
    b. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
14. *For GH treatment naïve participants:* Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]
15. *For GH treatment naïve participants:* Clinical diagnosis of NS according to van der Burgt score list and genetic test result[3] *OR* confirmed mutation in any of the genes associated with NS before allocation.

Applicable to children with ISS:

16. Age:
    a. Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
    b. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
17. *For GH treatment naïve participants:* Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]
18. *For GH treatment naïve participants:* Normal GH secretion (GH peak above 7 ng/mL) during GH stimulation test performed within 18 months prior to screening.
    For Korea: Please see local requirements in Appendix 11 (Section 10.11)
19. *For GH treatment naïve participants:* Bone age not delayed more than 2 years compared to chronological age at screening.

Source: Protocol for trial 4469, Section 5.1 Inclusion Criteria, pages 46 and 47.

Figure 36. Exclusion Criteria, Trial NN8640-4469

Participants are excluded from the study if any of the following criteria apply:

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous allocation into same sub-study in this study.
3. Receipt of any investigational medicinal product within 3 months before screening or participation in another clinical study at the time of allocation.
4. Children with suspected or confirmed growth hormone deficiency according to local practice.
5. Children diagnosed with diabetes mellitus or screening values from the central laboratory of
    a. fasting plasma glucose above or equal to 126 mg/dL (7.0 mmol/L) or
    b. HbA_{1c} above or equal to 6.5%.
6. Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.
7. Children requiring inhaled glucocorticoid therapy at a dose greater than 400 µg/day of inhaled budesonide or equivalent (i.e., 250 µg/day for fluticasone propionate) for longer than 4 consecutive weeks within the last 12 months prior to screening.
8. History or known presence of any malignancy, intracranial tumour, or intracranial cyst.
9. History or known presence of active Hepatitis B or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B).

10. Any disorder, which in the investigator's opinion, might jeopardise participant's safety or compliance with the protocol.
11. The participant or the parent/legally acceptable representative is likely to be non-compliant in respect to study conduct, as judged by the investigator.
12. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive method, as defined in Appendix 4 (Section 10.4).
13. Male of reproductive age who, or whose female partner(s), is not using an adequate contraceptive method, as defined in Appendix 4 (Section 10.4).

Applicable to children with SGA:

14. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism).
    e. NS.
    f. Poorly controlled or uncontrolled hormonal deficiencies.
    g. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.
    h. Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.

Applicable to children with TS:

15. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. NS.
    e. Mosaicism below 10%.
    f. TS with Y-chromosome mosaicism where gonadectomy has not been performed.
    g. NYHA class II or above or requiring medication for any heart condition.
    h. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.
    i. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.

Applicable to children with NS:

16. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism).
    e. Noonan-related disorders including but not limited to: Noonan syndrome with multiple lentigines (formerly called 'LEOPARD' syndrome), Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome (CFC), Costello syndrome, neurofibromatosis type 1 (NF1) and Legius syndrome.
    f. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.
    g. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.

Applicable to children with ISS:

17. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism).
    e. NS.
    f. Poorly controlled or uncontrolled hormonal deficiencies.
    g. Born small for gestational age (defined as birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards).
    h. Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.
    i. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.

Source: Protocol for trial 4469, Section 5.2 Exclusion Criteria, pages 47 to 49.

15.4.2. Protocol Deviations in Trials NN8640-4467, NN8640-4245, and NN8640-4469

Table 51. Major Subject Level Protocol Deviations by Category in the SGA Population, Trial NN8640-4467

	Participant level PDs				
Protocol deviation category	Norditropin 0.035 mg/kg/day N	Norditropin 0.067 mg/kg/day N	somapacitan 0.24 mg/kg/week N	Not allocated N	Total N
Total	22	25	47	0	94
Informed consent	4	3	7	0	14
Inclusion/exclusion criteria	1	1	5	0	7
Treatment administration	3	5	5	0	13
Study procedures/assessments	11	15	21	0	47
AE and other safety procedures	2	0	1	0	3
Concomitant medication/medical intervention	0	0	0	0	0
Subject visit schedule	0	0	0	0	0
Privacy and data protection	0	1	5	0	6
Participant contact schedule	1	0	3	0	4
Other	0	0	0	0	0

AE: Adverse event, N: Number of PDs within category, PD: Protocol deviation
Source: Clinical Trial Report for trial 4467, SGA, Table 4-3, page 51

Table 52. Major Subject Level Protocol Deviations by Category in the NS Population, Trial NN8640-4467

	Participant level PDs			
Protocol deviation category	Norditropin 0.050 mg/kg/day N	somapacitan 0.24 mg/kg/week N	Not allocated N	Total N
Total	34	56	0	90
Informed consent	7	7	0	14
Inclusion/exclusion criteria	0	3	0	3
Treatment administration	5	9	0	14
Study procedures/assessments	17	27	0	44
AE and other safety procedures	1	2	0	3
Concomitant medication/medical intervention	0	0	0	0
Subject visit schedule	0	0	0	0
Privacy and data protection	2	4	0	6
Participant contact schedule	2	4	0	6
Other	0	0	0	0

AE: Adverse event, N: Number of PDs within category, PD: Protocol deviation
Source: Clinical Trial Report for trial 4467, NS, Table 4-3, page 50

Table 53. Major Subject Level Protocol Deviations by Category in the ISS Population, Trial NN8640-4467

	Participant level PDs			
Protocol deviation category	Norditropin 0.050 mg/kg/day N	somapacitan 0.24 mg/kg/week N	Not allocated N	Total N
Total	17	26	5	48
Informed consent	1	4	2	7
Inclusion/exclusion criteria	4	3	0	7
Treatment administration	4	3	0	7
Study procedures/assessments	7	12	1	20
AE and other safety procedures	0	3	0	3
Concomitant medication/medical intervention	0	0	0	0
Subject visit schedule	0	0	0	0
Privacy and data protection	0	0	2	2
Participant contact schedule	1	1	0	2
Other	0	0	0	0

AE: Adverse event, N: Number of PDs within category, PD: Protocol deviation

Source: Clinical Trial Report for trial 4467, ISS, Table 4-3, page 51

Table 54. Major Subject Level Protocol Deviations by Category, Trial NN8640-4245

	Subject level PDs					
Protocol deviation category	Norditropin (0.035mg/kg/day) N	Norditropin (0.067mg/kg/day) N	somapacitan (0.16mg/kg/week) N	somapacitan (0.20mg/kg/week) N	somapacitan (0.24mg/kg/week) N	Not allocated N
Total	17	30	15	23	19	0
Informed consent	3	4	1	5	2	0
Inclusion/ exclusion criteria	0	0	2	1	0	0
Treatment administration	2	9	1	2	1	0
Trial procedures/ assessment	10	15	9	11	16	0
Concomitant medication	0	0	0	0	0	0
Subject visit schedule	1	0	0	1	0	0
SAE notification/ safety procedure	1	1	0	3	0	0
Privacy and data protection	0	1	2	0	0	0

N: Number of PDs within category, PD: Protocol deviation, SAE: Serious adverse event
Not allocated: PDs for screening failures and subjects not allocated to treatment.

Source: Clinical Trial Report for trial 4245, Table 4-3, page 44

Table 55. Major Subject Level Protocol Deviations by Category in the SGA Population, Trial NN8640-4469

	Participant level PDs			
Protocol deviation category	somapacitan (0.24 mg/kg/week) GH treatment naive N	somapacitan (0.24 mg/kg/week) previously treated with GH N	Screen failure N	Total N
Total	1	1	0	2
Informed consent	0	0	0	0
Inclusion/exclusion criteria	0	0	0	0
Treatment administration	0	0	0	0
Study procedures/assessments	0	0	0	0
AE and other safety procedures	0	1	0	1
Concomitant medication/medical intervention	0	0	0	0
Subject visit schedule	0	0	0	0
Privacy and data protection	0	0	0	0
Participant contact schedule	1	0	0	1
Other	0	0	0	0

SGA: small for gestational age, AE: Adverse event, GH: Growth hormone, N: Number of PDs within category, PD: Protocol deviation

Source: Clinical Trial Report for trial 4469, Appendix 9.2.2, Table 9.2.11, page 12

Table 56. Major Subject Level Protocol Deviations by Category in the NS Population, Trial NN8640-4469

	Participant level PDs			
Protocol deviation category	somapacitan (0.24 mg/kg/week) GH treatment naive N	somapacitan (0.24 mg/kg/week) previously treated with GH N	Screen failure N	Total N
Total	0	2	1	3
Informed consent	0	0	0	0
Inclusion/exclusion criteria	0	0	0	0
Treatment administration	0	0	0	0
Study procedures/assessments	0	0	0	0
AE and other safety procedures	0	0	0	0
Concomitant medication/medical intervention	0	0	0	0
Subject visit schedule	0	0	0	0
Privacy and data protection	0	0	1	1
Participant contact schedule	0	2	0	2
Other	0	0	0	0

NS: Noonan syndrome, AE: Adverse event, GH: Growth hormone, N: Number of PDs within category, PD: Protocol deviation

Source: Clinical Trial Report for trial 4469, Appendix 9.2.2, Table 9.2.10, page 11

Table 57. Major Subject Level Protocol Deviations by Category in the ISS Population, Trial NN8640-4469

	Participant level PDs			
Protocol deviation category	somapacitan (0.24 mg/kg/week) GH treatment naive N	somapacitan (0.24 mg/kg/week) previously treated with GH N	Screen failure N	Total N
Total	1	4	0	5
Informed consent	0	3	0	3
Inclusion/exclusion criteria	0	0	0	0
Treatment administration	0	0	0	0
Study procedures/assessments	1	0	0	1
AE and other safety procedures	0	0	0	0
Concomitant medication/medical intervention	0	0	0	0
Subject visit schedule	0	0	0	0
Privacy and data protection	0	1	0	1
Participant contact schedule	0	0	0	0
Other	0	0	0	0

ISS: idiopathic short stature, AE: Adverse event, GH: Growth hormone, N: Number of PDs within category, PD: Protocol deviation

Source: Clinical Trial Report for trial 4469, Appendix 9.2.2, Table 9.2.9, page 10

Table 58. (b) (4)

(b) (4)

15.4.3. Additional Figures and Tables From Trials NN8640-4467, NN8640-4245, and NN8640-4469

15.4.3.1. Trial NN8640-4467

Table 59. Results of Genetic Analyses for Subjects in the NS Subtrial, Trial 4467

	Norditropin 0.050 mg/kg/day N	(%)	somapacitan 0.24 mg/kg/week N	(%)	Total N	(%)
BRAF gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		3	(6.1)	3	(3.9)
Not Detected	26	(92.9)	39	(79.6)	65	(84.4)
Not Done	2	(7.1)	7	(14.3)	9	(11.7)
CBL gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		0		0	
Not Detected	25	(89.3)	41	(83.7)	66	(85.7)
Not Done	3	(10.7)	8	(16.3)	11	(14.3)
HRAS gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		0		0	
Not Detected	24	(85.7)	40	(81.6)	64	(83.1)
Not Done	4	(14.3)	9	(18.4)	13	(16.9)
KRAS gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		3	(6.1)	3	(3.9)
Not Detected	26	(92.9)	40	(81.6)	66	(85.7)
Not Done	2	(7.1)	6	(12.2)	8	(10.4)
LZTR1 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		3	(6.1)	3	(3.9)
Not Detected	20	(71.4)	36	(73.5)	56	(72.7)
Not Done	8	(28.6)	10	(20.4)	18	(23.4)
MAP2K1 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	1	(3.6)	0		1	(1.3)
Not Detected	22	(78.6)	40	(81.6)	62	(80.5)
Not Done	5	(17.9)	9	(18.4)	14	(18.2)
MAP2K2 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		1	(2.0)	1	(1.3)
Not Detected	23	(82.1)	39	(79.6)	62	(80.5)
Not Done	5	(17.9)	9	(18.4)	14	(18.2)
NF1 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		0		0	
Not Detected	17	(60.7)	33	(67.3)	50	(64.9)
Not Done	11	(39.3)	16	(32.6)	27	(35.1)
NRAS gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		0		0	
Not Detected	25	(89.3)	41	(83.7)	66	(85.7)
Not Done	3	(10.7)	8	(16.3)	11	(14.3)
PTPN11 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	24	(85.7)	29	(59.2)	53	(68.8)
Not Detected	4	(14.3)	20	(40.8)	24	(31.2)
Not Done	0		0		0	
RAF1 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	1	(3.6)	0		1	(1.3)
Not Detected	25	(89.3)	43	(87.8)	68	(88.3)
Not Done	2	(7.1)	6	(12.2)	8	(10.4)
RASA2 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		0		0	
Not Detected	20	(71.4)	37	(75.5)	57	(74.0)
Not Done	8	(28.6)	12	(24.5)	20	(26.0)

RIT1 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	1	(3.6)	0		1	(1.3)
Not Detected	24	(85.7)	42	(85.7)	66	(85.7)
Not Done	3	(10.7)	7	(14.3)	10	(13.0)
SHOC2 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		0		0	
Not Detected	24	(85.7)	41	(83.7)	65	(84.4)
Not Done	4	(14.3)	8	(16.3)	12	(15.6)
SOS1 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	1	(3.6)	4	(8.2)	5	(6.5)
Not Detected	25	(89.3)	39	(79.6)	64	(83.1)
Not Done	2	(7.1)	6	(12.2)	8	(10.4)
SOS2 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		1	(2.0)	1	(1.3)
Not Detected	20	(71.4)	37	(75.5)	57	(74.0)
Not Done	8	(28.6)	11	(22.4)	19	(24.7)
SPRED1 gene mutation						
N	28	(100.0)	49	(100.0)	77	(100.0)
Detected	0		0		0	
Not Detected	21	(75.0)	36	(73.5)	57	(74.0)
Not Done	7	(25.0)	13	(26.5)	20	(26.0)

N: Number of participants, %: Percentage
Source: Clinical Trial Report for trial 4467, NS, Table 8.2.8, page 162.

Table 60. The Most Commonly (≥ 5% Subjects in Any Treatment Group) Reported Comorbidities in the SGA Population, Trial 4467

Comorbidities	Norditropin 0.035 mg/kg/day (N=37)	Norditropin 0.067 mg/kg/day (N=35)	Somapacitan 0.24 mg/kg/week (N=70)	Total (N=142)
Any comorbidity, n (%)	37 (100.0)	35 (100.0)	70 (100.0)	142 (100.0)
Small for dates baby	37 (100.0)	35 (100.0)	70 (100.0)	142 (100.0)
Asthma	0	4 (11.4)	5 (7.1)	9 (6.3)
Dermatitis atopic	2 (5.4)	1 (2.9)	4 (5.7)	7 (4.9)
Eczema	2 (5.4)	2 (5.7)	2 (2.9)	6 (4.2)
Rhinitis allergic	3 (8.1)	0	3 (4.3)	6 (4.2)
Food allergy	2 (5.4)	1 (2.9)	2 (2.9)	5 (3.5)
Atrial septal defect	1 (2.7)	2 (5.7)	1 (1.4)	4 (2.8)
Cardiac murmur	2 (5.4)	0	2 (2.9)	4 (2.8)
Conjunctivitis allergic	1 (2.7)	2 (5.7)	1 (1.4)	4 (2.8)
Retinopathy of prematurity	0	2 (5.7)	2 (2.9)	4 (2.8)
Cerebral palsy	0	2 (5.7)	1 (1.4)	3 (2.1)
Constipation	0	2 (5.7)	1 (1.4)	3 (2.1)
Gastroesophageal reflux disease	0	2 (5.7)	1 (1.4)	3 (2.1)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

Table 61. The Most Commonly (≥ 5% Subjects in Any Treatment Group) Reported Comorbidities in the NS Population, Trial 4467

Comorbidities	Norditropin 0.050 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=49)	Total (N=77)
Any comorbidity, n (%)	28 (100.0)	49 (100.0)	77 (100.0)
Noonan syndrome	28 (100.0)	49 (100.0)	77 (100.0)
Pulmonary valve stenosis	8 (28.6)	9 (18.4)	17 (22.1)
Atrial septal defect	2 (7.1)	8 (16.3)	10 (13.0)
Cryptorchism	2 (7.1)	5 (10.2)	7 (9.1)

Comorbidities	Norditropin 0.050 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=49)	Total (N=77)
Constipation	0	4 (8.2)	4 (5.2)
Pneumonia	1 (3.6)	3 (6.1)	4 (5.2)
Psychomotor retardation	0	4 (8.2)	4 (5.2)
Pulmonary artery stenosis	1 (3.6)	3 (6.1)	4 (5.2)
Atrial septal defect repair	2 (7.1)	1 (2.0)	3 (3.9)
Developmental delay	0	3 (6.1)	3 (3.9)
Orchidopexy	0	3 (6.1)	3 (3.9)
Ventricular septal defect	2 (7.1)	1 (2.0)	3 (3.9)
Eyelid ptosis	2 (7.1)	0	2 (2.6)
Pulmonary artery stenosis congenital	2 (7.1)	0	2 (2.6)
Von Willebrand's disease	2 (7.1)	0	2 (2.6)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

Table 62. The Most Commonly (≥ 5% Subjects in Any Treatment Group) Reported Comorbidities in the ISS Population, Trial 4467

Comorbidities	Norditropin 0.050 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=60)	Total (N=88)
Any comorbidity, n (%)	28 (100.0)	60 (100.0)	88 (100.0)
Short stature	28 (100.0)	60 (100.0)	88 (100.0)
Seasonal allergy	2 (7.1)	4 (6.7)	6 (6.8)
Constipation	1 (3.6)	4 (6.7)	5 (5.7)
Rhinitis	1 (3.6)	3 (5)	4 (4.5)
Asthma	2 (7.1)	1 (1.7)	3 (3.4)
Adenoidectomy	2 (7.1)	0	2 (2.3)
Ear tube insertion	2 (7.1)	0	2 (2.3)
Tongue tie operation	2 (7.1)	0	2 (2.3)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

Table 63. The Most Commonly (≥ 10% Subjects in Any Treatment Group) Concomitant Medications in the SGA Population, Trial 4467

Medication Name	Norditropin 0.035 mg/kg/day (N=37)	Norditropin 0.067 mg/kg/day (N=35)	Somapacitan 0.24 mg/kg/week (N=70)	Total (N=142)
Any medication, n (%)	33 (89.2)	31 (88.6)	57 (81.4)	121 (85.2)
PARACETAMOL	18 (48.6)	13 (37.1)	22 (31.4)	53 (37.3)
IBUPROFEN	8 (21.6)	9 (25.7)	19 (27.1)	36 (25.4)
AMBROXOL HYDROCHLORIDE	5 (13.5)	7 (20.0)	10 (14.3)	22 (15.5)
AZITHROMYCIN	5 (13.5)	6 (17.1)	10 (14.3)	21 (14.8)
LEVOCETIRIZINE DIHYDROCHLORIDE	6 (16.2)	6 (17.1)	7 (10)	19 (13.4)
CARBOCISTEINE	7 (18.9)	2 (5.7)	9 (13.9)	18 (12.7)
BUDESONIDE	5 (13.5)	7 (20.0)	5 (7.1)	17 (12.0)
AMOXICILLIN TRIHYDRATE	4 (10.8)	4 (11.4)	6 (8.6)	14 (9.9)
CLARITHROMYCIN	3 (8.1)	5 (14.3)	6 (8.6)	14 (9.9)
LORATADINE	2 (5.4)	1 (2.9)	10 (14.3)	13 (9.2)
AMOXICILLIN	4 (10.8)	3 (8.6)	5 (7.1)	12 (8.5)
SALBUTAMOL	4 (10.8)	4 (11.4)	4 (5.7)	12 (8.5)
SALBUTAMOL SULFATE	4 (10.8)	3 (8.6)	4 (5.7)	11 (7.7)

Medication Name	Norditropin 0.035 mg/kg/day (N=37)	Norditropin 0.067 mg/kg/day (N=35)	Somapacitan 0.24 mg/kg/week (N=70)	Total (N=142)
TIPEPIDINE HIBENZATE	4 (10.8)	1 (2.9)	6 (8.6)	11 (7.7)
TULOBUTEROL	6 (16.2)	1 (2.9)	4 (5.7)	11 (7.7)
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	5 (13.5)	3 (8.6)	2 (2.9)	10 (7.0)
MONTELUKAST SODIUM	2 (5.4)	5 (14.3)	3 (4.3)	10 (7.0)
OFLOXACIN	5 (13.5)	1 (2.9)	4 (5.7)	10 (7.0)
FLUTICASONE PROPIONATE	4 (10.8)	4 (11.4)	1 (1.4)	9 (6.3)
CEFDINIR	2 (5.4)	4 (11.4)	2 (2.9)	8 (5.6)
DEXTROMETHORPHAN HYDROBROMIDE	5 (13.5)	0	3 (4.3)	8 (5.6)
CEFPROZIL	4 (10.8)	1 (2.9)	1 (1.4)	6 (4.2)
CHLORPHENAMINE MALEATE	4 (10.8)	1 (2.9)	0	5 (3.5)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

Table 64. The Most Commonly (≥ 10% Subjects in Any Treatment Group) Concomitant Medications in the NS Population, Trial 4467

Medication Name	Norditropin 0.050 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=49)	Total (N=77)
Any Medication, n (%)	22 (78.6)	44 (89.8)	66 (85.7)
PARACETAMOL	13 (46.4)	19 (38.8)	32 (41.6)
IBUPROFEN	4 (14.3)	13 (26.5)	17 (22.1)
AMOXICILLIN	5 (17.9)	8 (16.3)	13 (16.9)
COLECALCIFEROL	5 (17.9)	8 (16.3)	13 (16.9)
AMBROXOL HYDROCHLORIDE	4 (14.3)	5 (10.2)	9 (11.7)
AZITHROMYCIN	3 (10.7)	6 (12.2)	9 (11.7)
CARBOCISTEINE	5 (17.9)	4 (8.2)	9 (11.7)
AMOXICILLIN;CLAVULANIC ACID	2 (7.1)	6 (12.2)	8 (10.4)
CLARITHROMYCIN	3 (10.7)	5 (10.2)	8 (10.4)
OSELTAMIVIR PHOSPHATE	4 (14.3)	3 (6.1)	7 (9.1)
TULOBUTEROL	4 (14.3)	1 (2.0)	5 (6.5)
MONTELUKAST	3 (10.7)	1 (2.0)	4 (5.2)
TIPEPIDINE HIBENZATE	4 (14.3)	0	4 (5.2)
ACICLOVIR	3 (10.7)	0	3 (3.9)
CLOSTRIDIUM BUTYRICUM	3 (10.7)	0	3 (3.9)
FENTANYL	3 (10.7)	0	3 (3.9)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

Table 65. The Most Commonly (≥ 10% Subjects in Any Treatment Group) Concomitant Medications in the ISS Population, Trial 4467

Medication Name	Norditropin 0.050 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=60)	Total (N=88)
Any Medication, n (%)	23 (82.1)	46 (76.7)	69 (78.4)
PARACETAMOL	9 (32.1)	17 (28.3)	26 (29.5)
IBUPROFEN	10 (35.7)	11 (18.3)	21 (23.9)
AMOXICILLIN	2 (7.1)	11 (18.3)	13 (14.8)
CARBOCISTEINE	2 (7.1)	7 (11.7)	9 (10.2)

Medication Name	Norditropin 0.050 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=60)	Total (N=88)
AMBROXOL HYDROCHLORIDE	3 (10.7)	5 (8.3)	8 (9.1)
AZITHROMYCIN	4 (14.3)	4 (6.7)	8 (9.1)
CLARITHROMYCIN	3 (10.7)	4 (6.7)	7 (8.0)
SALBUTAMOL	4 (14.3)	3 (5)	7 (8.0)
MONTELUKAST SODIUM	3 (10.7)	3 (5)	6 (6.8)
COLECALCIFEROL	3 (10.7)	1 (1.7)	4 (4.5)
OLOPATADINE HYDROCHLORIDE	3 (10.7)	1 (1.7)	4 (4.5)
MULTIVITAMINS, PLAIN	3 (10.7)	0	3 (3.4)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

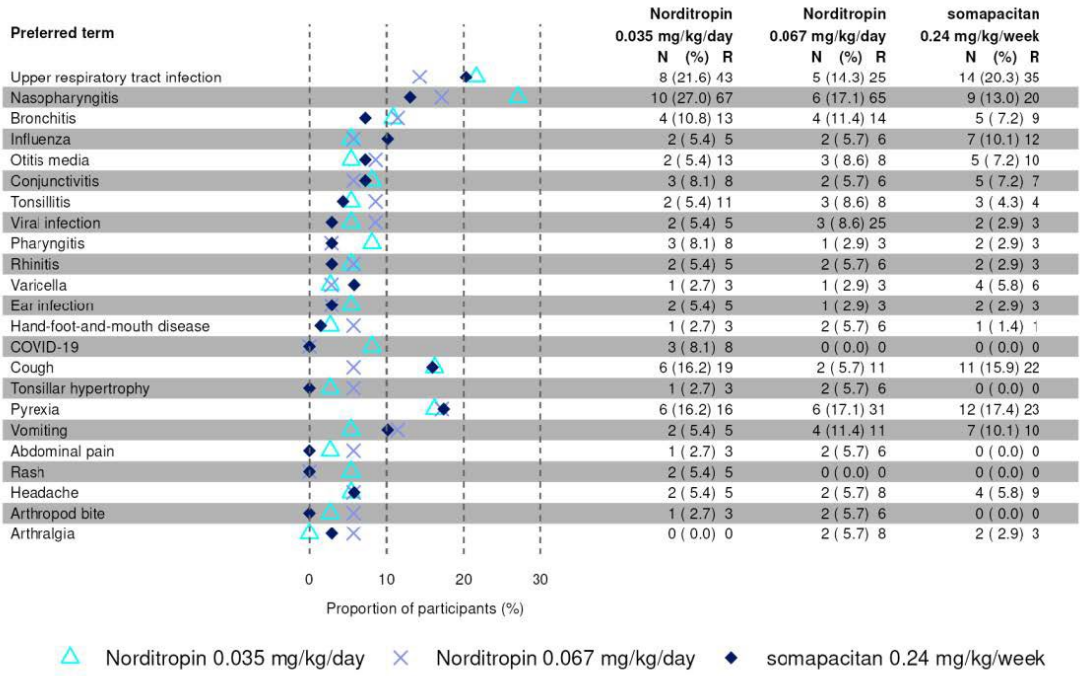
Table 66. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Including Individual PTs Within the Combined Terms, Main Period, SGA Safety Population, Trial 4467

OCMQ/GQ Term Preferred Term	Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)	Risk Difference Somapacitan - 0.035 mg/kg/day Norditropin (%) (95% CI)	Risk Difference Somapacitan - 0.067 mg/kg/day Norditropin (%) (95% CI)	Total (N=141) n (%)
Any AE	32 (86.5)	28 (80.0)	60 (87.0)	0.5 (--13.1, 14.1)	7 (-8.5, 22.4)	120 (85.1)
Cough	6 (16.2)	3 (8.6)	11 (15.9)	-0.3 (-15, 14.4)	7.4 (-5.3, 20)*	20 (14.2)
Cough	6 (16.2)	2 (5.7)	11 (15.9)	-0.3 (-15, 14.4)	10.2 (-1.3, 21.8)*	19 (13.5)
Productive cough	1 (2.7)	1 (2.9)	0	-2.7 (-7.9, 2.5)	-2.9 (-8.4, 2.7)	2 (1.4)
Respiratory Tract Infection	11 (29.7)	7 (20)	18 (26.1)	-3.6 (-21.7, 14.4)	6.1 (-10.7, 22.9)*	36 (25.5)
Upper respiratory tract infection	8 (21.6)	5 (14.3)	14 (20.3)	-1.3 (-17.6, 15)	6 (-9, 21)*	27 (19.1)
Influenza	2 (5.4)	2 (5.7)	7 (10.1)	4.7 (-5.5, 14.9)*	4.4 (-6.1, 14.9)*	11 (7.8)
Respiratory syncytial virus infection	1 (2.7)	0	1 (1.4)	-1.3 (-7.2, 4.7)	1.4 (-1.4, 4.3)	2 (1.4)
Mycoplasma infection	0	0	1 (1.4)	1.4 (-1.4, 4.3)	1.4 (-1.4, 4.3)	1 (0.7)
Pneumonia	0	0	1 (1.4)	1.4 (-1.4, 4.3)	1.4 (-1.4, 4.3)	1 (0.7)
Pneumonia bacterial	0	0	1 (1.4)	1.4 (-1.4, 4.3)	1.4 (-1.4, 4.3)	1 (0.7)
Pneumonia mycoplasmal	0	0	1 (1.4)	1.4 (-1.4, 4.3)	1.4 (-1.4, 4.3)	1 (0.7)
Croup infectious	1 (2.7)	0	0	-2.7 (-7.9, 2.5)	0	1 (0.7)
Pneumonia haemophilus	1 (2.7)	0	0	-2.7 (-7.9, 2.5)	0	1 (0.7)
Pneumonia streptococcal	1 (2.7)	0	0	-2.7 (-7.9, 2.5)	0	1 (0.7)
Respiratory tract infection	0	1 (2.9)	1 (1.4)	1.4 (-1.4, 4.3)	-1.4 (-7.6, 4.8)	2 (1.4)
Metapneumovirus infection	0	1 (2.9)	1 (1.4)	1.4 (-1.4, 4.3)	-1.4 (-7.6, 4.8)	2 (1.4)

OCMQ/GQ Term Preferred Term	Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)	Risk Difference Somapacitan - 0.035 mg/kg/day Norditropin (%) (95% CI)	Risk Difference Somapacitan - 0.067 mg/kg/day Norditropin (%) (95% CI)	Total (N=141) n (%)
Diarrhea	3 (8.1)	2 (5.7)	7 (10.1)	2 (-9.3, 13.4)*	4.4 (-6.1, 14.9)*	12 (8.5)
Diarrhea	1 (2.7)	1 (2.9)	3 (4.3)	1.6 (-5.5, 8.7)	1.5 (-5.8, 8.8)	5 (3.5)
Gastroenteritis	1 (2.7)	1 (2.9)	3 (4.3)	1.6 (-5.5, 8.7)	1.5 (-5.8, 8.8)	5 (3.5)
Gastrointestinal viral infection	0	0	1 (1.4)	1.4 (-1.4, 4.3)	1.4 (-1.4, 4.3)	1 (0.7)
Gastroenteritis viral	1 (2.7)	0	0	-2.7 (-7.9, 2.5)	0	1 (0.7)
Pyrexia	6 (16.2)	6 (17.1)	13 (18.8)	2.6 (-12.4, 17.7)*	1.7 (-13.8, 17.2)*	25 (17.7)
Vomiting	4 (10.8)	4 (11.4)	7 (10.1)	-0.7 (-12.9, 11.6)	-1.3 (-14, 11.4)	15 (10.6)
Gastritis	1 (2.7)	0	0	-2.7 (-7.9, 2.5)	0	1 (0.7)
Infantile vomiting	1 (2.7)	0	0	-2.7 (-7.9, 2.5)	0	1 (0.7)
Vomiting	2 (5.4)	4 (11.4)	7 (10.1)	4.7 (-5.5, 14.9)*	-1.3 (-14, 11.4)	13 (9.2)
Nasopharyngitis	14 (37.8)	10 (28.6)	18 (26.1)	-11.8 (-30.5, 7)	-2.5 (-20.7, 15.7)	42 (29.8)
Viral rhinitis	0	0	1 (1.4)	1.4 (-1.4, 4.3)	1.4 (-1.4, 4.3)	1 (0.7)
Sinusitis	1 (2.7)	0	1 (1.4)	-1.3 (-7.2, 4.7)	1.4 (-1.4, 4.3)	2 (1.4)
Pharyngitis	3 (8.1)	1 (2.9)	2 (2.9)	-5.2 (-14.9, 4.4)	0 (-6.8, 6.8)	6 (4.3)
Nasopharyngitis	10 (27.0)	6 (17.1)	11 (15.9)	-11.1 (-27.8, 5.6)	-1.2 (-16.4, 14)	27 (19.1)
Pharyngitis streptococcal	1 (2.7)	1 (2.9)	1 (1.4)	-1.3 (-7.2, 4.7)	-1.4 (-7.6, 4.8)	3 (2.1)
Rhinitis	2 (5.4)	2 (5.7)	2 (2.9)	-2.5 (-10.8, 5.8)	-2.8 (-11.5, 5.8)	6 (4.3)
Ear, nose and throat infection	0	1 (2.9)	0	0	-2.9 (-8.4, 2.7)	1 (0.7)
Ear Infection	6 (16.2)	6 (17.1)	9 (13.0)	-3.2 (-17.5, 11.1)	-4.1, (-18.9, 10.7)	21 (14.9)
Otitis externa	1 (2.7)	0	1 (1.4)	-1.3 (-7.2, 4.7)	1.4 (-1.4, 4.3)	2 (1.4)
Ear infection	2 (5.4)	1 (2.9)	2 (2.9)	-2.5 (-10.8, 5.8)	0 (-6.8, 6.8)	5 (3.5)
Otitis media	2 (5.4)	3 (8.6)	5 (7.2)	1.8 (-7.7, 11.4)*	-1.3 (-12.4, 9.8)	10 (7.1)
Otitis media acute	1 (2.7)	1 (2.9)	1 (1.4)	-1.3 (-7.2, 4.7)	-1.4 (-7.6, 4.8)	3 (2.1)
Ear, nose and throat infection	0	1 (2.9)	0	0	-2.9 (-8.4, 2.7)	1 (0.7)
Bronchitis	4 (10.8)	4 (11.4)	5 (7.2)	-3.6 (-15.3, 8.2)	-4.2 (-16.4, 8)	13 (9.2)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool, MAED, and JMP clinical.
* Denotes terms where the risk difference between somapacitan and Norditropin ≥ 1%.

Figure 37. Applicant's Analysis of the Most Frequent Adverse Events by Preferred Term (≥ 5%), Main Period, Trial 4467, SGA Safety Population



%: Percentage, R: Event rate per 100 patient years at risk, MedDRA version 27.0
Only adverse events with an onset after first study intervention and up until visit 7 (week 52), last study contact, or 14 days after last administration, whichever comes first, are included.

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Source: Clinical Trial Report for trial 4467, SGA, Figure 5-21, page 91.

Table 67. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Including *Individual PTs* Withing the Combined Terms, Main Period, Trial 4467, NS Safety Population

OCMQ/GQ Term Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan0.24 mg/kg/week (N=49) n (%)	Risk Difference Somapacitan - Norditropin (%) (95% CI)	Total (N=77) n (%)
Any AE	23 (82.1)	44 (89.8)	7.7 (-8.9, 24.2)	67 (87.0)
Respiratory Tract Infection	8 (28.6)	21 (42.9)	14.3 (-7.4, 36)*	29 (37.7)
Pneumonia	0	3 (6.1)	6.1 (-0.6, 12.8)*	3 (3.9)
Upper respiratory tract infection bacterial	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Influenza like illness	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Respiratory tract infection	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Respiratory syncytial virus infection	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Viral upper respiratory tract infection	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Upper respiratory tract infection	6 (21.4)	10 (20.4)	-1 (-20, 17.9)	16 (20.8)
Respiratory tract infection viral	1 (3.6)	1 (2.0)	-1.5 (-9.5, 6.4)	2 (2.6)
Lower respiratory tract infection	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
Influenza	4 (14.3)	5 (10.2)	-4.1 (-19.6, 11.4)	9 (11.7)
Diarrhea	4 (14.3)	11 (22.4)	8.2 (-9.3, 25.6)*	15 (19.5)
Gastroenteritis	2 (7.1)	7 (14.3)	7.1 (-6.5, 20.8)*	9 (11.7)
Gastroenteritis viral	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Parasitic gastroenteritis	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Diarrhea	2 (7.1)	3 (6.1)	-1 (-12.7, 10.6)	5 (6.5)
Enterocolitis	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
Nasopharyngitis	7 (25.0)	14 (28.6)	3.6 (-16.9, 24)*	21 (27.3)
Nasopharyngitis	1 (3.6)	12 (24.5)	20.9 (7.1, 34.8)*	13 (16.9)
Bacterial infection[1]	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Herpes pharyngitis	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Pharyngotonsillitis	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Pharyngitis streptococcal	1 (3.6)	1 (2.0)	-1.5 (-9.5, 6.4)	2 (2.6)
Pharyngitis	2 (7.1)	2 (4.1)	-3.1 (-14.1, 8)	4 (5.2)
Sinusitis	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
Rhinitis	3 (10.7)	1 (2.0)	-8.7 (-2.8, 3.4)	4 (5.2)
Headache	2 (7.1)	5 (10.2)	3.1 (-9.7, 15.8)*	7 (9.1)
Ear Infection	4 (14.3)	8 (16.3)	2 (-14.5, 18.6)*	12 (15.6)
Otitis externa	0	2 (4.1)	4.1 (-1.5, 9.6)*	2 (2.6)
Otitis media acute	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Otitis media	2 (7.1)	4 (8.2)	1 (-11.2, 13.3)*	6 (7.8)
Ear infection	1 (3.6)	1 (2.0)	-1.5 (-9.5, 6.4)	2 (2.6)
Otitis media chronic	1 (3.6)	1 (2.0)	-1.5 (-9.5, 6.4)	2 (2.6)
Vomiting	3 (10.7)	6 (12.2)	1.5 (-13.1, 16.2)*	9 (11.7)
Gastritis	0	2 (4.1)	4.1 (-1.5, 9.6)*	2 (2.6)
Vomiting	3 (10.7)	4 (8.2)	-2.6 (-16.3, 11.2)	7 (9.1)
Cough	4 (14.3)	7 (14.3)	0 (-16.2, 16.2)	11 (14.3)
Bacterial infection[1]	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Cough	4 (14.3)	6 (12.2)	-2 (-17.9, 13.8)	10 (13.0)

OCMQ/GQ Term Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan0.24 mg/kg/week (N=49) n (%)	Risk Difference Somapacitan - Norditropin (%) (95% CI)	Total (N=77) n (%)
Injection Site Reaction	4 (14.3)	4 (8.2)	-6.1 (-21.2, 8.9)	8 (10.4)
Injection site hemorrhage	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Injection site hematoma	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
Injection site induration	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
Injection site bruising	3 (10.7)	3 (6.1)	-4.6 (-17.9, 8.7)	6 (7.8)
Abdominal Pain	3 (10.7)	1 (2.0)	-8.7 (-20.8, 3.4)	4 (5.2)
Abdominal distension	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Dyspepsia	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
Abdominal pain	2 (7.1)	0	-7.1 (-16.7, 2.4)	2 (2.6)
Wound	3 (10.7)	0	-10.7 (-22.2, 0.7)	3 (3.9)
Pyrexia	7 (25.0)	5 (10.2)	-14.8 (-32.9, 3.3)	12 (15.6)
Febrile convulsion[2]	0	1 (2.0)	2 (-1.9, 6)*	1 (1.3)
Cough[2]	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
COVID-19[2]	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.3)
Pyrexia	5 (17.9)	4 (8.2)	-9.7 (-25.8, 6.4)	9 (11.7)

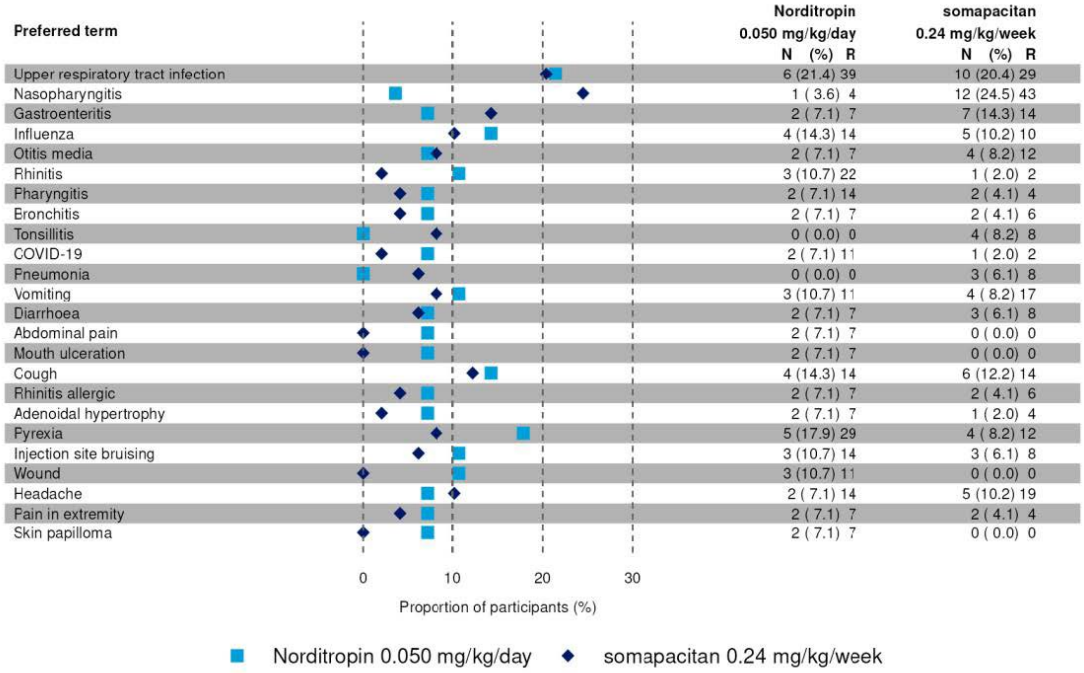
Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool, MAED, and JMP clinical.

* Denotes terms where the risk difference between somapacitan and Norditropin ≥ 1%.

[1] One AE with a PT of bacterial infection was also grouped under the nasopharyngitis and cough OCMQ terms because the reported term for this AE was "common cold, cough bacterial infection".

[2] In addition to being grouped into OCMQ terms of febrile convulsion, cough, and COVID-19, these PTs were also included in the OCMQ term pyrexia as the reported term for each included the words "fever" or "febrile".

Figure 38. Applicant's Analysis of the Most Frequent Adverse Events by Preferred Term (≥ 5%), Main Period, Trial 4467, NS Safety Population



%: Percentage, R: Event rate per 100 patient years at risk, MedDRA version 27.1
Only adverse events with an onset after first study intervention and up until visit 7 (week 52), last study contact, or 14 days after last administration, whichever comes first, are included.

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Source: Clinical Trial Report for trial 4467, NS, Figure 5-20, page 85.

Table 68. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Including Individual PTs Within the Combined Terms, Main Period, Trial 4467, ISS Safety Population

OCMQ/GQ Term Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)	Risk Difference Somapacitan - Norditropin (%) (95% CI)	Total (N=87) n (%)
Any AE	22 (78.6)	47 (79.7)	1.1 (-17.3, 19.4)	69 (79.3)
Ear Infection	2 (7.1)	7 (11.9)	4.7 (-7.9, 17.3)*	9 (10.3)
Otitis media	1 (3.6)	4 (6.8)	3.2 (-6.2, 12.6)*	5 (5.7)
Otitis media acute	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Ear infection	1 (3.6)	2 (3.4)	-0.2 (-8.5, 8.1)	3 (3.4)

OCMQ/GQ Term Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)	Risk Difference Somapacitan - Norditropin (%) (95% CI)	Total (N=87) n (%)
Injection Site Reaction	2 (7.1)	6 (10.2)	3 (-9.2, 15.3)*	8 (9.2)
Application site reaction	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Injection site bruising	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Injection site hematoma	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Injection site hemorrhage	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Injection site urticaria	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Injection site pruritus	1 (3.6)	1 (1.7)	-1.9 (-9.5, 5.7)	2 (2.3)
Injection site pain	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.1)
Respiratory Tract Infection	8 (28.6)	18 (30.5)	1.9 (-18.5, 22.4)*	26 (29.9)
Influenza	1 (3.6)	10 (16.9)	13.4 (1.6, 25.2)*	11 (12.6)
Pneumonia	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Pneumonia bacterial	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Respiratory tract infection viral	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Viral upper respiratory tract infection	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Upper respiratory tract infection bacterial	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.1)
Respiratory tract infection[1]	2 (7.1)	2 (3.4)	-3.8 (-14.4, 6.8)	4 (4.6)
Upper respiratory tract infection[2]	5 (17.9)	4 (6.8)	-11.1 (-26.6, 4.5)	9 (10.3)
Nasopharyngitis	6 (21.4)	13 (22.0)	0.6 (-17.9, 19.1)	19 (21.8)
Pharyngitis streptococcal	0	3 (5.1)	5.1 (-0.5, 10.7)*	3 (3.4)
Sinusitis	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Tracheitis	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Nasopharyngitis	4 (14.3)	9 (15.3)	1 (-14.9, 16.8)*	13 (14.9)
Pharyngitis	1 (3.6)	1 (1.7)	-1.9 (-9.5, 5.7)	2 (2.3)
Rhinitis	1 (3.6)	1 (1.7)	-1.9 (-9.5, 5.7)	2 (2.3)
Headache	3 (10.7)	6 (10.2)	-0.5 (-14.4, 13.3)	9 (10.3)
Cough	3 (10.7)	3 (5.1)	-5.6 (-18.4, 7.1)	6 (6.9)
Cough	2 (7.1)	3 (5.1)	-2.1 (-13.1, 9)	5 (5.7)
Respiratory tract infection[1]	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.1)
Upper respiratory tract infection[2]	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.1)
Vomiting	3 (10.7)	3 (5.1)	-5.6 (-18.4, 7.1)	6 (6.9)
Vomiting	2 (7.1)	3 (5.1)	-2.1 (-13.1, 3)	5 (5.7)
Gastrointestinal infection[3]	1 (3.6)	0	-3.6 (-10.4, 3.3)	1 (1.1)
Diarrhea	7 (25.0)	6 (10.2)	-14.8 (-32.6, 3)	13 (14.9)
Enterobiasis	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Parasitic gastroenteritis	0	1 (1.7)	1.7 (-1.6, 5)*	1 (1.1)
Diarrhea	1 (3.6)	1 (1.7)	-1.9 (-9.5, 5.7)	2 (2.3)
Gastroenteritis viral	3 (10.7)	2 (3.4)	-7.3, (-19.7, 5)	5 (5.7)
Gastroenteritis	4 (14.3)	2 (3.4)	-10.9 (-24.7, 2.9)	6 (6.9)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool, MAED, and JMP clinical.

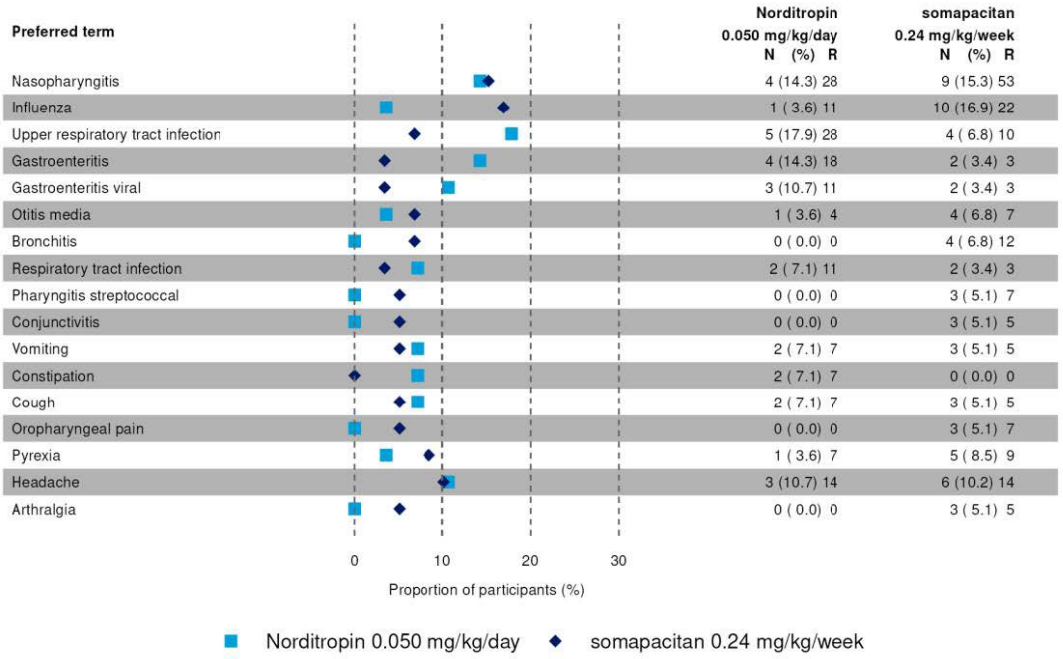
* Denotes terms where the risk difference between somapacitan and Norditropin ≥ 1%

[1] One AE with the PT of respiratory tract infection was also grouped under the pyrexia and cough OCMQ terms because the reported term for this AE included the terms "respiratory tract infection (fever, cough)."

[2] One subject with ISS reported 2 AEs with the PT of upper respiratory tract infection that were also grouped under the cough OCMQ term because the reported terms for these AEs included the terms "upper respiratory tract infection (runny nose, cough)".

[3] This AE of gastrointestinal infection was grouped under the OCMQ term vomiting because the reported term specified an occurrence of "vomiting".

Figure 39. Applicant's Analysis of the Most Frequent Adverse Events by Preferred Term (≥ 5%), Main Period, Trial 4467, ISS Safety Population



%: Percentage, R: Event rate per 100 patient years at risk, MedDRA version 27.0
Only adverse events with an onset after first study intervention and up until visit 7 (week 52), last study contact, or 14 days after last administration, whichever comes first, are included.

nn8640/nn8640-4467iss/csr_wk52_20241118_er
19DEC2024:15:28:59 - faemostfreqsas.R/faemostfreq5sasiss.png

Source: Clinical Trial Report for trial 4467, ISS, Figure 5-21, page 89.

Table 69. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Including Individual PTs Within the Combined Terms, Extension Period, Trial 4467, SGA Safety Population

OCMQ/GQ Term Preferred Term	Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=34) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)	Total (N=140) n (%)
Treatment During Extension Period		0.24 mg/kg/week Somapacitan		
Any AE	20 (54.1)	15 (44.1)	32 (46.4)	67 (47.5)
Respiratory Tract Infection	4 (10.8)	2 (5.9)	9 (13.0)	15 (10.7)
Upper respiratory tract infection	2 (5.4)	1 (2.9)	4 (5.8)	7 (5.0)
Pneumonia	1 (2.7)	0	2 (2.9)	3 (2.1)
Adenoviral upper respiratory infection	0	0	1 (1.4)	1 (0.7)
Atypical pneumonia	0	0	1 (1.4)	1 (0.7)
Metapneumovirus infection	0	1 (2.9)	0	1 (0.7)
Mycoplasma infection	0	0	1 (1.4)	1 (0.7)
Respiratory tract infection bacterial	1 (2.7)	0	0	1 (0.7)
Tracheitis	1 (2.7)	0	0	1 (0.7)
Tracheobronchitis	1 (2.7)	0	0	1 (0.7)

OCMQ/GQ Term Preferred Term	Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=34) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)	Total (N=140) n (%)
Treatment During Extension Period		0.24 mg/kg/week Somapacitan		
Nasopharyngitis	5 (13.5)	4 (11.8)	7 (10.1)	16 (11.4)
Nasopharyngitis	4 (10.8)	4 (11.8)	5 (7.2)	13 (9.3)
Pharyngitis	0	0	1 (1.4)	1 (0.7)
Rhinitis	1 (2.7)	0	0	1 (0.7)
Sinusitis	0	0	1 (1.4)	1 (0.7)
Diarrhea	4 (10.8)	3 (8.8)	4 (5.8)	11 (7.9)
Gastroenteritis	1 (2.7)	2 (5.9)	1 (1.4)	4 (2.9)
Diarrhea	1 (2.7)	1 (2.9)	1 (1.4)	3 (2.1)
Enteritis	1 (2.7)	0	1 (1.4)	2 (1.4)
Anal incontinence	1 (2.7)	0	0	1 (0.7)
Gastroenteritis bacterial	0	0	1 (1.4)	1 (0.7)
Gastroenteritis viral	0	1 (2.9)	0	1 (0.7)
Conjunctivitis	4 (10.8)	1 (2.9)	1 (1.4)	6 (4.3)
Tonsillitis	4 (10.8)	1 (2.9)	1 (1.4)	6 (4.3)
Tonsillitis	3 (8.1)	1 (2.9)	0	4 (2.9)
Tonsillitis bacterial	0	0	1 (1.4)	1 (0.7)
Tonsillitis streptococcal	1 (2.7)	0	0	1 (0.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

Table 70. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Including Individual PTs Within the Combined Terms, Extension Period, Trial 4467, NS Safety Population

OCMQ/GQ Term Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=48) n (%)	Total (N=76) n (%)
Treatment During Extension Period	0.24 mg/kg/week Somapacitan		
Any AE	14 (50)	25 (52.1)	39 (51.3)
Respiratory tract infection	6 (21.4)	5 (10.4)	11 (14.5)
Upper respiratory tract infection	3 (10.7)	2 (4.2)	5 (6.6)
Influenza	2 (7.1)	1 (2.1)	3 (3.9)
Pneumonia	0	3 (6.3)	3 (3.9)
Mycoplasma infection	1 (3.6)	0	1 (1.3)
Pneumonia bacterial	0	1 (2.1)	1 (1.3)
Pneumonia mycoplasmal	0	1 (2.1)	1 (1.3)
Nasopharyngitis	1 (3.6)	5 (10.4)	6 (7.9)
Nasopharyngitis	0	4 (8.3)	4 (5.3)
Pharyngitis	0	1 (2.1)	1 (1.3)
Rhinitis	1 (3.6)	0	1 (1.3)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

Table 71. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Including Individual PTs Within the Combined Terms, Extension Period, Trial 4467, ISS Safety Population

OCMQ/GQ Term Preferred Term	Norditropin 0.050 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=57) n (%)	Total (N=85) n (%)
Treatment During Extension Period	0.24 mg/kg/week Somapacitan		
Any AE	18 (64.3)	27 (47.4)	45 (52.9)
Respiratory Tract Infection	6 (21.4)	5 (8.8)	11 (12.9)
Upper respiratory tract infection	3 (10.7)	3 (5.3)	6 (7.1)
Influenza	1 (3.6)	2 (3.5)	3 (3.5)
Pneumonia bacterial	1 (3.6)	0	1 (1.2)
Respiratory tract infection	1 (3.6)	0	1 (1.2)
Viral upper respiratory tract infection	0	1 (1.8)	1 (1.2)
Nasopharyngitis	3 (10.7)	8 (14)	11 (12.9)
Nasopharyngitis	1 (3.6)	7 (12.3)	8 (9.4)
Rhinitis	2 (7.1)	1 (1.8)	3 (3.5)
Pharyngitis	1 (3.6)	0	1 (1.2)
Pharyngitis streptococcal	0	1 (1.8)	1 (1.2)
Sinusitis	1 (3.6)	0	1 (1.2)
Ear Infection	3 (10.7)	2 (3.5)	5 (5.9)
Otitis media	2 (7.1)	1 (1.8)	3 (3.5)
Ear infection	1 (3.6)	1 (1.8)	2 (2.4)
Pyrexia	3 (10.7)	1 (1.8)	4 (4.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

Table 72. Mean (SD) Hematology Parameters, Main Period, Trial 4467, SGA Safety Population

Treatment		Norditropin 0.035 mg/kg/day (N=37)		Norditropin 0.067 mg/kg/day (N=35)		Somapacitan 0.24 mg/kg/week (N=69)	
Evaluation		Value	Change From baseline	Value	Change From baseline	Value	Change From baseline
Leukocytes (10^9/L)							
Baseline	Mean (SD)	8.6 (2.7)	-	8.3 (2.5)	-	8.8 (2.8)	-
	n		36		34		69
Week 26	Mean (SD)	7.5 (2.5)	-0.8 (3.1)	7.9 (2.1)	-0.4 (2.4)	8 (2.6)	-0.7 (2.9)
	n		36		33		66
Week 52	Mean (SD)	7.7 (2.5)	-0.7 (3.5)	7.2 (1.9)	-0.9 (2)	7.8 (2.4)	-1 (3)
	n		36		32		65
Hematocrit (%)							
Baseline	Mean (SD)	39.2 (3.7)	-	38.8 (2.2)	-	38.2 (2.4)	-
	n		35		33		68
Week 26	Mean (SD)	38.4 (3.2)	-0.6 (2.2)	38.4 (3)	-0.7 (2.2)	37.9 (2.8)	-0.3 (2.1)
	n		36		32		67
Week 52	Mean (SD)	38.8 (3.2)	0.1 (2.2)	38.6 (2.9)	-0.1 (2.4)	38.4 (2.9)	0.4 (2.3)
	n		35		32		63

Treatment		Norditropin 0.035 mg/kg/day (N=37)		Norditropin 0.067 mg/kg/day (N=35)		Somapacitan 0.24 mg/kg/week (N=69)	
Evaluation		Value	Change From baseline	Value	Change From baseline	Value	Change From baseline
Thrombocytes (10^9/L)							
Baseline	Mean (SD)	364.7 (85.6)	-	349.9 (79.2)	-	351.3 (99.2)	-
	n	35		32		69	
Week 26	Mean (SD)	375.5 (97.6)	16.8 (101.9)	357.3 (88.6)	11.5 (80.4)	349.3 (82.1)	-0.5 (81.1)
	n	36		32		66	
Week 52	Mean (SD)	360.8 (78.2)	-3.9 (71.4)	332.4 (63.1)	-16.5 (63.5)	348.4 (85.5)	-6.6 (91.6)
	n	37		31		63	

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data

Table 73. Mean (SD) Hematology Parameters, Main Period, Trial 4467, NS Safety Population

Treatment		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=49)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Leukocytes (10^9/L)					
Baseline	Mean (SD)	7 (2.9)	-	8.1 (2.5)	-
	n		27		47
Week 26	Mean (SD)	6.8 (2.1)	-0.2 (2.5)	7.8 (2.8)	-0.4 (2.9)
	n		26		45
Week 52	Mean (SD)	7.5 (2.5)	0.4 (2.4)	7.1 (2)	-1 (2.2)
	n		27		46
Hematocrit (%)					
Baseline	Mean (SD)	38.2 (2.6)	-	37.5 (2.6)	-
	n		26		47
Week 26	Mean (SD)	38.2 (2.2)	0 (2.2)	38 (2.8)	0.3 (2.5)
	n		24		43
Week 52	Mean (SD)	38.7 (1.9)	0.5 (2)	38.6 (2.2)	1 (1.9)
	n		27		45
Thrombocytes (10^9/L)					
Baseline	Mean (SD)	257.6 (66.2)	-	300.4 (98)	-
	n		27		48
Week 26	Mean (SD)	278 (78.9)	24.4 (55)	284.7 (88.3)	-22 (54.1)
	n		25		45
Week 52	Mean (SD)	266.6 (92)	14.3 (66.1)	282.8 (82.7)	-18.8 (5.9)
	n		27		45

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data

Table 74. Mean (SD) Coagulation Parameters, Main Period, Trial 4467, NS Safety Population

Treatment		Norditropin 0.05 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=49)
Prothrombin time (s)			
Week 4	Mean (SD)	12.4 (1)	12.9 (1.2)
	n	25	39

Treatment		Norditropin 0.05 mg/kg/day (N=28)	Somapacitan 0.24 mg/kg/week (N=49)
Week 39	Mean (SD)	12.4 (1.1)	12.6 (1.3)
	n	23	36
Partial thromboplastin time (s)			
Week 4	Mean (SD)	36.8 (7.1)	36.6 (7.4)
	n	25	40
Week 39	Mean (SD)	37.8 (5.5)	37.2 (5)
	n	23	25

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Per protocol, pretreatment values for coagulation parameters were not evaluated. Week 4 was the first visit where these were assessed.
n = number of subjects with available data

Table 75. Mean (SD) Hematology Parameters, Main Period, Trial 4467, ISS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=59)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Leukocytes (10^9/L)					
Baseline	Mean (SD)	7.1 (2.5)	-	7.3 (2)	-
	n		25		59
Week 26	Mean (SD)	6.9 (2.2)	-0.3 (2.3)	7.9 (3.3)	0.8 (3.1)
	n		28		57
Week 52	Mean (SD)	6.8 (1.9)	-0.4 (2.6)	6.9 (1.9)	-0.3 (2.3)
	n		28		56
Hematocrit (%)					
Baseline	Mean (SD)	38.8 (2.1)	-	38.3 (2.4)	-
	n		25		59
Week 26	Mean (SD)	38.5 (1.7)	-0.4 (2)	38.8 (2.6)	0.6 (2.2)
	n		28		56
Week 52	Mean (SD)	38.8 (1.8)	-0.1 (2.3)	39.3 (2.6)	0.8 (2.2)
	n		27		52
Thrombocytes (10^9/L)					
Baseline	Mean (SD)	330.45 (67.9)	-	347.6 (94.2)	-
	n		26		59
Week 26	Mean (SD)	333.8 (62)	6.6 (55.4)	334.2 (95.2)	-13.8 (89.1)
	n		28		57
Week 52	Mean (SD)	331.6 (62.6)	10.1 (73.4)	339.2 (82.4)	-6.9 (79.6)
	n		27		53

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n = number of subjects with available data

Table 76. Number (%) of Subjects With Hematology Parameters Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, SGA Safety Population

Parameter		Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)
Leukocytes				
Total	n	37	34	69
	Low (< LLN)	1 (2.7)	3 (8.8)	5 (7.2)
	High (> ULN)	3 (8.1)	2 (5.7)	4 (5.8)
Hematocrit				
Total	n	37	34	69
	Low (< LLN)	0	0	0
	High (> ULN)	4 (10.8)	3 (8.8)	4 (5.8)
Thrombocytes				
Total	n	37	33	68
	Low (< LLN)	0	0	0
	High (> ULN)	10 (27)	6 (18.2)	9 (13.2)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data

Table 77. Number (%) of Subjects With Hematology Parameters Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, NS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Leukocytes			
Total	n	28	47
	Low (< LLN)	5 (17.9)	9 (19.1)
	High (> ULN)	1 (3.6)	3 (6.4)
Hematocrit			
Total	n	28	47
	Low (< LLN)	0	0
	High (> ULN)	1 (3.6)	2 (4.3)
Thrombocytes			
Total	n	28	47
	Low (< LLN)	2 (7.1)	2 (4.3)
	High (> ULN)	2 (7.1)	1 (2.1)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 78. Number (%) of Subjects With Coagulation Parameters Outside of Normal Range, Main Period, Trial 4467, NS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Prothrombin time			
Week 4	Low (< LLN)	0	1 (2.6%)
	High (> ULN)	1 (4%)	3 (7.7%)
	n	25	39
Week 39	Low (< LLN)	0	0
	High (> ULN)	2 (8.7%)	2 (5.6%)
	n	23	36
Partial thromboplastin time			
Week 4	Low (< LLN)	0	0
	High (> ULN)	5 (20%)	11 (27.5%)
	n	25	40
Week 39	Low (< LLN)	0	0
	High (> ULN)	6 (26.1%)	10 (27.8%)
	n	23	36

Source: Data compiled from the Clinical Trial Report for trial 4467 NS, Table 8.3.5.65, page 591.
Per protocol, pretreatment values for coagulation parameters were not evaluated. Week 4 was the first visit where these were assessed.
Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 79. Number (%) of Subjects With Hematology Parameters Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, ISS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)
Leukocytes			
Total	n	28	58
	Low (< LLN)	3 (10.7)	6 (10.2)
	High (> ULN)	0	7 (11.9)
Hematocrit			
Total	n	28	58
	Low (< LLN)	0	1 (1.7)
	High (> ULN)	0	5 (8.6)
Thrombocytes			
Total	n	28	58
	Low (< LLN)	0	0
	High (> ULN)	2 (7.1)	9 (15.5)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 80. Mean (SD) Lipid Parameters, Main Period, Trial 4467, SGA Safety Population

		Norditropin 0.035 mg/kg/day (N=37)		Norditropin 0.067 mg/kg/day (N=35)		Somapacitan 0.24 mg/kg/week (N=69)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Cholesterol (mg/dL)							
Baseline	Mean (SD)	168 (33.2)	-	165.4 (25.7)	-	159.7 (28.3)	-
	n		37		35		67
Week 26	Mean (SD)	170.2 (33.6)	3.4 (22.9)	160.6 (23.4)	-5.5 (20.1)	158.1 (28.3)	-1 (24.2)
	n		37		34		66
Week 52	Mean (SD)	162.4 (29.1)	-4.8 (22.1)	164.4 (26.8)	-1.6 (25.7)	162.3 (24)	2.8 (21.3)
	n		36		34		69
Low density lipoprotein (mg/dL)							
Baseline	Mean (SD)	96.8 (29.6)	-	92.4 (20.1)	-	89.3 (21.8)	-
	n		37		35		67
Week 26	Mean (SD)	99.5 (30.3)	2.8 (16.9)	89.2 (20.9)	-3.6 (15.8)	92 (22.3)	3.4 (20)
	n		37		34		66
Week 52	Mean (SD)	90.3 (28.4)	-5.9 (20.3)	89.8 (22.6)	-2.9 (17.7)	94.8 (20.9)	5.4 (16.7)
	n		36		34		69
High density lipoprotein (mg/dL)							
Baseline	Mean (SD)	54.3 (10.6)	-	57.5 (11)	-	53.8 (13.5)	-
	n		37		35		68
Week 26	Mean (SD)	53 (11.7)	-1.1 (10)	56.4 (13.1)	-1 (8.2)	49.7 (12.2)	-4.3 (11)
	n		37		35		67
Week 52	Mean (SD)	51.2 (12.6)	-2.9 (12.9)	60 (12.3)	2.4 (11.3)	52.4 (11.1)	-1.3 (11.1)
	n		36		34		69
Triglycerides (mg/dL)							
Baseline	Mean (SD)	37.1 (20.4)	-	33.8 (14.9)	-	36.1 (19.8)	-
	n		37		35		67
Week 26	Mean (SD)	91.5 (37.8)	6.6 (52.5)	73 (23.3)	-3 (41.1)	81.2 (31.2)	-1.5 (41.2)
	n		37		34		66
Week 52	Mean (SD)	104.9 (71)	20.3 (78.3)	72.6 (27.5)	-5.6 (41.5)	74.7 (26.3)	-7.9 (43.2)
	n		36		34		69

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided cholesterol, lipoproteins, and triglycerides in units of mmol/L.
To provide cholesterol and lipoproteins in mg/dL in this table, this reviewer multiplied the mmol/L value by 38.67.
To provide triglycerides in mg/dL in this table, this reviewer multiplied the mmol/L value by 88.57.
n = number of subjects with available data

Table 81. Mean (SD) Lipid Parameters, Main Period, Trial 4467, NS Safety Population

Treatment		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=49)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Cholesterol (mg/dL)					
Baseline	Mean (SD)	165.7 (30.2)	-	155.7 (29)	-
	n		28		49
Week 26	Mean (SD)	163.5 (33.9)	-0.8 (25.3)	157 (35.4)	0.6 (24.6)
	n		26		46
Week 52	Mean (SD)	159 (31.7)	-7.6 (24.8)	156 (31.8)	0.8 (22.9)
	n		27		48
Low density lipoprotein (mg/dL)					
Baseline	Mean (SD)	99.9 (26)	-	90.3 (25.4)	-
	n		27		46
Week 26	Mean (SD)	100.6 (30.8)	1.1 (21.8)	90.6 (33.8)	0.3 (25)
	n		26		46
Week 52	Mean (SD)	96.1 (28)	-4.9 (20)	93.4 (27.7)	2.6 (19.6)
	n		26		48
High density lipoprotein (mg/dL)					
Baseline	Mean (SD)	47.7 (10.2)	-	47.8 (14.7)	-
	n		28		48
Week 26	Mean (SD)	46.8 (9.5)	-0.6 (8.6)	48.5 (13.1)	0.3 (10.8)
	n		26		46
Week 52	Mean (SD)	45.3 (9.8)	-2 (10.7)	47.5 (13.4)	-0.1 (9.7)
	n		27		48
Triglycerides (mg/dL)					
Baseline	Mean (SD)	86.1 (42.1)	-	94.2 (72.4)	-
	n		27		47
Week 26	Mean (SD)	81.2 (30.2)	-6.8 (43.2)	89.1 (63.1)	-4.5 (75.1)
	n		26		46
Week 52	Mean (SD)	85.2 (29.2)	-1.2 (41.7)	75.2 (30)	-17.5 (70.1)
	n		26		48

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided cholesterol, lipoproteins, and triglycerides in units of mmol/L.
To provide cholesterol and lipoproteins in mg/dL in this table, this reviewer multiplied the mmol/L value by 38.67.
To provide triglycerides in mg/dL in this table, this reviewer multiplied the mmol/L value by 88.57.
n = number of subjects with available data

Table 82. Mean (SD) Lipid Parameters, Main Period, Trial 4467, ISS Safety Population

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=59)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Cholesterol (mg/dL)					
Baseline	Mean (SD)	166.7 (32.9)	-	170.1 (36.9)	-
	n		28		57
Week 26	Mean (SD)	166 (31.2)	-0.7 (17.5)	169.3 (27.6)	-1.3 (27.8)
	n		28		58
Week 52	Mean (SD)	161 (34)	-5.7 (16.1)	171.6 (30)	1.2 (22.4)
	n		28		56

		Norditropin 0.05 mg/kg/day (N=28)		Somapacitan 0.24 mg/kg/week (N=59)	
Evaluation		**Value**	**Change From Baseline**	**Value**	**Change From Baseline**
Low density lipoprotein (mg/dL)					
Baseline	Mean (SD)	92.5 (29.3)	-	96.6 (34.4)	-
	n		28		57
Week 26	Mean (SD)	93.1 (26.3)	0.6 (16.1)	98.5 (25.1)	1.6 (23.7)
	n		28		58
Week 52	Mean (SD)	90.5 (28)	-2 (14.6)	102 (28)	5.6 (16.5)
	n		28		56
High density lipoprotein (mg/dL)					
Baseline	Mean (SD)	57.5 (14.1)	-	55.2 (11.3)	-
	n		28		57
Week 26	Mean (SD)	59.9 (12.2)	2.5 (11)	52.6 (11.4)	-2.2 (10)
	n		28		58
Week 52	Mean (SD)	56.3 (13.3)	-1.2 (14.1)	53.2 (12.2)	-1.9 (10.1)
	n		28		56
Triglycerides (mg/dL)					
Baseline	Mean (SD)	83.3 (47.8)	-	89.9 (50.9)	-
	n		28		58
Week 26	Mean (SD)	64.6 (20.2)	-18.7 (45.8)	91.4 (37.3)[1]	-1.3 (60.3)[1]
	n		28		58
Week 52	Mean (SD)	70.5 (24.8)	-12.8 (49)	81.8 (33.1)[1]	-12.2 (51.8)[1]
	n		28		56

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided cholesterol, lipoproteins, and triglycerides in units of mmol/L.
To provide cholesterol and lipoproteins in mg/dL in this table, this reviewer multiplied the mmol/L value by 38.67.
To provide triglycerides in mg/dL in this table, this reviewer multiplied the mmol/L value by 88.57.
[1] One subject (ID (b) (6)) did not have baseline values recorded but did have values recorded at the Weeks 26 and 52 visits, which are included in the mean (SD) values at Weeks 26 and 52. However, without a baseline value, the values for change from baseline in this table do not include this subject. This likely contributes to the discrepancies seen in the mean changes from baseline, compared to the mean values at each visit, for some of these values, especially for triglycerides: this subject had elevated triglycerides (ULN: 89.5 mg/dL) at Week 26 (235.6 mg/dL) and Week 52 (214.3 mg/dL), and it is unclear whether these values were also elevated at baseline. Not including this subject in this table, mean (SD) triglycerides would be 88.7 (32.7) mg/dL at Week 26 and 79.5 (28.2) mg/dL at Week 52.
n = number of subjects with available data

Table 83. Number (%) of Subjects With Lipid Parameters That Shift to Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, SGA Safety Population

		Norditropin 0.035 mg/kg/day (N=37)	Norditropin 0.067 mg/kg/day (N=35)	Somapacitan 0.24 mg/kg/week (N=69)
Parameter		**n (%)**	**n (%)**	**n (%)**
Cholesterol				
Total	n	29	21	47
	Low (< LLN)	0	0	0
	High (> ULN)	7 (36.8)	6 (28.6)	13 (27.7)
Baseline	n	37	35	66
	Low (< LLN)	0	0	0
	High (> ULN)	18 (48.6)	14 (40)	19 (28.8)
Week 26	n	19	20	45
	High (> ULN)	4 (21.1)	3 (15)	9 (20)

Parameter		Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)
Week 52	n	19	20	47
	High (> ULN)	6 (31.6)	4 (20)	11 (23.4)
Low density lipoprotein				
Total	n	24	26	56
	Low (< LLN)	0	0	0
	High (> ULN)	5 (20.8)	4 (15.4)	13 (23.2)
Baseline	n	37	35	66
	Low (< LLN)	0	0	0
	High (> ULN)	13 (35.1)	9 (25.7)	10 (15.2)
Week 26	n	24	25	54
	High (> ULN)	4 (16.6)	2 (8)	6 (11.1)
Week 52	n	24	25	56
	High (> ULN)	2 (8.3)	3 (12)	11 (19.6)
High density lipoprotein				
Total	n	30	31	49
	Low (< LLN)	11 (26.7)	9 (29)	18 (36.7)
	High (> ULN)	0	0	0
Baseline	n	37	35	67
	Low (< LLN)	7 (18.9)	4 (11.4)	18 (26.9)
	High (> ULN)	0	0	0
Week 26	n	30	31	49
	Low (< LLN)	8 (26.7)	6 (19.4)	14 (28.6)
Week 52	n	29	30	49
	Low (< LLN)	7 (24.1)	4 (13.3)	11 (22.4)
Triglycerides				
Total	n	20	21	32
	Low (< LLN)	0	0	0
	High (> ULN)	14 (70)	11 (52.4)	20 (62.5)
Baseline	n	37	35	66
	Low (< LLN)	0	0	0
	High (> ULN)	17 (45.9)	14 (40)	34 (51.5)
Week 26	n	18	21	31
	High (> ULN)	9 (50)	9 (42.9)	11 (35.5)
Week 52	n	20	20	32
	High (> ULN)	10 (50)	7 (35)	15 (46.9)

Source: Compiled from data present in the Applicant's response to information request, submitted October 01, 2025, Appendix 1, pages 10 through 30.

LLN = lower limit of normal; ULN = upper limit of normal.

Total: n = number of subjects in the trial with available data who normal values at baseline. "Low" and "High" represents the number (proportion) of subjects with a normal parameter at baseline with available data that shifted to values < LLN and > ULN, respectively, at least once after starting treatment in the trial.

Baseline: n = number of subjects with available baseline data. "Low" and "High" represent the number (proportion) of subjects with available data who have values < LLN or > ULN, respectively, at baseline.

Weeks 26 and 52: n = number of subjects at each visit with available data who had normal values at baseline. "Low" and "High" represents the number (proportion) of subjects with a normal parameter at baseline with available data that shifted to values < LLN and > ULN, respectively, at that visit.

Table 84. Number (%) of Subjects With Lipid Parameters That Shift to Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, NS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Cholesterol			
Total	n	16	35
	Low (< LLN)	0	0
	High (> ULN)	5 (31.3)	8 (22.9)
Baseline	n	28	48
	Low (< LLN)	0	0
	High (> ULN)	12 (42.9)	13 (27.1)
Week 26	n	16	33
	High (> ULN)	4 (25)	4 (12.1)
Week 52	n	15	33
	High (> ULN)	4 (26.7)	7 (21.2)
Low density lipoprotein			
Total	n	18	39
	Low (< LLN)	0	1 (2.6)
	High (> ULN)	6 (33.3)	5 (12.8)
Baseline	n	27	45
	Low (< LLN)	0	0
	High (> ULN)	9 (33.3)	6 (13.3)
Week 26	n	18	38
	Low (< LLN)	0	1 (2.6)
	High (> ULN)	6 (33.3)	1 (2.6)
Week 52	n	16	37
	Low (< LLN)	0	0
	High (> ULN)	4 (25)	5 (13.5)
High density lipoprotein			
Total	n	13	24
	Low (< LLN)	6 (46.2)	10 (41.7)
	High (> ULN)	0	0
Baseline	n	28	47
	Low (< LLN)	15 (53.6)	23 (48.9)
	High (> ULN)	0	0
Week 26	n	12	24
	Low (< LLN)	3 (25)	7 (29.2)
Week 52	n	12	23
	Low (< LLN)	4 (33.3)	7 (30.4)

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Triglycerides			
Total	n	15	25
	Low (< LLN)	0	0
	High (> ULN)	8 (53.3)	10 (40)
Baseline	n	27	46
	Low (< LLN)	0	0
	High (> ULN)	12 (44.4)	21 (45.7)
Week 26	n	14	25
	High (> ULN)	7 (50)	8 (32)
Week 52	n	14	23
	High (> ULN)	6 (42.9)	5 (21.7)

Source: Compiled from data present in the Applicant's response to information request, submitted October 01, 2025, Appendix 2, pages 31 through 47.
LLN = lower limit of normal; ULN = upper limit of normal.
Total: n = number of subjects in the trial with available data who normal values at baseline. "Low" and "High" represents the number (proportion) of subjects with a normal parameter at baseline with available data that shifted to values < LLN and > ULN, respectively, at least once after starting treatment in the trial.
Baseline: n = number of subjects with available baseline data. "Low" and "High" represent the number (proportion) of subjects with available data who have values < LLN or > ULN, respectively, at baseline.
Weeks 26 and 52: n = number of subjects at each visit with available data who had normal values at baseline. "Low" and "High" represents the number (proportion) of subjects with a normal parameter at baseline with available data that shifted to values < LLN and > ULN, respectively, at that visit.

Table 85. Number (%) of Subjects With Lipid Parameters That Shift to Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, ISS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)
Cholesterol			
Total	n	16	29
	Low (< LLN)	0	0
	High (> ULN)	4 (25)	8 (27.6)
Baseline	n	28	56
	Low (< LLN)	0	0
	High (> ULN)	12 (42.9)	27 (48.2)
Week 26	n	16	29
	High (> ULN)	2 (12.5)	4 (13.8)
Week 52	n	15	28
	High (> ULN)	3 (20)	4 (14.3)
Low density lipoprotein			
Total	n	24	40
	Low (< LLN)	0	0
	High (> ULN)	4 (16.7)	7 (17.5)
Baseline	n	28	56
	Low (< LLN)	0	0
	High (> ULN)	4 (14.3)	16 (28.6)
Week 26	n	24	40
	High (> ULN)	3 (12.5)	3 (7.5)

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)
Week 52	n	23	39
	High (> ULN)	1 (4.3)	6 (15.4)
High density lipoprotein			
Total	n	23	46
	Low (< LLN)	3 (13)	14 (30.4)
	High (> ULN)	0	0
Baseline	n	28	56
	Low (< LLN)	5 (17.9)	10 (17.9)
	High (> ULN)	0	0
Week 26	n	23	46
	Low (< LLN)	2 (8.7)	8 (17.4)
Week 52	n	22	44
	Low (< LLN)	2 (9.1)	8 (18.2)
Triglycerides			
Total	n	18	29
	Low (< LLN)	0	0
	High (> ULN)	6 (35.3)	18 (62.1)
Baseline	n	28	57
	Low (< LLN)	0	0
	High (> ULN)	11 (39.3)	28 (49.1)
Week 26	n	17	29
	High (> ULN)	2 (11.8)	13 (44.8)
Week 52	n	16	27
	High (> ULN)	5 (31.3)	9 (33.3)

Source: Compiled from data present in the Applicant's response to information request, submitted October 01, 2025, Appendix 3, pages 48 through 64.
LLN = lower limit of normal; ULN = upper limit of normal.
Total: n = number of subjects in the trial with available data who normal values at baseline. "Low" and "High" represents the number (proportion) of subjects with a normal parameter at baseline with available data that shifted to values < LLN and > ULN, respectively, at least once after starting treatment in the trial.
Baseline: n = number of subjects with available baseline data. "Low" and "High" represent the number (proportion) of subjects with available data who have values < LLN or > ULN, respectively, at baseline.
Weeks 26 and 52: n = number of subjects at each visit with available data who had normal values at baseline. "Low" and "High" represents the number (proportion) of subjects with a normal parameter at baseline with available data that shifted to values < LLN and > ULN, respectively, at that visit.

Table 86. Number (%) of Subjects With Glucose Metabolism Parameters Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, SGA Safety Population

Parameter		Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)
Fasting glucose				
Total	n	37	35	69
	Low (< LLN)	1 (2.7)	0	0
	High (> ULN)	3 (8.1)	1 (2.9)	6 (8.7)
Week 26	n	37	35	69
	Low (< LLN)	0	0	0
	High (> ULN)	3 (8.1)	1 (2.9)	5 (7.2)
Week 52	n	37	34	65
	Low (< LLN)	1 (2.7)	0	0
	High (> ULN)	1 (2.7)	0	1 (1.4)
HbA1c				
Total	n	37	35	69
	Low (< LLN)	0	0	0
	High (> ULN)	0	0	0
Fasting insulin				
Total	n	37	35	68
	Low (< LLN)	0	1 (2.9)	1 (1.5)
	High (> ULN)	0	0	1 (1.5)
Week 26	n	36	34	67
	Low (< LLN)	0	1 (2.9)	0
	High (> ULN)	0	0	1 (1.5)
Week 52	n	36	34	67
	Low (< LLN)	0	0	1 (1.5)
	High (> ULN)	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 87. Number (%) of Subjects With Glucose Metabolism Parameters Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, NS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Fasting glucose			
Total	n	28	47
	Low (< LLN)	0	0
	High (> ULN)	2 (7.1)	4 (8.5)
Week 26	n	28	45
	Low (< LLN)	0	0
	High (> ULN)	2 (7.1)	3 (6.7)
Week 52	n	27	47
	Low (< LLN)	0	0
	High (> ULN)	1 (3.7)	1 (2.1)

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
HbA1c			
Total	n	28	47
	Low (< LLN)	1 (3.6)	0
	High (> ULN)	0	0
Week 26	n	28	46
	Low (< LLN)	1 (3.6)	0
	High (> ULN)	0	0
Week 52	n	27	47
	Low (< LLN)	1 (3.7)	0
	High (> ULN)	0	0
Fasting insulin			
Total	n	28	48
	Low (< LLN)	0	0
	High (> ULN)	0	1 (2)
Week 26	n	28	46
	Low (< LLN)	0	0
	High (> ULN)	0	1 (2.2)
Week 52	n	27	48
	Low (< LLN)	0	0
	High (> ULN)	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 88. Number (%) of Subjects With Glucose Metabolism Parameters Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, ISS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)
Fasting glucose			
Total	n	28	58
	Low (< LLN)	0	0
	High (> ULN)	1 (3.6)	3 (5.2)
Week 26	n	28	58
	Low (< LLN)	0	0
	High (> ULN)	1 (3.6)	2 (3.4)
Week 52	n	28	55
	Low (< LLN)	0	0
	High (> ULN)	0	1 (1.8)
HbA1c			
Total	n	28	58
	Low (< LLN)	0	0
	High (> ULN)	0	0

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)
Fasting insulin			
Total	n	28	58
	Low (< LLN)	2 (7.1)	0
	High (> ULN)	0	0
Week 26	n	28	58
	Low (< LLN)	2 (7.1)	
	High (> ULN)	0	0
Week 52	n	27	57
	Low (< LLN)	2 (7.4)	0
	High (> ULN)	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 89. Number (%) of Subjects With Alkaline Phosphatase Levels Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, SGA Safety Population

Parameter		Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)
Alkaline phosphatase				
Total	n	37	35	69
	Low (< LLN)	0	0	0
	High (> ULN)	30 (81.1)	24 (68.6)	42 (60.9)
Week 26	n	37	34	66
	Low (< LLN)	0	0	0
	High (> ULN)	27 (56.8)	19 (55.9)	29 (43.9)
Week 52	n	36	34	69
	Low (< LLN)	0	0	0
	High (> ULN)	24 (66.7)	19 (55.9)	36 (52.2)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 90. Number (%) of Subjects With Alkaline Phosphatase Levels Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, NS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Alkaline phosphatase			
Total	n	28	49
	Low (< LLN)	0	0
	High (> ULN)	4 (14.3)	12 (24.5)
Week 26	n	26	46
	Low (< LLN)	0	0
	High (> ULN)	1 (3.8)	10 (21.7)

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Week 52	n	27	48
	Low (< LLN)	0	0
	High (> ULN)	3 (11.1)	9 (18.8)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 91. Number (%) of Subjects With Alkaline Phosphatase Levels Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, ISS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)
Alkaline phosphatase			
Total	n	28	59
	Low (< LLN)	0	0
	High (> ULN)	14 (50)	34 (57.6)
Week 26	n	28	58
	Low (< LLN)	0	0
	High (> ULN)	12 (42.9)	27 (46.6)
Week 52	n	28	56
	Low (< LLN)	0	0
	High (> ULN)	10 (35.7)	26 (46.4)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 92. Number (%) of Subjects With Phosphate Levels Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Trial 4467, SGA Safety Population

Parameter		Norditropin 0.035 mg/kg/day (N=37) n (%)	Norditropin 0.067 mg/kg/day (N=35) n (%)	Somapacitan 0.24 mg/kg/week (N=69) n (%)
Phosphate				
Total	n	37	35	69
	Low (< LLN)	0	1 (2.9)	0
	High (> ULN)	17 (45.9)	25 (71.4)	50 (72.5)
Week 26	n	37	34	66
	Low (< LLN)	0	1 (2.9)	0
	High (> ULN)	13 (35.1)	17 (50)	30 (45.5)
Week 52	n	36	34	69
	Low (< LLN)	0	1 (2.9)	0
	High (> ULN)	12 (33.3)	17 (50)	44 (63.8)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 93. Number (%) of Subjects With Phosphate Levels Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, NS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=49) n (%)
Phosphate			
Total	n	28	49
	Low (< LLN)	0	0
	High (> ULN)	11 (39.3)	35 (71.4)
Week 26	n	26	46
	Low (< LLN)	0	0
	High (> ULN)	7 (26.9)	21 (45.7)
Week 52	n	27	48
	Low (< LLN)	0	0
	High (> ULN)	8 (29.6)	31 (64.6)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 94. Number (%) of Subjects With Phosphate Levels Outside of Normal Range After Initiation of Norditropin or Somapacitan Therapy, Main Period, Trial 4467, ISS Safety Population

Parameter		Norditropin 0.05 mg/kg/day (N=28) n (%)	Somapacitan 0.24 mg/kg/week (N=59) n (%)
Phosphate			
Total	n	28	59
	Low (< LLN)	1 (3.6)	0
	High (> ULN)	20 (71.4)	44 (74.6)
Week 26	n	28	58
	Low (< LLN)	1 (3.6)	0
	High (> ULN)	14 (50)	29 (50)
Week 52	n	28	56
	Low (< LLN)	1 (3.6)	0
	High (> ULN)	17 (60.7)	38 (67.9)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 95. Mean (SD) IGF-1 SDS, SGA Population, Trial 4467, Main Period

Treatment		0.035 mg/kg/day Norditropin (N=37)	0.067 mg/kg/day Norditropin (N=35)	0.24 mg/kg/week Somapacitan (N=69)
IGF-1 SDS				
Baseline	Mean (SD)	-0.6 (1.2)	-0.5 (1.1)	-0.5 (1.2)
	n	37	35	69
Week 4	Mean (SD)	0.8 (1.4)	1.5 (1.4)	1.4 (1.5)
	n	37	35	69
Week 13	Mean (SD)	0.9 (1.2)	1.9 (1.3)	0.5 (1.2)
	n	37	34	68

Treatment		0.035 mg/kg/day Norditropin (N=37)	0.067 mg/kg/day Norditropin (N=35)	0.24 mg/kg/week Somapacitan (N=69)
Week 26	Mean (SD)	1.2 (1.5)	1.9 (1.4)	2.9 (1.4)
	n	36	35	67
Week 39	Mean (SD)	1.2 (1.3)	1.9 (1.5)	1 (1.4)
	n	37	35	69
Week 52	Mean (SD)	1.1 (1.3)	2 (1.4)	1.9 (1.2)
	n	36	35	69

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data

Table 96. Mean (SD) IGF-1 SDS, NS Population, Trial 4467, Main Period

Treatment		0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=49)
IGF-1 SDS			
Baseline	Mean (SD)	-1.5 (0.8)	-1.3 (1.1)
	n	28	48
Week 4	Mean (SD)	-0.2 (0.9)	0.4 (1.3)
	n	28	48
Week 13	Mean (SD)	0.1 (1.1)	-0.1 (1.3)
	n	27	49
Week 26	Mean (SD)	0.2 (1)	1.9 (1.6)
	n	28	47
Week 39	Mean (SD)	0.1 (1)	0.2 (1.3)
	n	27	48
Week 52	Mean (SD)	0.2 (1.1)	1 (1.3)
	n	28	48

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data

Table 97. Mean (SD) IGF-1 SDS, ISS Population, Trial 4467, Main Period

Treatment		0.05 mg/kg/day Norditropin (N=28)	0.24 mg/kg/week Somapacitan (N=59)
IGF-1 SDS			
Baseline	Mean (SD)	-1 (0.8)	-0.9 (0.9)
	n	28	58
Week 4	Mean (SD)	0.8 (1)	1.3 (1.3)
	n	28	59
Week 13	Mean (SD)	1 (1)	0.3 (1.2)
	n	27	58
Week 26	Mean (SD)	0.9 (0.9)	2.4 (1.3)
	n	28	58
Week 39	Mean (SD)	1.4 (1.1)	0.8 (1.2)
	n	28	55
Week 52	Mean (SD)	1.3 (1.1)	1.6 (1.3)
	n	28	57

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n = number of subjects with available data

Table 98. Adverse Events Reported by Subjects in the SGA Population of Trial 4467 While IGF-1 > 3 SDS on at Least Two Consecutive Visits

Adverse Event	0.035 mg/kg/day Norditropin (N=37) n (%)	0.067 mg/kg/day Norditropin (N=35) n (%)	0.24 mg/kg/week Somapacitan (N=69) n (%)
IGF-1 > 3 SDS for two or more consecutive visits	3 (8.1)	9 (25.7)	6 (8.7)
Any AE in subjects while IGF-1 >3 for two or more consecutive visits	1 (2.7)	8 (22.9)	4 (5.8)
Nasopharyngitis	1 (2.7)	3 (8.6)	0
Upper respiratory tract infection	0	2 (5.7)	1 (1.4)
Cough	0	1 (2.9)	1 (1.4)
Aspartate aminotransferase increased	0	0	1 (1.4)
Alanine aminotransferase increased	0	0	1 (1.4)
Rash	0	0	1 (1.4)
Angular cheilitis	0	0	1 (1.4)
Diarrhea	0	0	1 (1.4)
Pharyngitis	0	1 (2.9)	0
Arthralgia	0	1 (2.9)	0
Hordeolum	0	1 (2.9)	0
Rhinorrhea	0	1 (2.9)	0
Rhinitis	0	1 (2.9)	0
Viral Infection	0	1 (2.9)	0
Arthropod bite	0	1 (2.9)	0
Abdominal pain	0	1 (2.9)	0
Influenza	0	1 (2.9)	0
Scarlet fever	0	1 (2.9)	0
Pyrexia	0	1 (2.9)	0
Conjunctivitis	0	1 (2.9)	0
Vomiting	0	1 (2.9)	0
Eczema	0	1 (2.9)	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical, and the Clinical Trial Report for trial 4467, SGA population, Appendix 9.2.7.14, pages 90 to 97.

Table 99. Adverse Events Reported by Subjects in the NS Population of Trial 4467 While IGF-1 > 3 SDS on at Least Two Consecutive Visits

Treatment	0.050 mg/kg/day Norditropin (N=28) n (%)	0.24 mg/kg/week Somapacitan (N=59) n (%)
IGF-1 > 3 SDS for two or more consecutive visits	1 (3.6)	4 (6.8)
Any AE in subjects while IGF-1 >3 for two or more consecutive visits	1 (3.6)	4 (6.8)
Insulin-like growth factor 1 increased	0	1 (1.7)
Bacterial pneumonia	0	1 (1.7)
Pain in extremity	0	1 (1.7)
Influenza	0	1 (1.7)
Viral infection	0	1 (1.7)
Bronchitis	0	1 (1.7)
Respiratory tract infection	0	1 (1.7)
Upper respiratory tract infection	1 (3.6)	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical, and the Clinical Trial Report for trial 4467, ISS population, Appendix 9.2.7.14, pages 55 to 57.

Table 100. The Number (%) of Subjects, by Sex, Reporting AEs, Main Period, Trial 4467, SGA Safety Population

Sex	Norditropin 0.035 mg/kg/day	Norditropin 0.067 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
Male				
Number of subjects	17	17	35	69
Any AEs	15 (88.2%)	14 (82.4%)	30 (85.7%)	59 (85.5%)
Serious AEs	1 (5.8%)	4 (23.5%)	2 (5.7%)	7 (10.1%)
Treatment discontinued due to AEs	1 (5.8%)[1]	0	0	1 (1.4%)[1]
Female				
Number of subjects	20	18	34	72
Any AEs	17 (85%)	14 (77.8%)	30 (88.2%)	61 (84.7%)
Serious AEs	2 (10%)	0	1 (2.9%)	3 (4.2%)
Treatment discontinued due to AEs	0	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical
[1] While this subject did not discontinue treatment until the Extension Period, the AE that resulted in discontinuation of treatment was first reported in the Main Period of the trial, as per Section 8.3.5. Thus, this reviewer decided to include it in this table.

Table 101. The Number (%) of Subjects, by Age, Reporting AEs, Main Period, Trial 4467, SGA Safety Population

Age	Norditropin 0.035 mg/kg/day	Norditropin 0.067 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
< 6 years of age				
Number of subjects	23	22	43	88
Any AEs	18 (78.3%)	18 (81.8%)	39 (90.7%)	75 (85.2%)
Serious AEs	2 (8.7%)	3 (13.6%)	3 (7%)	8 (9.1%)
Treatment discontinued due to AEs	1 (4.3%)[1]	0	0	1 (1.1%)[1]

Age	Norditropin 0.035 mg/kg/day	Norditropin 0.067 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
≥ 6 years of age				
Number of subjects	14	13	26	53
Any AEs	14 (100%)	10 (76.9%)	21 (80.8%)	45 (84.9%)
Serious AEs	1 (7.1%)	1 (7.7%)	0	2 (3.8%)
Treatment discontinued due to AEs	0	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical
[1] While this subject did not discontinue treatment until the Extension Period, the AE that resulted in discontinuation of treatment was first reported in the Main Period of the trial, as per Section 8.3.5. Thus, this reviewer decided to include it in this table.

Table 102. The Number (%) of Subjects, by Race, Reporting AEs, Main Period, Trial 4467, SGA Safety Population

Race	Norditropin 0.035 mg/kg/day	Norditropin 0.067 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
Asian				
Number of subjects	18	10	22	50
Any AEs	17 (94.4%)	8 (80%)	19 (86.4%)	44 (88%)
Serious AEs	2 (11.%)	2 (20%)	1 (4.5%)	5 (10%)
Treatment discontinued due to AEs	0	0	0	0
Black or African American				
Number of subjects	0	0	2	2
Any AEs	-	-	2 (100%)	2 (100%)
Serious AEs	-	-	1 (50%)	1 (50%)
Treatment discontinued due to AEs	-	-	0	0
White				
Number of subjects	17	24	42	83
Any AEs	13 (76.5%)	19 (79.2%)	36 (85.7%)	68 (81.9%)
Serious AEs	1 (5.9%)	2 (8.3%)	1 (2.4%)	4 (4.8%)
Treatment discontinued due to AEs	1 (5.9%)[1]	0	0	1 (1.2%)[1]
Not reported				
Number of subjects	2	1	3	6
Any AEs	2 (100%)	1 (100%)	3 (100%)	6 (100%)
Serious AEs	0	0	0	0
Treatment discontinued due to AEs	0	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical
[1] While this subject did not discontinue treatment until the Extension Period, the AE that resulted in discontinuation of treatment was first reported in the Main Period of the trial, as per Section 8.3.5. Thus, this reviewer decided to include it in this table.

Table 103. The Number (%) of Subjects, by Sex, Reporting AEs, Main Period, Trial 4467, NS Safety Population

Sex	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
Male			
Number of subjects	17	30	47
Any AEs	12 (70.6%)	25 (83.3%)	37 (78.7%)
Serious AEs	3 (17.6%)	1 (3.3%)	4 (8.5%)
Treatment discontinued due to AEs	0	0	0
Female			
Number of subjects	11	19	30
Any AEs	11 (100%)	19 (100%)	30 (100%)
Serious AEs	0	3 (15.8%)	3 (10%)
Treatment discontinued due to AEs	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical

A higher proportion of female subjects (100%), compared to male subjects (83.3%), treated with somapacitan reported at least 1 AE, and at least 1 SAE (3.3% vs. 15.8%, respectively), during the pivotal phase 3 trial. The reason for this imbalance is unclear, however, a similar imbalance in reporting of all AEs was seen in the Norditropin arm, and the nearly 2 to 1 enrollment of males to females and relatively small overall enrollment in the NS population may have contributed to imbalances in reporting of AEs.

Table 104. The Number (%) of Subjects, by Age, Reporting AEs, Main Period, Trial 4467, NS Safety Population

Age	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
< 6 years of age			
Number of subjects	15	23	38
Any AEs	13 (86.7%)	21 (91.3%)	34 (89.5%)
Serious AEs	3 (20%)	2 (8.7%)	5 (13.2%)
Treatment discontinued due to AEs	0	0	0
≥ 6 years of age			
Number of subjects	13	26	39
Any AEs	10 (76.9%)	23 (88.5%)	33 (84.6%)
Serious AEs	0	2 (7.7%)	2 (5.1%)
Treatment discontinued due to AEs	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical

Table 105. The Number (%) of Subjects, by Race, Reporting AEs, Main Period, Trial 4467, NS Safety Population

Race	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
Asian			
Number of subjects	9	15	24
Any AEs	9 (100%)	11 (73.3%)	20 (83.3%)
Serious AEs	2 (22.2%)	2 (13.3%)	4 (16.7%)
Treatment discontinued due to AEs	0	0	0

Race	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
Black or African American			
Number of subjects	0	4	4
Any AEs	-	4 (100%)	4 (100%)
Serious AEs	-	0	0
Treatment discontinued due to AEs	-	0	0
Multiple			
Number of subjects	1	0	1
Any AEs	0	-	0
Serious AEs	0	-	0
Treatment discontinued due to AEs	0	-	0
White			
Number of subjects	14	25	39
Any AEs	11 (78.6%)	24 (96%)	35 (89.7%)
Serious AEs	1 (7.1%)	2 (8%)	3 (7.7%)
Treatment discontinued due to AEs	0	0	0
Not reported			
Number of subjects	4	5	9
Any AEs	3 (75%)	5 (100%)	8 (88.9%)
Serious AEs	0	0	0
Treatment discontinued due to AEs	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical

Table 106. The Number (%) of Subjects, by Sex, Reporting AEs, Main Period, Trial 4467, ISS Safety Population

Sex	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
Male			
Number of subjects	11	25	36
Any AEs	9 (81.8%)	20 (80%)	29 (80.6%)
Serious AEs	0	0	0
Treatment discontinued due to AEs	0	0	0
Female			
Number of subjects	17	34	51
Any AEs	13 (76.5%)	27 (79.4%)	40 (78.4%)
Serious AEs	0	3 (8.8%)	3 (5.9%)
Treatment discontinued due to AEs	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical

Table 107. The Number (%) of Subjects, by Age, Reporting AEs, Main Period, Trial 4467, ISS Safety Population

Age	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
< 6 years of age			
Number of subjects	10	22	32
Any AEs	8 (80%)	19 (86.4%)	27 (84.4%)
Serious AEs	0	2 (9.1%)	2 (6.2%)
Treatment discontinued due to AEs	0	0	0

Age	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
≥ 6 years of age			
Number of subjects	18	37	55
Any AEs	14 (77.8%)	28 (75.7%)	42 (76.4%)
Serious AEs	0	1 (2.7%)	1 (1.8%)
Treatment discontinued due to AEs	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical

Table 108. The Number (%) of Subjects, by Race, Reporting AEs, Main Period, Trial 4467, ISS Safety Population

Race	Norditropin 0.5 mg/kg/day	Somapacitan 0.24 mg/kg/week	Total
American Indian or Alaska Native			
Number of subjects	0	1	1
Any AEs	-	0	0
Serious AEs	-	0	0
Treatment discontinued due to AEs	-	0	0
Asian			
Number of subjects	7	19	26
Any AEs	7 (100%)	16 (84.2%)	23 (88.5%)
Serious AEs	0	3 (15.8%)	3 (11.5%)
Treatment discontinued due to AEs	0	0	0
Black or African American			
Number of subjects	0	1	1
Any AEs	-	1 (100%)	1 (100%)
Serious AEs	-	0	0
Treatment discontinued due to AEs	-	0	0
Multiple			
Number of subjects	1	1	2
Any AEs	1 (100%)	1 (100%)	2 (100%)
Serious AEs	0	0	0
Treatment discontinued due to AEs	0	0	0
White			
Number of subjects	19	36	55
Any AEs	13 (68.4%)	28 (77.8%)	41 (74.5%)
Serious AEs	0	0	0
Treatment discontinued due to AEs	0	0	0
Not reported			
Number of subjects	1	1	2
Any AEs	1 (100%)	1 (100%)	2 (100%)
Serious AEs	0	0	0
Treatment discontinued due to AEs	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP Clinical

15.4.3.2. Trial NN8640-4245

Table 109. Mean (SD) Bone Age to Chronological Age Ratio, Main Period and Extension Period I (Weeks 0 to 52), Trial 4245

Treatment		0.035 mg/kg/day Norditropin (N=12)	0.067 mg/kg/day Norditropin (N=13)	0.16 mg/kg/week Somapacitan (N=12)	0.2 mg/kg/week Somapacitan (N=13)	0.24 mg/kg/week Somapacitan (N=12)
Bone Age to Chronological Age Ratio						
Baseline	Mean (SD)	0.73 (0.24)	0.71 (0.19)	0.67 (0.18)	0.76 (0.16)	0.82 (0.28)
	n	12	13	12	13	12
Week 52	Mean (SD)	0.71 (0.21)	0.78 (0.19)	0.74 (0.14)	0.79 (0.14)	0.81 (0.28)
	n	11	13	12	11	12

Source: Clinical Trial Report for trial 4245, Table 8.2.110, pages 466 to 467.
Abbreviations: n = number of subjects with available data

Table 110. The Most Commonly (≥ 2 Subjects) Reported Comorbidities in Trial 4245

Comorbidities	Norditropin (0.035mg/kg/day) (N=12)	Norditropin (0.067mg/kg/day) (N=13)	Somapacitan (0.16mg/kg/week) (N=12)	Somapacitan (0.20mg/kg/week) (N=13)	Somapacitan (0.24mg/kg/week) (N=12)	Total (N=62)
Any comorbidity, n (%)	7 (58.3)	11 (84.6)	12 (100.0)	12 (92.3)	11 (91.7)	53 (85.5)
Constipation	1 (8.3)	1 (7.7)	1 (8.3)	2 (15.4)	0	5 (8.1)
Rhinitis allergic	0	0	2 (16.7)	0	2 (16.7)	4 (6.5)
Asthma	0	1 (7.7)	0	2 (15.4)	0	3 (4.8)
Foot deformity	1 (8.3)	1 (7.7)	0	0	1 (8.3)	3 (4.8)
Short stature	1 (8.3)	1 (7.7)	1 (8.3)	0	0	3 (4.8)
Adenoidal hypertrophy	0	1 (7.7)	0	0	1 (8.3)	2 (3.2)
Autism spectrum disorder	0	0	0	1 (7.7)	1 (8.3)	2 (3.2)
Febrile convulsion	0	2 (15.4)	0	0	0	2 (3.2)
Hypoglycemia	0	0	0	2 (15.4)	0	2 (3.2)
Iron deficiency anemia	1 (8.3)	0	0	0	1 (8.3)	2 (3.2)
Vitamin D deficiency	1 (8.3)	0	0	0	1 (8.3)	2 (3.2)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

Table 111. The Most Commonly (≥ 10% Subjects in Any Treatment Group) Concomitant Medications in Trial 4245

Medication	Norditropin (0.035mg/kg/day) (N=12)	Norditropin (0.067mg/kg/day) (N=13)	Somapacitan (0.16mg/kg/week) (N=12)	Somapacitan (0.20mg/kg/week) (N=13)	Somapacitan (0.24mg/kg/week) (N=12)	Total (N=62)
Any medication, n (%)	8 (66.7)	11 (84.6)	11 (91.7)	13 (100.0)	11 (91.7)	54 (87.1)
PARACETAMOL	2 (16.7)	6 (46.2)	6 (50.0)	6 (46.2)	7 (58.3)	27 (43.5)
IBUPROFEN	2 (16.7)	3 (23.1)	2 (16.7)	5 (38.5)	3 (25.0)	15 (24.2)
CARBOCISTEINE	2 (16.7)	4 (30.8)	4 (33.3)	2 (15.4)	2 (16.7)	14 (22.6)
TIPEPIDINE HIBENZATE	2 (16.7)	3 (23.1)	3 (25.0)	2 (15.4)	3 (25.0)	13 (21.0)
COLECALCIFEROL	0	2 (15.4)	2 (16.7)	2 (15.4)	5 (41.7)	11 (17.7)
LEVOCETIRIZINE DIHYDROCHLORIDE	2 (16.7)	2 (15.4)	2 (16.7)	2 (15.4)	3 (25.0)	11 (17.7)
TULOBUTEROL	2 (16.7)	3 (23.1)	2 (16.7)	2 (15.4)	2 (16.7)	11 (17.7)
AMBROXOL HYDROCHLORIDE	2 (16.7)	2 (15.4)	2 (16.7)	2 (15.4)	1 (8.3)	9 (14.5)
CLARITHROMYCIN	0	2 (15.4)	1 (8.3)	4 (30.8)	1 (8.3)	8 (12.9)
TRANEXAMIC ACID	2 (16.7)	3 (23.1)	0	2 (15.4)	1 (8.3)	8 (12.9)
L-CARBOCISTEINE	0	1 (7.7)	1 (8.3)	2 (15.4)	3 (25.0)	7 (11.3)

Medication	Norditropin (0.035mg/kg/day) (N=12)	Norditropin (0.067mg/kg/day) (N=13)	Somapacitan (0.16mg/kg/week) (N=12)	Somapacitan (0.20mg/kg/week) (N=13)	Somapacitan (0.24mg/kg/week) (N=12)	Total (N=62)
AMOXICILLIN TRIHYDRATE	1 (8.3)	2 (15.4)	2 (16.7)	1 (7.7)	0	6 (9.7)
CEFDITOREN PIVOXIL	0	1 (7.7)	1 (8.3)	4 (30.8)	0	6 (9.7)
HEPARINOID	1 (8.3)	1 (7.7)	1 (8.3)	1 (7.7)	2 (16.7)	6 (9.7)
MONTELUKAST SODIUM	1 (8.3)	1 (7.7)	1 (8.3)	2 (15.4)	1 (8.3)	6 (9.7)
OLOPATADINE HYDROCHLORIDE	0	1 (7.7)	2 (16.7)	2 (15.4)	1 (8.3)	6 (9.7)
TOSUFLOXACIN TOSILATE	0	1 (7.7)	2 (16.7)	2 (15.4)	1 (8.3)	6 (9.7)
CETIRIZINE HYDROCHLORIDE	2 (16.7)	0	1 (8.3)	1 (7.7)	1 (8.3)	5 (8.1)
DOMPERIDONE	0	2 (15.4)	2 (16.7)	1 (7.7)	0	5 (8.1)
INFLUENZA VACCINE	1 (8.3)	1 (7.7)	1 (8.3)	2 (15.4)	0	5 (8.1)
OFLOXACIN	0	0	2 (16.7)	3 (23.1)	0	5 (8.1)
ACICLOVIR	0	0	1 (8.3)	3 (23.1)	0	4 (6.5)
AMBROXOL	0	0	0	1 (7.7)	3 (25.0)	4 (6.5)
CEFDINIR	0	1 (7.7)	2 (16.7)	1 (7.7)	0	4 (6.5)
CLOSTRIDIUM BUTYRICUM	0	1 (7.7)	1 (8.3)	2 (15.4)	0	4 (6.5)
ENTEROCOCCUS FAECALIS	2 (16.7)	1 (7.7)	0	1 (7.7)	0	4 (6.5)
MEQUITAZINE	0	1 (7.7)	2 (16.7)	0	1 (8.3)	4 (6.5)
MONTELUKAST	0	3 (23.1)	1 (8.3)	0	0	4 (6.5)
OXYMETAZOLINE HYDROCHLORIDE	0	2 (15.4)	0	1 (7.7)	1 (8.3)	4 (6.5)
POTASSIUM IODIDE	0	1 (7.7)	0	1 (7.7)	2 (16.7)	4 (6.5)
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	0	0	2 (16.7)	0	1 (8.3)	3 (4.8)
BETAMETHASONE	1 (8.3)	0	2 (16.7)	0	0	3 (4.8)
BROMHEXINE HYDROCHLORIDE	1 (8.3)	2 (15.4)	0	0	0	3 (4.8)
CEFACLOR	1 (8.3)	0	0	2 (15.4)	0	3 (4.8)
CEFAZOLIN SODIUM	0	2 (15.4)	0	1 (7.7)	0	3 (4.8)
DEQUALINIUM CHLORIDE	0	1 (7.7)	2 (16.7)	0	0	3 (4.8)
HEXETIDINE	0	0	0	2 (15.4)	1 (8.3)	3 (4.8)
LIDOCAINE	0	1 (7.7)	0	2 (15.4)	0	3 (4.8)
METHYLPREDNISOLONE;NEOMYCIN SULFATE	0	0	3 (25.0)	0	0	3 (4.8)
NITROUS OXIDE	0	2 (15.4)	1 (8.3)	0	0	3 (4.8)
PRANLUKAST	2 (16.7)	0	0	0	1 (8.3)	3 (4.8)
VITAMIN D NOS	2 (16.7)	0	1 (8.3)	0	0	3 (4.8)

Medication	Norditropin (0.035mg/kg/day) (N=12)	Norditropin (0.067mg/kg/day) (N=13)	Somapacitan (0.16mg/kg/week) (N=12)	Somapacitan (0.20mg/kg/week) (N=13)	Somapacitan (0.24mg/kg/week) (N=12)	Total (N=62)
BENZYDAMINE	0	0	0	0	2 (16.7)	2 (3.2)
BIFIDOBACTERIUM INFANTIS;BIFIDOBACTERIUM LONGUM	0	2 (15.4)	0	0	0	2 (3.2)
GLYCEROL	0	0	0	2 (15.4)	0	2 (3.2)
MACROGOL 4000	0	0	2 (16.7)	0	0	2 (3.2)
MIRAMISTIN	0	0	0	0	2 (16.7)	2 (3.2)
POLYGALA SENEGA SYRUP	2 (16.7)	0	0	0	0	2 (3.2)
PRANLUKAST HYDRATE	0	0	0	0	2 (16.7)	2 (3.2)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.

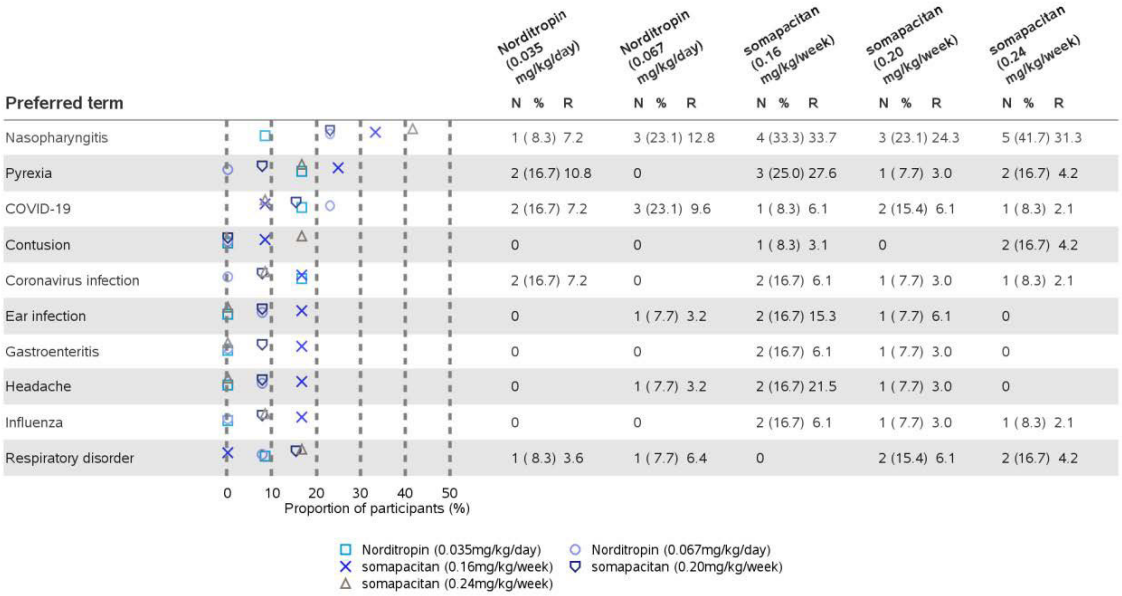
Table 112. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

OCMQ/GQ Term Preferred Term	Norditropin 0.035mg/kg/day (N=12) n (%)	Norditropin 0.067mg/kg/day (N=13) n (%)	Somapacitan 0.16mg/kg/week (N=12) n (%)	Somapacitan 0.20mg/kg/week (N=13) n (%)	Somapacitan 0.24mg/kg/week (N=12) n (%)	Total (N=62) n (%)
Any AE	7 (58.3)	6 (46.2)	7 (58.3)	9 (69.2)	9 (75.0)	38 (61.3)
Nasopharyngitis	1 (8.3)	2 (15.4)	4 (33.3)	2 (15.4)	4 (33.3)	13 (21.0)
Nasopharyngitis	1 (8.3)	1 (7.7)	3 (25.0)	2 (15.4)	4 (33.3)	11 (17.7)
Rhinitis	0	1 (7.7)	2 (16.7)	0	0	3 (4.8)
Pharyngitis	0	0	1 (8.3)	0	0	1 (1.6)
Ear Infection	0	1 (7.7)	4 (33.3)	4 (30.8)	0	9 (14.5
Otitis media	0	1 (7.7)	1 (8.3)	1 (7.7)	0	3 (4.8)
Ear infection	0	0	1 (8.3)	1 (7.7)	0	2 (3.2)
Otitis externa	0	0	1 (8.3)	1 (7.7)	0	2 (3.2)
Otitis media acute	0	0	1 (8.3)	1 (7.7)	0	2 (3.2)

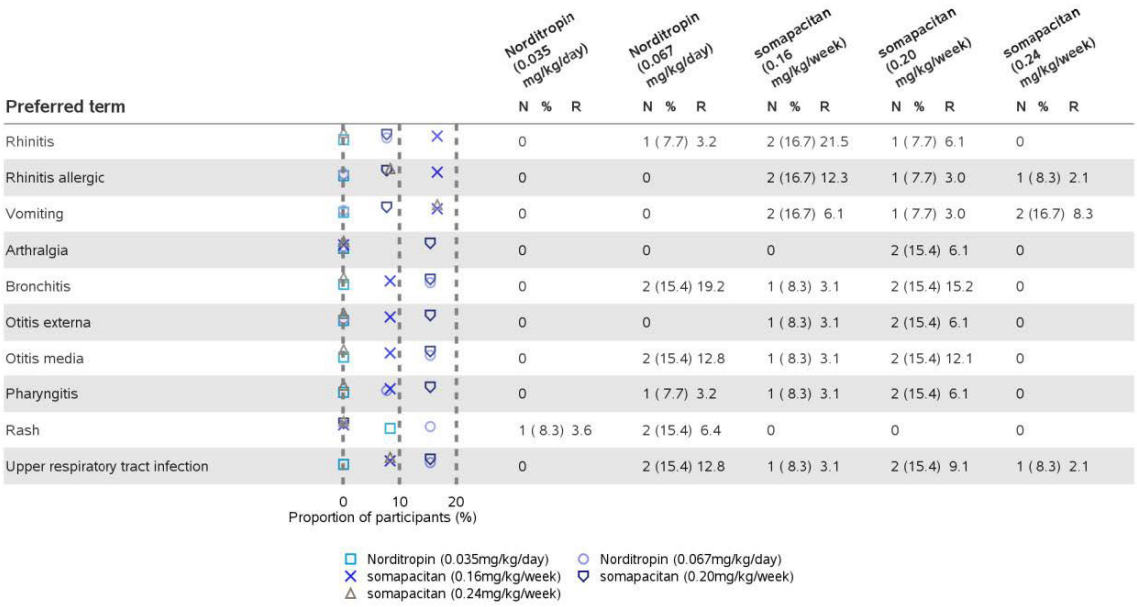
OCMQ/GQ Term Preferred Term	Norditropin 0.035mg/kg/day (N=12) n (%)	Norditropin 0.067mg/kg/day (N=13) n (%)	Somapacitan 0.16mg/kg/week (N=12) n (%)	Somapacitan 0.20mg/kg/week (N=13) n (%)	Somapacitan 0.24mg/kg/week (N=12) n (%)	Total (N=62) n (%)
Respiratory Tract Infection	1 (8.3)	2 (15.4)	0	4 (30.8)	1 (8.3)	8 (12.9)
Upper respiratory tract infection	0	2 (15.4)	0	2 (15.4)	0	4 (6.5)
Respiratory tract infection viral	1 (8.3)	0	0	1 (7.7)	0	2 (3.2)
Influenza	0	0	0	1 (7.7)	0	1 (1.6)
Influenza like illness	0	0	0	0	1 (8.3)	1 (1.6)
Pneumonia	0	1 (7.7)	0	0	0	1 (1.6)
Respiratory syncytial virus infection	0	0	0	1 (7.7)	0	1 (1.6)
Vomiting	0	0	2 (16.7)	1 (7.7)	1 (8.3)	4 (6.5)
Hemorrhage	0	0	1 (8.3)	0	2 (16.7)	3 (4.8)
Contusion	0	0	1 (8.3)	0	2 (16.7)	3 (4.8)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical

Figure 40. Applicant's Analysis of the Most Frequent Adverse Events by Preferred Term (≥ 10%), Before Switch, Trial 4245 Safety Population



%: Percentage, R: Event rate per 100 patient years at risk, MedDRA version 27.1
Only adverse events with an onset after the first administration of trial product and up until 14 days after last trial drug administration for withdrawn participants, and with an onset after the first administration of trial product and up until visit 20 (week 208) or 14 days after last trial drug administration, which ever comes first, for all other participants, are included.
Switch date: Date when participants changed the treatment and had the first dose of somapacitan 0.24mg/kg/week. This date itself belongs to the before switch period.
nn8640/nn8640-4245/csr_wk208_20250204_er
12FEB2025:18:31:31 - faemostfreqsas.sas/faemos:freq101bfsas.png



%: Percentage, R: Event rate per 100 patient years at risk, MedDRA version 27.1
Only adverse events with an onset after the first administration of trial product and up until 14 days after last trial drug administration for withdrawn participants, and with an onset after the first administration of trial product and up until visit 20 (week 208) or 14 days after last trial drug administration, which ever comes first, for all other participants, are included.
Switch date: Date when participants changed the treatment and had the first dose of somapacitan 0.24mg/kg/week. This date itself belongs to the before switch period.
nn8640/nn8640-4245/csr_wk208_20250204_er
12FEB2025:18:31:36 - faemostfreqsas.sas/faemos:freq102bfsas.png

Source: Clinical Trial Report for trial 4245, ISS, Figures 5-6 and 5-7, pages 84 and 85.

Table 113. The Most Commonly Reported (≥ 10% of Subjects in Any Treatment Arm) Adverse Events by OCMQ Analysis, Extension Periods II and III, Trial 4245, Safety Population

OCMQ/GQ Term Preferred Term	Norditropin 0.035mg/kg/day (N=12) n (%)	Norditropin 0.067mg/kg/day (N=13) n (%)	Somapacitan 0.16mg/kg/week (N=12) n (%)	Somapacitan 0.20mg/kg/week (N=13) n (%)	Somapacitan 0.24mg/kg/week (N=12) n (%)	Total (N=62) N (%) n (%)
Treatment during Extension Periods II and III: Transitioned to 0.24 mg/kg/week Somapacitan						
Any AE	11 (91.7)	11 (84.6)	10 (83.3)	13 (100.0)	10 (83.3)	55 (88.7)
Nasopharyngitis	3 (25.0)	7 (53.8)	6 (50.0)	6 (46.2)	5 (41.7)	27 (43.5)
Nasopharyngitis	2 (16.7)	4 (30.8)	4 (33.3)	2 (15.4)	5 (41.7)	17 (27.4)
Rhinitis	1 (8.3)	2 (15.4)	2 (16.7)	4 (30.8)	0	9 (14.5)
Pharyngitis	0	1 (7.7)	0	2 (15.4)	0	3 (4.8)
Sinusitis	0	0	1 (8.3)	1 (7.7)	0	2 (3.2)
Viral pharyngitis	0	0	1 (8.3)	0	0	1 (1.6)
Respiratory Tract Infection	2 (16.7)	4 (30.8)	5 (41.7)	7 (53.8)	2 (16.7)	20 (32.3)
Influenza	0	1 (7.7)	5 (41.7)	3 (23.1)	1 (8.3)	10 (16.1)
Respiratory tract infection viral	2 (16.7)	2 (15.4)	0	2 (15.4)	0	6 (9.7)
Upper respiratory tract infection	0	1 (7.7)	1 (8.3)	2 (15.4)	1 (8.3)	5 (8.1)
Respiratory tract infection	0	1 (7.7)	0	1 (7.7)	0	2 (3.2)
Respiratory syncytial virus infection	0	0	1 (8.3)	0	0	1 (1.6)
Viral upper respiratory tract infection	1 (8.3)	0	0	0	0	1 (1.6)
Covid-19	3 (25.0)	4 (30.8)	1 (8.3)	4 (30.8)	1 (8.3)	13 (21.0)
Ear Infection	0	3 (23.1)	3 (25.0)	4 (30.8)	1 (8.3)	11 (17.7)
Otitis media	0	2 (15.4)	1 (8.3)	2 (15.4)	0	5 (8.1)
Ear infection	0	1 (7.7)	2 (16.7)	0	0	3 (4.8)
Otitis media acute	0	0	0	1 (7.7)	1 (8.3)	2 (3.2)
Otitis externa	0	0	0	1 (7.7)	0	1 (1.6)

OCMQ/GQ Term Preferred Term	Norditropin 0.035mg/kg/day (N=12) n (%)	Norditropin 0.067mg/kg/day (N=13) n (%)	Somapacitan 0.16mg/kg/week (N=12) n (%)	Somapacitan 0.20mg/kg/week (N=13) n (%)	Somapacitan 0.24mg/kg/week (N=12) n (%)	Total (N=62) N (%) n (%)
Diarrhea	0	0	3 (25.0)	3 (23.1)	4 (33.3)	10 (16.1)
Gastroenteritis	0	0	1 (8.3)	3 (23.1)	0	4 (6.5)
Diarrhea	0	0	1 (8.3)	1 (7.7)	1 (8.3)	3 (4.8)
Enterobiasis	0	0	1 (8.3)	0	1 (8.3)	2 (3.2)
Enteritis	0	0	0	0	1 (8.3)	1 (1.6)
Enterocolitis	0	0	0	1 (7.7)	0	1 (1.6)
Gastroenteritis viral	0	0	0	0	1 (8.3)	1 (1.6)
Viral diarrhea	0	0	1 (8.3)	0	0	1 (1.6)
Pyrexia	1 (8.3)	1 (7.7)	3 (25.0)	2 (15.4)	2 (16.7)	9 (14.5)
Pyrexia	1 (8.3)	1 (7.7)	3 (25.0)	2 (15.4)	2 (16.7)	9 (14.5)
Rhinitis[1]	0	0	1 (8.3)	0	0	1 (1.6)
Coronavirus Infection	2 (16.7)	0	2 (16.7)	1 (7.7)	1 (8.3)	6 (9.7)
Bronchitis	0	2 (15.4)	1 (8.3)	3 (23.1)	0	6 (9.7)
Eczema	1 (8.3)	1 (7.7)	2 (16.7)	0	1 (8.3)	5 (8.1)
Eczema	1 (8.3)	0	1 (8.3)	0	1 (8.3)	3 (4.8)
Eczema asteatotic	0	1 (7.7)	1 (8.3)	0	0	2 (3.2)
Hemorrhage	1 (8.3)	0	1 (8.3)	3 (23.1)	0	5 (8.1)
Contusion	1 (8.3)	0	0	1 (7.7)	0	2 (3.2)
Hematoma	0	0	1 (8.3)	1 (7.7)	0	2 (3.2)
Epistaxis	0	0	0	1 (7.7)	0	1 (1.6)
Respiratory Disorder	1 (8.3)	1 (7.7)	0	1 (7.7)	2 (16.7)	5 (8.1)
Attention Deficit Hyperactivity Disorder	1 (8.3)	0	0	2 (15.4)	1 (8.3)	4 (6.5)
Rhinitis Allergic	0	0	2 (16.7)	1 (7.7)	1 (8.3)	4 (6.5)
Viral Infection	0	0	1 (8.3)	1 (7.7)	2 (16.7)	4 (6.5)
Abdominal Pain	0	2 (15.4)	1 (8.3)	0	0	3 (4.8)
Abdominal pain	0	1 (7.7)	1 (8.3)	0	0	2 (3.2)
Abdominal pain lower	0	1 (7.7)	0	0	0	1 (1.6)
Abdominal pain upper	0	1 (7.7)	0	0	0	1 (1.6)
Acne	0	0	0	2 (15.4)	1 (8.3)	3 (4.8)
Cough	0	0	1 (8.3)	2 (15.4)	0	3 (4.8)
Varicella	0	0	1 (8.3)	2 (15.4)	0	3 (4.8)

OCMQ/GQ Term Preferred Term	Norditropin 0.035mg/kg/day (N=12) n (%)	Norditropin 0.067mg/kg/day (N=13) n (%)	Somapacitan 0.16mg/kg/week (N=12) n (%)	Somapacitan 0.20mg/kg/week (N=13) n (%)	Somapacitan 0.24mg/kg/week (N=12) n (%)	Total (N=62) N (%) n (%)
Headache	0	0	2 (16.7)	0	0	2 (3.2)
Pain In Extremity	2 (16.7)	0	0	0	0	2 (3.2)
Pain in extremity	1 (8.3)	0	0	0	0	1 (1.6)
Sever's disease	1 (8.3)	0	0	0	0	1 (1.6)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
[1] One AE with a PT of rhinitis was also grouped under the pyrexia OCMQ terms because the reported term for this AE was "rhinitis with fever".

Table 114. Mean (SD) Hematology Parameters, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

Treatment		Norditropin 0.035 mg/kg/day (N=12)		Norditropin 0.067 mg/kg/day (N=13)		Somapacitan 0.16 mg/kg/week (N=12)		Somapacitan 0.20 mg/kg/week (N=13)		Somapacitan 0.24 mg/kg/week (N=12)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Leukocytes (10^9/L)											
Baseline	Mean (SD)	6.1 (2)	-	6.6 (1.3)	-	7.7 (2.4)	-	7.3 (2.5)	-	7.8 (2.9)	-
	n		10		13		12		13		12
Week 52	Mean (SD)	6.4 (1.9)	-0.4 (2.1)	6.9 (1.4)	0.3 (1.4)	6.6 (1)	-1 (2.7)	6.9 (1.5)	-0.6 (2.8)	7 (1.7)	-0.9 (2.9)
	n		10		13		12		12		11
Hematocrit (%)											
Baseline	Mean (SD)	38.8 (2.5)	-	38.5 (1.8)	-	37.8 (1.9)	-	38.1 (2.4)	-	37.6 (3.3)	-
	n		11		13		12		13		12
Week 52	Mean (SD)	38.9 (2.4)	-0.2 (1.5)	39.3 (2.2)	0.8 (2)	38 (2.2)	0.2 (1.7)	38.7 (2.8)	0.5 (1.5)	38 (3.4)	0.4 (1.7)
	n		10		13		12		12		10
Thrombocytes (10^9/L)											
Baseline	Mean (SD)	330.3 (75.7)	-	300.6 (81.2)	-	322.1 (71.9)	-	367.4 (106.2)	-	325.2 (58.3)	-
	n		10		12		12		13		11

Treatment		Norditropin 0.035 mg/kg/day (N=12)		Norditropin 0.067 mg/kg/day (N=13)		Somapacitan 0.16 mg/kg/week (N=12)		Somapacitan 0.20 mg/kg/week (N=13)		Somapacitan 0.24 mg/kg/week (N=12)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Week 52	Mean (SD)	305.5 (55)	-24 (77.8)	322.5 (52.7)	21.9 (63.6)	304.2 (53.7)	-17.8 (41.6)	328.8 (115.2)	-40.7 (61.5)	329.5 (60)	-1.7 (61.9)
	n		10		12		12		12		11

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n = number of subjects with available data.

Table 115. Number (%) of Subjects With Hematology Parameters Outside the Normal Range, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

Parameter		Norditropin 0.035 mg/kg/day (N=12) n (%)	Norditropin 0.067 mg/kg/day (N=13) n (%)	Somapacitan 0.16 mg/kg/week (N=12) n (%)	Somapacitan 0.20 mg/kg/week (N=13) n (%)	Somapacitan 0.24 mg/kg/week (N=12) n (%)
Leukocytes						
Total	n	11	13	12	13	12
	Low (< LLN)	3 (27.3)	0	1 (8.3)	2 (15.4)	1 (8.3)
	High (> ULN)	1 (9.1)	1 (7.7)	0	0	0
Hematocrit						
Total	n	11	13	12	13	12
	Low (< LLN)	0	0	0	1 (7.7)	0
	High (> ULN)	1 (9.1)	3 (23.1)	0	1 (7.7)	2 (16.7)
Thrombocytes						
Total	n	11	13	12	13	12
	Low (< LLN)	0	0	0	0	0
	High (> ULN)	0	2 (15.4)	0	4 (30.8)	2 (16.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; ULN, upper limit of normal; n, number of subjects with available data

Table 116. Mean (SD) Lipid Parameters, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

Treatment		Norditropin 0.035 mg/kg/day (N=12)		Norditropin 0.067 mg/kg/day (N=13)		Somapacitan 0.16 mg/kg/week (N=12)		Somapacitan 0.20 mg/kg/week (N=13)		Somapacitan 0.24 mg/kg/week (N=12)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Cholesterol (mg/dL)											
Baseline	Mean (SD)	152.8 (33.7)	-	150.5 (24)	-	180.1 (31.4)	-	157.9 (25.9)	-	153.7 (27.7)	-
	n		12		13		12		13		12
Week 39	Mean (SD)	154.4 (25.4)	-2.1 (29.2)	138.4 (25.8)	-12.1 (23.1)	185.8 (36.5)	5.7 (14.9)	163.6 (25.5)	1.5 (18.6)	158.6 (30.2)	4.9 (21)
	n		11		13		12		12		12
Low density lipoprotein (mg/dL)											
Baseline	Mean (SD)	79.6 (22.9)	-	78.5 (18.2)	-	103.4 (28.5)	-	88.4 (16.9)	-	81 (23.9)	-
	n		12		13		11		12		12
Week 39	Mean (SD)	78.9 (18.8)	-2.6 (19.2)	66.4 (19.9)	-12.1 (14)	105.3 (30.8)	4.1 (12.1)	93.4 (21.1)	5 (16.4)	86 (26.2)	4.9 (21.6)
	n		11		13		12		12		12
High density lipoprotein (mg/dL)											
Baseline	Mean (SD)	56.2 (15.6)	-	55.9 (11.3)	-	59.8 (16.8)	-	54.3 (10.3)	-	55.9 (10.5)	-
	n		12		13		12		13		12
Week 39	Mean (SD)	53.7 (13.6)	-3.4 (15)	50.3 (11.3)	-5.6 (10.7)	57 (14.3)	-2.8 (7.4)	53.3 (11.9)	-2.9 (9)	56.2 (15)	0.2 (11.8)
	n		11		13		12		12		12
Triglycerides (mg/dL)											
Baseline	Mean (SD)	84.9 (46.4)	-	80.2 (21.9)	-	114.3 (133.5)	-	113.8 (107.7)	-	83.8 (26.7)	-
	n		12		13		12		13		12
Week 39	Mean (SD)	108.1 (51.5)	19.2 (40.8)	108.7 (55.8)	28.5 (52.3)	116.8 (60.4)	2.5 (127.5)	84.3 (38.2)	-4.1 (67.6)	82 (33.6)	-1.8 (33.8)
	n		11		13		12		12		12

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided cholesterol, lipoproteins, and triglycerides in units of mmol/L.
To provide cholesterol and lipoproteins in mg/dL in this table, this reviewer multiplied the mmol/L value by 38.67.
To provide triglycerides in mg/dL in this table, this reviewer multiplied the mmol/L value by 88.57.
Abbreviations: n = number of subjects with available data.

Table 117. Number (%) of Subjects With Lipid Parameters Outside the Normal Range, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

Parameter		Norditropin 0.035 mg/kg/day (N=12) n (%)	Norditropin 0.067 mg/kg/day (N=13) n (%)	Somapacitan 0.16 mg/kg/week (N=12) n (%)	Somapacitan 0.20 mg/kg/week (N=13) n (%)	Somapacitan 0.24 mg/kg/week (N=12) n (%)
Cholesterol						
Total	n	12	13	12	13	12
	Low (< LLN)	0	0	0	0	0
	High (> ULN)	4 (33.3)	6 (46.2)	9 (75)	7 (53.8)	6 (50)
Low density lipoprotein						
Total	n	12	13	12	13	12
	Low (< LLN)	0	0	0	0	0
	High (> ULN)	2 (16.7)	1 (7.7)	5 (41.7)	5 (38.5)	4 (33.3)
High density lipoprotein						
Total	n	12	13	12	13	12
	Low (< LLN)	5 (41.7)	7 (53.8)	3 (25)	6 (46.2)	7 (58.3)
	High (> ULN)	0	0	0	0	0
Triglycerides						
Total	n	12	13	12	13	12
	Low (< LLN)	0	0	0	0	0
	High (> ULN)	8 (66.7)	10 (76.9)	11 (91.7)	10 (76.9)	11 (91.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 118. Mean (SD) Fasting Glucose, HbA1c, and Insulin Values, Main Period and Extension Period I, Trial 4245, Safety Population

		Norditropin 0.035 mg/kg/day (N=12)		Norditropin 0.067 mg/kg/day (N=13)		Somapacitan 0.16 mg/kg/week (N=12)		Somapacitan 0.20 mg/kg/week (N=13)		Somapacitan 0.24 mg/kg/week (N=12)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Fasting glucose (mg/dL)											
Baseline	Mean (SD)	81.5 (10.3)	-	86.7 (7.4)	-	84.2 (8.3)	-	90.1 (12.6)	-	86.3 (14.1)	-
	n		12		13		12		13		12
Week 4	Mean (SD)	91.5 (16.5)	10.1 (22)	91.8 (9.1)	5.3 (10.4)	90.2 (5.7)	6.1 (8.9)	86.7 (7.2)	-3.5 (8.1)	92 (7.4)	5.7 (12.4)
	n		12		12		10		13		12
Week 13	Mean (SD)	82.3 (11.2)	2.1 (12.7)	89.5 (7.9)	2.5 (11.4)	83.9 (6.3)	-0.7 (10.5)	86.7 (7.5)	-3.5 (12.8)	80 (7.6)	3.8 (12)
	n		11		11		11		13		12
Week 26	Mean (SD)	87.9 (7.3)	6.9 (9)	80.1 (6.9)	3.5 (7.5)	87.2 (6.6)	3 (8.7)	93.6 (13)	3.6 (16.4)	91.2 (6)	5 (12.5)
	n		11		13		12		12		12
Week 52	Mean (SD)	88.9 (7.6)	7.9 (11.8)	88.2 (8)	1.5 (10.9)	86.7 (6.1)	2.6 (7.7)	113.1 (80.1)[1]	23 (82.3)[1]	91.1 (6.8)	4.8 (13.1)
	n		11		13		12		13		12
HbA1c (%)											
Baseline	Mean (SD)	5.4 (0.3)	-	5.3 (0.3)	-	5.2 (0.3)	-	5.2 (0.3)	-	5.3 (0.3)	-
	n		11		13		12		13		12
Week 13	Mean (SD)	5.3 (0.3)	-0.1 (0.3)	5.4 (0.3)	0.1 (0.2)	5.3 (0.3)	0.2 (0.2)	5.3 (0.3)	0.2 (0.3)	5.4 (0.3)	0.1 (0.3)
	n		11		13		12		13		12
Week 26	Mean (SD)	5.3 (0.3)	-0.1 (0.4)	5.3 (0.3)	0 (0.2)	5.3 (0.3)	0.1 (0.1)	5.3 (0.2)	0.1 (0.3)	5.3 (0.3)	0.1 (0.2)
	n		11		13		12		12		12
Week 52	Mean (SD)	5.3 (0.3)	-0.1 (0.3)	5.4 (0.4)	0.2 (0.2)	5.3 (0.2)	0.1 (0.2)	5.8 (1.8)[1]	0.6 (1.6)[1]	5.3 (0.4)	0.1 (0.3)
	n		11		13		12		13		12

Evaluation		Norditropin 0.035 mg/kg/day (N=12) Value	Norditropin 0.035 mg/kg/day (N=12) Change From Baseline	Norditropin 0.067 mg/kg/day (N=13) Value	Norditropin 0.067 mg/kg/day (N=13) Change From Baseline	Somapacitan 0.16 mg/kg/week (N=12) Value	Somapacitan 0.16 mg/kg/week (N=12) Change From Baseline	Somapacitan 0.20 mg/kg/week (N=13) Value	Somapacitan 0.20 mg/kg/week (N=13) Change From Baseline	Somapacitan 0.24 mg/kg/week (N=12) Value	Somapacitan 0.24 mg/kg/week (N=12) Change From Baseline
Fasting insulin (uIU/L)											
Baseline	Mean (SD)	3.9 (2.5)	-	3.3 (1.8)	-	4 (3.1)	-	6.7 (7.2)	-	6.6 (4.7)	-
	n		12		13		12		13		12
Week 4	Mean (SD)	7.4 (7.4)	3.6 (7.9)	7.5 (5.2)	4.1 (4.7)	4.2 (1.9)	0.1 (3.3)	4.3 (2.3)	-2.4 (5.7)	8.4 (6.6)	1.8 (3.6)
	n		13		13		11		13		12
Week 13	Mean (SD)	4.7 (2.9)	1.2 (4.4)	12.3 (18.7)	9 (18.4)	4.9 (3)	0.8 (4.2)	4.1 (2.2)	-2.5 (7.3)	6.7 (4)	0.1 (3.5)
	n		10		13		12		13		12
Week 26	Mean (SD)	7.5 (4.5)	3.5 (3.7)	8.5 (4.8)	5.1 (3.7)	5.9 (4.1)	1.9 (2.2)	7.9 (7.5)	1.7 (10.1)	12.7 (11.2)	6.2 (8.4)
	n		11		12		12		12		12
Week 52	Mean (SD)	8.1 (4.4)	4.2 (4.3)	9.3 (6.2)	6 (5.9)	5.6 (3.2)	1.6 (4.3)	10 (6.6)[1]	3.2 (5.9)[1]	12.1 (7.2)	5.5 (6.3)
	n		11		13		12		12		12

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided glucose in units of mmol/L. To provide glucose in mg/dL in this table, this reviewer multiplied the mmol/L value by 18.
The Applicant provided insulin in units of pmol/L. To provide insulin in uIU/L in this table, this reviewer divided the pmol/L value by 6.
[1] At the Week 52 visit, 1/13 (7.7%) subject in the 0.2 mg/kg/week somapacitan group had a fasting glucose of 378 mg/dL (a change from baseline of 293.4 mg/dL) and reported an AE with the PT of type 1 diabetes mellitus. For the other subjects in this group, the mean (SD) glucose and change from baseline in glucose was 91.1 (9.7) mg/dL and 0.5 (13.8) mg/dL, respectively; the mean (SD) HbA1c and change from baseline in HbA1c was 5.3 (0.2)% and 0.2 (0.2)%, respectively; the mean (SD) insulin and change from baseline in insulin was 10.7 (6.3) uIU/L and 3.7 (5.9) uIU/L, respectively.
Abbreviations: n = number of subjects with available data.

Table 119. Number (%) of Subjects With Glucose Parameters Outside the Normal Range, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

Parameter		Norditropin 0.035 mg/kg/day (N=12) n (%)	Norditropin 0.067 mg/kg/day (N=13) n (%)	Somapacitan 0.16 mg/kg/week (N=12) n (%)	Somapacitan 0.20 mg/kg/week (N=13) n (%)	Somapacitan 0.24 mg/kg/week (N=12) n (%)
Fasting glucose						
Total	n	12	13	12	13	12
	Low (< LLN)	0	0	0	0	0
	High (> ULN)	2 (16.7)	2 (15.4)	0	2 (15.4)	2 (16.7)

Parameter		Norditropin 0.035 mg/kg/day (N=12) n (%)	Norditropin 0.067 mg/kg/day (N=13) n (%)	Somapacitan 0.16 mg/kg/week (N=12) n (%)	Somapacitan 0.20 mg/kg/week (N=13) n (%)	Somapacitan 0.24 mg/kg/week (N=12) n (%)
HbA1c						
Total	n	11	13	12	13	12
	Low (< LLN)	0	0	0	0	0
	High (> ULN)	0	0	0	1 (7.7)	0
Fasting insulin						
Total	n	12	13	12	13	12
	Low (< LLN)	0	0	0	1 (7.7)	1 (8.3)
	High (> ULN)	0	0	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
LLN = lower limit of normal; ULN = upper limit of normal; n = number of subjects with available data.

Table 120. Mean (SD) Alkaline Phosphatase Values, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

Evaluation		Norditropin 0.035 mg/kg/day (N=12) Value	Norditropin 0.035 mg/kg/day (N=12) Change From Baseline	Norditropin 0.067 mg/kg/day (N=13) Value	Norditropin 0.067 mg/kg/day (N=13) Change From Baseline	Somapacitan 0.16 mg/kg/week (N=12) Value	Somapacitan 0.16 mg/kg/week (N=12) Change From Baseline	Somapacitan 0.20 mg/kg/week (N=13) Value	Somapacitan 0.20 mg/kg/week (N=13) Change From Baseline	Somapacitan 0.24 mg/kg/week (N=12) Value	Somapacitan 0.24 mg/kg/week (N=12) Change From Baseline
Alkaline phosphatase (U/L)											
Baseline	Mean (SD)	223.6 (85.7)	-	225.6 (58.9)	-	222.8 (42.8)	-	209.1 (40.4)	-	204.9 (79.2)	-
	n		12		13		12		13		12
Week 4	Mean (SD)	224.5 (75)	0.9 (21.3)	250.5 (67.2)	24.8 (37.1)	255.3 (40.4)	27.1 (42)	254.9 (53)	45.8 (31)	274.8 (71.8)	69.9 (95)
	n		12		13		11		13		12
Week 8	Mean (SD)	249 (84.5)	25.4 (28.7)	286.6 (65.5)	56.8 (48.3)	265.6 (31.5)	42.8 (40.2)	251.8 (65.6)	43.9 (53.6)	251.8 (64.4)	46.8 (58.8)
	n		12		12		12				12
Week 13	Mean (SD)	278.7 (96.9)	42.8 (56.2)	284.8 (81.5)	58.1 (50.1)	277.8 (42.3)	54.9 (36.6)	263.8 (57.4)	54.7 (43.3)	254.6 (85.5)	49.7 (58.4)
	n		10		12		12		13		12

Evaluation		Norditropin 0.035 mg/kg/day (N=12)		Norditropin 0.067 mg/kg/day (N=13)		Somapacitan 0.16 mg/kg/week (N=12)		Somapacitan 0.20 mg/kg/week (N=13)		Somapacitan 0.24 mg/kg/week (N=12)	
		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Week 26	Mean (SD)	273.5 (103.3)	42.5 (49)	311.5 (80.1)	85.8 (38.9)	256.8 (46.8)	34 (37.1)	269.6 (52.5)	58.4 (46.5)	266.8 (54.3)	61.8 (63.9)
	n		11		13		12		12		12
Week 39	Mean (SD)	255.3 (89)	24.4 (38.6)	311 (80.2)	85.4 (37.4)	266.1 (38.6)	43.2 (41.7)	265.8 (50.6)	52.8 (47.7)	282.2 (65)	77.3 (61.6)
	n		11		13		12		12		12

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
n = number of subjects with available data.

Table 121. Number (%) of Subjects With Alkaline Phosphatase Levels Outside the Normal Range, Main Period and Extension Period I (Week 0 to Week 52), Trial 4245, Safety Population

Parameter		Norditropin 0.035 mg/kg/Day (N=12) n (%)	Norditropin 0.067 mg/kg/Day (N=13) n (%)	Somapacitan 0.16 mg/kg/Week (N=12) n (%)	Somapacitan 0.20 mg/kg/Week (N=13) n (%)	Somapacitan 0.24 mg/kg/Week (N=12) n (%)
Alkaline phosphatase						
Total	n	12	13	12	13	12
	Low (< LLN)	0	0	0	0	0
	High (> ULN)	4 (33.3)	10 (76.9)	7 (58.3)	7 (53.8)	7 (58.3)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; ULN, upper limit of normal; n, number of subjects with available data.

Table 122. Mean (SD) IGF-1 SDS, Main Period and Extension Period I (Weeks 0 to 52), Trial 4245

Treatment		0.035 mg/kg/Day Norditropin (N=12)	0.067 mg/kg/Day Norditropin (N=13)	0.16 mg/kg/Week somapacitan (N=12)	0.2 mg/kg/Week somapacitan (N=13)	0.24 mg/kg/Week somapacitan (N=12)
IGF-1 SDS						
Baseline	Mean (SD)	-0.9 (1.1)	-0.6 (0.8)	-0.5 (0.8)	-0.3 (0.9)	-0.2 (1)
	n	12	13	12	13	12
Week 4	Mean (SD)	0.8 (1)	1.3 (1)	0.2 (1.2)	0.4 (0.8)	1.1 (1.6)
	n	12	13	11	13	12
Week 8	Mean (SD)	0.7 (1.1)	1.7 (0.8)	1.3 (1.3)	2.2 (1.3)	2.6 (1.4)
	n	12	12	12	13	12
Week 13	Mean (SD)	0.6 (1)	2.1 (1.1)	0.3 (1.3)	0.4 (0.6)	0.9 (1.1)
	n	11	13	12	13	12
Week 26	Mean (SD)	0.7 (1)	1.5 (1.2)	1 (1.2)	1.7 (1.1)	2.8 (1.6)
	n	11	13	12	12	12
Week 39	Mean (SD)	0.9 (1.3)	1.6 (1.2)	1.5 (1.3)	1.7 (1.2)	2.8 (1.6)
	n	11	13	11	12	9
Week 52	Mean (SD)	1.1 (1.2)	1.8 (1.5)	0.9 (0.9)	1.7 (1.6)	2.8 (1.5)
	n	11	13	11	12	12

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n, number of subjects with available data

Table 123. Adverse Events Reported by Subjects in the Main and Extension Period I (While on Randomized Therapy) of Trial 4245 While IGF-1 > 3 SDS on at Least Two Consecutive Visits

Treatment	Norditropin 0.035mg/kg/Day (N=12) n (%)	Norditropin 0.067mg/kg/Day (N=13) n (%)	Somapacitan 0.16mg/kg/Week (N=12) n (%)	Somapacitan 0.20mg/kg/Week (N=13) n (%)	Somapacitan 0.24mg/kg/Week (N=12) n (%)
IGF-1 > 3 SDS for two or more consecutive visits	0	2 (15.4)	1 (8.3)	0	4 (33.3)
Any AE in subjects while IGF-1 >3 for two or more consecutive visits	0	2 (15.4)	1 (8.3)	0	3 (25)
Nasopharyngitis	0	1 (7.7)	0	0	1 (7.7)
Otitis media/ear infection	0	1 (7.7)	1 (8.3)	0	0
Cough	0	1 (7.7)	1 (8.3)	0	0
Contusion	0	0	0	0	1 (7.7)
Urticaria	0	0	0	0	1 (7.7)
Eczema	0	0	0	0	1 (7.7)
Enteritis	0	0	0	0	1 (7.7)
Radius fracture	0	0	0	0	1 (7.7)
Varicella	0	0	0	0	1 (7.7)
Hyperglycemia	0	0	0	0	1 (7.7)
Glycosylated hemoglobin increased	0	0	0	0	1 (7.7)
Lipoatrophy	0	0	1 (8.3)	0	0
Rhinitis	0	0	1 (8.3)	0	0
Lymphadenitis	0	1 (7.7)	0	0	0
Rhinorrhea	0	1 (7.7)	0	0	0
COVID19	0	1 (7.7)	0	0	0
Respiratory disorder	0	1 (7.7)	0	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical, and the Clinical Trial Report for trial 4245, Appendix 9.2.7.12, pages 96 to 106.

15.4.3.3. Trial NN8640-4469

Table 124. SGA Subject Disposition in Trial 4469

	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8) n (%)	Total (N = 12) n (%)
Exposed in 26-week Main Period	4 (100)	8 (100)	12 (100)
Completed treatment in the 26-week Main Period	4 (100)	8 (100)	12 (100)
Early withdrawal from treatment in 26-week Main Period	0	0	0
Early withdrawal from trial during the 26-week Main Period	0	0	0
Rolled over into Extension Period I	4 (100)	8 (100)	12 (100)
Early withdrawal from treatment in Extension Period I	0	0	0
Early withdrawal from trial during the Extension Period I	0	0	0

Source: Data compiled from trial 4469 ADSL datasets and from the Clinical Trial Report for trial 4469, Table 4-1, page 50.
Abbreviations: SGA, small for gestational age

Table 125. NS Subject Disposition in Trial 4469

	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7) n (%)	Total (N = 13) n (%)
Exposed in 26-week Main Period	6 (100)	7 (100)	13 (100)
Completed treatment in the 26-week Main Period	6 (100)	7 (100)	13 (100)
Early withdrawal from treatment in 26-week Main Period	0	0	0
Early withdrawal from trial during the 26-week Main Period	0	0	0
Rolled over into Extension Period I	6 (100)	7 (100)	13 (100)
Early withdrawal from treatment in Extension Period I	0	0	0
Early withdrawal from trial during the Extension Period I	0	0	0

Source: Data compiled from trial 4469 ADSL datasets and from the Clinical Trial Report for trial 4469, Table 4-2, page 51.
Abbreviations: NS, Noonan syndrome

Table 126. ISS Subject Disposition in Trial 4469

	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9) n (%)	Total (N = 11) n (%)
Exposed in 26-week Main Period	2 (100)	9 (100)	11 (100)
Completed treatment in the 26-week Main Period	2 (100)	9 (100)	11 (100)
Early withdrawal from treatment in 26-week Main Period	0	0	0
Early withdrawal from trial during the 26-week Main Period	0	0	0
Rolled over into Extension Period I	2 (100)	9 (100)	11 (100)
Early withdrawal from treatment in Extension Period I	0	0	0
Early withdrawal from trial during the Extension Period I	0	0	0

Source: Data compiled from trial 4469 ADSL datasets and from the Clinical Trial Report for trial 4469, Table 4-3, page 53.
Abbreviations: ISS, idiopathic short stature

Table 127. Reported Comorbidities in the SGA Population, Trial 4469

Comorbidity	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=4)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=8)	Total (N=12)
Any comorbidity, n (%)	4 (100.0)	8 (100.0)	12 (100.0)
Small for dates baby	4 (100.0)	8 (100.0)	12 (100.0)
Seasonal allergy	0	3 (37.5)	3 (25.0)
Vitamin D deficiency	1 (25.0)	1 (12.5)	2 (16.7)
Appendicectomy	0	1 (12.5)	1 (8.3)
Asthma	0	1 (12.5)	1 (8.3)
Autism spectrum disorder	0	1 (12.5)	1 (8.3)
Cardiac murmur functional	0	1 (12.5)	1 (8.3)
Circumcision	1 (25.0)	0	1 (8.3)
Cleft palate repair	1 (25.0)	0	1 (8.3)
Cytogenetic abnormality	0	1 (12.5)	1 (8.3)
Eczema	1 (25.0)	0	1 (8.3)
Eye movement disorder	1 (25.0)	0	1 (8.3)
Food allergy	0	1 (12.5)	1 (8.3)
Headache	0	1 (12.5)	1 (8.3)
Hypercholesterolemia	0	1 (12.5)	1 (8.3)
Hypersensitivity	1 (25.0)	0	1 (8.3)
Mutism	0	1 (12.5)	1 (8.3)
Osteopenia	0	1 (12.5)	1 (8.3)
Otitis media acute	0	1 (12.5)	1 (8.3)
Otospondylomegaepiphyseal dysplasia	1 (25.0)	0	1 (8.3)
Precocious puberty	1 (25.0)	0	1 (8.3)
Refraction disorder	0	1 (12.5)	1 (8.3)

Comorbidity	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=4)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=8)	Total (N=12)
Tourette's disorder	0	1 (12.5)	1 (8.3)
Visual field defect	0	1 (12.5)	1 (8.3)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical
Abbreviations: SGA, small for gestational age

Table 128. Reported Comorbidities in the NS Population, Trial 4469

Comorbidity	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=6)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=7)	Total (N=13)
Any comorbidity, n (%)	6 (100.0)	7 (100.0)	13 (100.0)
Noonan syndrome	6 (100.0)	7 (100.0)	13 (100.0)
Pulmonary valve stenosis	2 (33.3)	3 (42.9)	5 (38.5)
Cryptorchism	2 (33.3)	0	2 (15.4)
Eyelid ptosis	1 (16.7)	1 (14.3)	2 (15.4)
Hypothyroidism	2 (33.3)	0	2 (15.4)
Vitamin D deficiency	1 (16.7)	1 (14.3)	2 (15.4)
Adenoidectomy	0	1 (14.3)	1 (7.7)
Adenotonsillectomy	0	1 (14.3)	1 (7.7)
Aortic valve incompetence	1 (16.7)	0	1 (7.7)
Arthralgia	0	1 (14.3)	1 (7.7)
Asthma exercise induced	0	1 (14.3)	1 (7.7)
Attention deficit hyperactivity disorder	0	1 (14.3)	1 (7.7)
Autoimmune thyroiditis	1 (16.7)	0	1 (7.7)
Bone density decreased	1 (16.7)	0	1 (7.7)
Coarctation of the aorta	1 (16.7)	0	1 (7.7)
Cognitive disorder	0	1 (14.3)	1 (7.7)
Concussion	0	1 (14.3)	1 (7.7)
Defect conduction intraventricular	0	1 (14.3)	1 (7.7)
Ear tube insertion	0	1 (14.3)	1 (7.7)
Entropion	0	1 (14.3)	1 (7.7)
Enuresis	1 (16.7)	0	1 (7.7)
Epilepsy	1 (16.7)	0	1 (7.7)
Gastroesophageal reflux disease	0	1 (14.3)	1 (7.7)
Goiter	1 (16.7)	0	1 (7.7)
Gynecomastia	0	1 (14.3)	1 (7.7)
Inguinal hernia	1 (16.7)	0	1 (7.7)
Iron deficiency	1 (16.7)	0	1 (7.7)
Learning disorder	0	1 (14.3)	1 (7.7)
Neurodevelopmental delay	0	1 (14.3)	1 (7.7)
Respiratory disorder	1 (16.7)	0	1 (7.7)
Scoliosis	0	1 (14.3)	1 (7.7)
Seasonal allergy	0	1 (14.3)	1 (7.7)
Separation anxiety disorder	0	1 (14.3)	1 (7.7)
Syncope	0	1 (14.3)	1 (7.7)

Comorbidity	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=6)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=7)	Total (N=13)
Tonsillar hypertrophy	1 (16.7)	0	1 (7.7)
Tonsillectomy	0	1 (14.3)	1 (7.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical
Abbreviations: NS, Noonan syndrome

Table 129. Reported Comorbidities in the ISS Population, Trial 4469

Comorbidity	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=2)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=9)	Total (N=11)
Any comorbidity, n (%)	2 (100.0)	9 (100.0)	11 (100.0)
Short stature	2 (100.0)	9 (100.0)	11 (100.0)
Hypothyroidism	0	2 (22.2)	2 (18.2)
Seasonal allergy	0	2 (22.2)	2 (18.2)
Bronchitis	0	1 (11.1)	1 (9.1)
Constipation	0	1 (11.1)	1 (9.1)
Developmental hip dysplasia	0	1 (11.1)	1 (9.1)
Dry skin	0	1 (11.1)	1 (9.1)
Headache	1 (50.0)	0	1 (9.1)
Hypersensitivity	1 (50.0)	0	1 (9.1)
Meningitis enteroviral	0	1 (11.1)	1 (9.1)
Nasopharyngitis	0	1 (11.1)	1 (9.1)
Otitis media chronic	1 (50.0)	0	1 (9.1)
Pneumonia	0	1 (11.1)	1 (9.1)
Spinal deformity	0	1 (11.1)	1 (9.1)
Ventricular septal defect	0	1 (11.1)	1 (9.1)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical
Abbreviations: ISS, idiopathic short stature

Table 130. Concomitant Medications in the SGA Population, Trial 4469

Medication	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=4)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=8)	Total (N=12)
Any medication, n (%)	4 (100.0)	5 (62.5)	9 (75)
IBUPROFEN	0	3 (37.5)	3 (25.0)
AMOXICILLIN;CLAVULANATE POTASSIUM	2 (50.0)	0	2 (16.7)
CLARITHROMYCIN	0	2 (25.0)	2 (16.7)
COLECALCIFEROL	1 (25.0)	1 (12.5)	2 (16.7)
LEVOCETIRIZINE DIHYDROCHLORIDE	1 (25.0)	1 (12.5)	2 (16.7)
MELATONIN	0	2 (25.0)	2 (16.7)
ACETYLSALICYLIC ACID;ASCORBIC ACID	1 (25.0)	0	1 (8.3)
ANASTROZOLE	0	1 (12.5)	1 (8.3)
ASCORBIC ACID;RUTOSIDE	1 (25.0)	0	1 (8.3)
AZITHROMYCIN	0	1 (12.5)	1 (8.3)
BACLOFEN	1 (25.0)	0	1 (8.3)
BROMHEXINE	1 (25.0)	0	1 (8.3)
CALCIUM CARBONATE	0	1 (12.5)	1 (8.3)

Medication	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=4)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=8)	Total (N=12)
CETIRIZINE	1 (25.0)	0	1 (8.3)
CETIRIZINE HYDROCHLORIDE	0	1 (12.5)	1 (8.3)
CHONDROITIN SULFATE;HYALURONIC ACID;POLOXAMER 407	0	1 (12.5)	1 (8.3)
DIMETICONE	0	1 (12.5)	1 (8.3)
DOXYCYCLINE	0	1 (12.5)	1 (8.3)
ERGOCALCIFEROL;RETINOL	1 (25.0)	0	1 (8.3)
FLUCONAZOLE	1 (25.0)	0	1 (8.3)
FLUTICASONE PROPIONATE;SALMETEROL XINAFOATE	0	1 (12.5)	1 (8.3)
HELICID	0	1 (12.5)	1 (8.3)
LACTIPLANTIBACILLUS PLANTARUM	0	1 (12.5)	1 (8.3)
LEVOSALBUTAMOL HYDROCHLORIDE	0	1 (12.5)	1 (8.3)
LORATADINE	0	1 (12.5)	1 (8.3)
MACROGOL 3350	0	1 (12.5)	1 (8.3)
MONTELUKAST	1 (25.0)	0	1 (8.3)
NASAL PREPARATIONS	0	1 (12.5)	1 (8.3)
OLOPATADINE	0	1 (12.5)	1 (8.3)
PARACETAMOL	0	1 (12.5)	1 (8.3)
PROBIOTICS [UMBRELLA TERM]	0	1 (12.5)	1 (8.3)
RIFAXIMIN	0	1 (12.5)	1 (8.3)
SALBUTAMOL	1 (25.0)	0	1 (8.3)
SOMATROPIN	0	1 (12.5)	1 (8.3)
TRIPTORELIN EMBONATE	1 (25.0)	0	1 (8.3)
TROSPIUM CHLORIDE	0	1 (12.5)	1 (8.3)
VITAMIN D NOS	1 (25.0)	0	1 (8.3)
VITAMINS NOS	0	1 (12.5)	1 (8.3)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: SGA, small for gestational age

Table 131. Concomitant Medications in the NS Population, Trial 4469

Medication	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=6)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=7)	Total (N=13)
Any medication, n (%)	6 (100.0)	5 (71.4)	11 (84.6)
AMOXICILLIN	1 (16.7)	2 (28.6)	3 (23.1)
CEFUROXIME	3 (50.0)	0	3 (23.1)
VITAMIN D NOS	2 (33.3)	1 (14.3)	3 (23.1)
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	1 (16.7)	1 (14.3)	2 (15.4)
IBUPROFEN	0	2 (28.6)	2 (15.4)
LEVOTHYROXINE SODIUM	2 (33.3)	0	2 (15.4)
LORATADINE	1 (16.7)	1 (14.3)	2 (15.4)
PARACETAMOL	1 (16.7)	1 (14.3)	2 (15.4)
SOMATROPIN	0	2 (28.6)	2 (15.4)

Medication	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=6)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=7)	Total (N=13)
AMMONIUM CHLORIDE;DIPHENHYDRAMINE;SODIUM CITRATE	1 (16.7)	0	1 (7.7)
ASCORBIC ACID;FERROUS SULFATE	1 (16.7)	0	1 (7.7)
BENZYDAMINE HYDROCHLORIDE	1 (16.7)	0	1 (7.7)
BROMHEXINE	1 (16.7)	0	1 (7.7)
CALCIUM CARBONATE	1 (16.7)	0	1 (7.7)
CEFACLOR	0	1 (14.3)	1 (7.7)
CEFALEXIN	0	1 (14.3)	1 (7.7)
CETIRIZINE	1 (16.7)	0	1 (7.7)
CETIRIZINE HYDROCHLORIDE	0	1 (14.3)	1 (7.7)
CIPROFLOXACIN HYDROCHLORIDE;DEXAMETHASONE	0	1 (14.3)	1 (7.7)
COLECALCIFEROL	1 (16.7)	0	1 (7.7)
COPTIS SPP. RHIZOME;HEDERA HELIX LEAF	0	1 (14.3)	1 (7.7)
DEXIBUPROFEN	0	1 (14.3)	1 (7.7)
DIPHENHYDRAMINE HYDROCHLORIDE	0	1 (14.3)	1 (7.7)
ERDOSTEINE	0	1 (14.3)	1 (7.7)
ESCITALOPRAM OXALATE	0	1 (14.3)	1 (7.7)
FERROUS SULFATE	1 (16.7)	0	1 (7.7)
FERROUS SULFATE;FOLIC ACID	1 (16.7)	0	1 (7.7)
INOSINE PRANOBEX;ZINC GLUCONATE	1 (16.7)	0	1 (7.7)
LACTOBACILLUS RHAMNOSUS	0	1 (14.3)	1 (7.7)
LAMOTRIGINE	1 (16.7)	0	1 (7.7)
LEVETIRACETAM	1 (16.7)	0	1 (7.7)
LEVOCETIRIZINE DIHYDROCHLORIDE	1 (16.7)	0	1 (7.7)
LEVODROPROPIZINE	0	1 (14.3)	1 (7.7)
LONAPEGSOMATROPIN TCGD	0	1 (14.3)	1 (7.7)
MEFENAMIC ACID	1 (16.7)	0	1 (7.7)
METHYLPHENIDATE	0	1 (14.3)	1 (7.7)
METHYLPHENIDATE HYDROCHLORIDE	0	1 (14.3)	1 (7.7)
METHYLPREDNISOLONE	0	1 (14.3)	1 (7.7)
MOMETASONE FUROATE	1 (16.7)	0	1 (7.7)
OLOPATADINE HYDROCHLORIDE	0	1 (14.3)	1 (7.7)
OMEPRAZOLE	0	1 (14.3)	1 (7.7)
REBAMIPIDE	0	1 (14.3)	1 (7.7)
SALBUTAMOL	0	1 (14.3)	1 (7.7)
SEA WATER	1 (16.7)	0	1 (7.7)
SIMETICONE	1 (16.7)	0	1 (7.7)
TETANUS VACCINE TOXOID	1 (16.7)	0	1 (7.7)
TOLTERODINE	1 (16.7)	0	1 (7.7)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: NS, Noonan syndrome

Table 132. Concomitant Medications in the ISS Population, Trial 4469

Medication	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=2)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=9)	Total (N=11)
Any medication, n (%)	2 (100.0)	8 (88.9)	10 (90.9)
IBUPROFEN	1 (50.0)	5 (55.6)	6 (54.5)
PARACETAMOL	2 (100.0)	1 (11.1)	3 (27.3)
AZITHROMYCIN	1 (50.0)	1 (11.1)	2 (18.2)
KETOTIFEN FUMARATE	0	2 (22.2)	2 (18.2)
LEVOTHYROXINE SODIUM	0	2 (22.2)	2 (18.2)
SACCHAROMYCES BOULARDII	0	2 (22.2)	2 (18.2)
SOMATROPIN	0	2 (22.2)	2 (18.2)
ACETYLCYSTEINE	0	1 (11.1)	1 (9.1)
AESCULUS HIPPOCASTANUM SEED;ESCULOSIDE;RUTOSIDE	0	1 (11.1)	1 (9.1)
AMOXICILLIN	0	1 (11.1)	1 (9.1)
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	0	1 (11.1)	1 (9.1)
ANASTROZOLE	1 (50.0)	0	1 (9.1)
BEPOTASTINE BESILATE	0	1 (11.1)	1 (9.1)
BUDESONIDE;FORMOTEROL FUMARATE	1 (50.0)	0	1 (9.1)
CALCIUM CARBONATE	1 (50.0)	0	1 (9.1)
CARBOCISTEINE;SOBREROL	0	1 (11.1)	1 (9.1)
CHLORPHENAMINE MALEATE	0	1 (11.1)	1 (9.1)
CHLORPHENAMINE MALEATE;PHENYLEPHRINE HYDROCHLORIDE	0	1 (11.1)	1 (9.1)
CLEMASTINE	0	1 (11.1)	1 (9.1)
COLECALCIFEROL	0	1 (11.1)	1 (9.1)
DEXTROMETHORPHAN HYDROBROMIDE;DIPHENHYDRAMINE HYDROCHLORIDE;GUAIFENESIN;PARACETAMOL;PHENYLEPHRINE HYDROCHLORIDE	0	1 (11.1)	1 (9.1)
DEXTROMETHORPHAN HYDROBROMIDE;DOXYLAMINE SUCCINATE;EPHEDRINE SULFATE;ETHANOL;PARACETAMOL	0	1 (11.1)	1 (9.1)
DEXTROMETHORPHAN HYDROBROMIDE;GUAIFENESIN;PARACETAMOL;PSEUDOEPHEDRINE HYDROCHLORIDE	0	1 (11.1)	1 (9.1)
DIOSMECTITE	0	1 (11.1)	1 (9.1)
DIPHENHYDRAMINE	1 (50.0)	0	1 (9.1)
ESSENTIAL OILS NOS;MENTHOL	1 (50.0)	0	1 (9.1)
FLUTICASONE PROPIONATE	1 (50.0)	0	1 (9.1)
ITRACONAZOLE	1 (50.0)	0	1 (9.1)
KETOCONAZOLE	1 (50.0)	0	1 (9.1)
LEUPRORELIN ACETATE	0	1 (11.1)	1 (9.1)
LEVODROPROPIZINE	0	1 (11.1)	1 (9.1)
LORATADINE	1 (50.0)	0	1 (9.1)
MACROGOL 3350	0	1 (11.1)	1 (9.1)
MELATONIN	0	1 (11.1)	1 (9.1)
METHYLPREDNISOLONE	0	1 (11.1)	1 (9.1)

Medication	Somapacitan 0.24 mg/kg/Week Treatment Naïve (N=2)	Somapacitan 0.24 mg/kg/Week Treatment Non-Naïve (N=9)	Total (N=11)
MONTELUKAST SODIUM	0	1 (11.1)	1 (9.1)
MULTIVITAMINS, PLAIN	0	1 (11.1)	1 (9.1)
PROBIOTICS [UMBRELLA TERM]	0	1 (11.1)	1 (9.1)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	1 (11.1)	1 (9.1)
SALBUTAMOL	1 (50.0)	0	1 (9.1)
SENNOSIDE A+B	0	1 (11.1)	1 (9.1)
SULFAMETHOXAZOLE;TRIMETHOPRIM	0	1 (11.1)	1 (9.1)
TERBINAFINE HYDROCHLORIDE	1 (50.0)	0	1 (9.1)
TRIMEBUTINE MALEATE	0	1 (11.1)	1 (9.1)
TRIPTORELIN	0	1 (11.1)	1 (9.1)
TRIPTORELIN EMBONATE	0	1 (11.1)	1 (9.1)
TULOBUTEROL	0	1 (11.1)	1 (9.1)
VITAMIN D NOS	0	1 (11.1)	1 (9.1)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: ISS, idiopathic short stature

Table 133. Mean (SD) Annualized Height Velocity, Trial 4469

Population	Treatment Status	SGA Naïve N = 4	SGA Non-Naïve N = 8	NS Naïve N = 6	NS Non-Naïve N = 7	ISS Naïve N = 2	ISS Non-Naïve N = 9	TS Naïve N = 3	TS Non-Naïve N = 8
AHV (cm/year)									
Baseline	Mean (SD)	4.6 (2.2)	7.2 (2.2)	4.2 (2.3)	6.2 (1.5)	3.3 (0.4)	8 (2.9)	(b) (4)	
	n	4	8	6	7	2	9		
Week 26	Mean (SD)	11.3 (3.8)	9.5 (2)	9.1 (2.3)	6.4 (2)	9.2 (3.5)	7.9 (2.4)	10.2 (2.2)	5.8 (2)
	n	4	8	6	7	2	9	3	8
Week 52	Mean (SD)	11 (-)	9.1 (1.7)	-	6.4 (2.7)	8.2 (3.5)	7.7 (2.2)	(b) (4)	
	n	1	4	-	3	2	8		
Week 78	Mean (SD)	-	9 (-)	-	5.7 (-)	9.2 (-)	9.4 (3.5)		
	n	-	1	-	1	1	2		

Source: Clinical Trial Report for trial 4469, Table 8.2.21, pages199 to 200; Table 8.2.22, page 201; Table 8.2.23, pages 202 to 203; Table 8.2.24, page 204.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome

Table 134. Mean (SD) Annualized Height Velocity SDS, Trial 4469

Population	Treatment Status	SGA Naïve N = 4	SGA Non-Naïve N = 8	NS Naïve N = 6	NS Non-Naïve N = 7	ISS Naïve N = 2	ISS Non-Naïve N = 9	TS Naïve N = 3	TS Non-Naïve N = 8
AHV SDS									
Baseline	Mean (SD)	-0.1 (1.5)	0.8 (1.1)	-0.4 (1.4)	0.5 (0.7)	-1.5 (0.2)	1.3 (1.1)	(b) (4)	
	n	4	8	6	7	2	9		
Week 26	Mean (SD)	3.5 (1.5)	1.8 (1)	3 (2.7)	0.7 (1.2)	1.4 (0.6)	1 (1.3)		
	n	4	8	6	7	2	9		

Population Treatment Status		SGA Naïve N = 4	SGA Non-Naïve N = 8	NS Naïve N = 6	NS Non-Naïve N = 7	ISS Naïve N = 2	ISS Non-Naïve N = 9	TS Naïve N = 3	TS Non-Naïve N = 8
Week 52	Mean (SD)	1.5 (-)	1.2 (0.6)	-	0.2 (0.5)	1.1 (0.6)	1 (1.2)		(b) (4)
	n	1	4	-	3	2	8		
Week 78	Mean (SD)	-	0.9 (-)	-	-0.8 (-)	1.9 (-)	1 (1.5)		
	n	-	1	-	1	1	2		

Source: Clinical Trial Report for trial 4469, Table 8.2.65, pages 241 to 242; Table 8.2.66, page 243; Table 8.2.67, pages 244 to 245; Table 8.2.68, page 246.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome

Table 135. Mean (SD) Height SDS, Treatment Naïve Subjects, Trial 4469

Population Treatment Status		SGA Naïve N = 4		NS Naïve N = 6		ISS Naïve N = 2		TS Naïve N = 3	
Height SDS		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Baseline	Mean (SD)	-2.9 (0.5)	-	-2.7 (0.5)	-	-2.7 (0.2)	-		(b) (4)
	n		4		6		2		
Week 26	Mean (SD)	-2.4 (0.6)	0.5 (0.2)	-2.3 (0.7)	0.4 (0.3)	-2.5 (0)	0.2 (0.2)		
	n		4		6		2		
Week 52	Mean (SD)	-2.1 (-)	0.5 (-)	-	-	-2.3 (0.1)	0.4 (0.3)		
	n		1		-		2		
Week 78	Mean (SD)	-	-	-	-	-2 (-)	0.8 (-)		
	n		-		-		1		

Source: Clinical Trial Report for trial 4469, Table 8.2.41, pages 219 to 220; Table 8.2.42, page 221; Table 8.2.43, pages 222 to 223; Table 8.2.44, page 224; Table 8.2.53, page 231; Table 8.2.54, page 232; Table 8.2.55, page 233; Table 8.2.56, page 234.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome

Table 136. Mean (SD) Height SDS, Treatment Non-Naïve Subjects, Trial 4469

Population Treatment Status		SGA Non-Naïve N = 8		NS Non-Naïve N = 7		ISS Non-Naïve N = 9		TS Non-Naïve N = 8	
Height SDS		Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline	Value	Change From Baseline
Baseline	Mean (SD)	-1.2 (0.6)	-	-1.5 (0.8)	-	-1.6 (1.3)	-		(b) (4)
	n		8		7		9		
Week 26	Mean (SD)	-1 (0.6)	0.2 (0.1)	-1.4 (0.8)	0.1 (0.1)	-1.5 (1.3)	0.1 (0.2)		
	n		8		7		9		
Week 52	Mean (SD)	-1.2 (0.3)	0.3 (0.2)	-1.3 (1.2)	0.1 (0.2)	-1.6 (1.2)	0.2 (0.4)		
	n		4		3		8		
Week 78	Mean (SD)	-0.9 (-)	0.4 (-)	-0.8 (-)	-0.1 (-)	-0.1 (1.4)	0.3 (0.1)		
	n		1		1		2		

Source: Clinical Trial Report for trial 4469, Table 8.2.41, pages 219 to 220; Table 8.2.42, page 221; Table 8.2.43, pages 222 to 223; Table 8.2.44, page 224; Table 8.2.53, page 231; Table 8.2.54, page 232; Table 8.2.55, page 233; Table 8.2.56, page 234.
Abbreviations: n, number of subjects with available data; ISS, idiopathic short stature; NS, Noonan syndrome; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome

Table 137. Mean (SD) Bone Age by Visit, Trial 4469

		SGA		NS		ISS		TS	
Population		Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve
Treatment Status		N = 4	N = 8	N = 6	N = 7	N = 2	N = 9	N = 3	N = 8
Change in bone age (years)									
Baseline	Mean (SD)	10.5 (1.8)	11.1 (1.7)	9.3 (2.6)	11.9 (1.5)	13.8 (1.8)	11.1 (2.3)	(b) (4)	
	n	4	8	6	7	2	9		
Week 52	Mean (SD)	12.5 (-)	12.4 (1)	-	14.3 (2.3)	14.5 (0.7)	12.3 (1.2)		
	n	1	4	-	3	2	8		

Source: Clinical Trial Report for trial 4469, Table 8.2.89, page 263; Table 8.2.90, page 263; Table 8.2.91, page 264; Table 8.2.92, page 264.
Abbreviations: n, number of subjects with available data; ISS, idiopathic short stature; NS, Noonan syndrome; SGA, small for gestational age; TS, Turner syndrome

Table 138. Adverse Events by OCMQ Analysis, Trial 4469, SGA Safety Population

	SGA	
	0.24 mg/kg/Week Somapacitan Treatment Naïve	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve
OCMQ/GQ Term Preferred Term	(N=4) n (%)	(N=8) n (%)
Any AE	3 (75.0)	6 (75.0)
Respiratory Tract Infection	0	3 (37.5)
Pneumonia	0	1 (12.5)
Pneumonia viral	0	1 (12.5)
Upper respiratory tract infection	0	1 (12.5)
Constipation	0	2 (25.0)
Nasopharyngitis	1 (25.0)	1 (12.5)
Nasopharyngitis	1 (25.0)	0
Viral pharyngitis	0	1 (12.5)
Abdominal Pain	0	1 (12.5)
Acne	0	1 (12.5)
Bronchitis	0	1 (12.5)
Concussion	0	1 (12.5)
Fatigue	1 (25.0)	0
Lethargy	1 (25.0)	0
Gastrointestinal Microorganism Overgrowth	0	1 (12.5)
Gastroesophageal Reflux Disease	0	1 (12.5)
Headache	0	1 (12.5)
Limb Injury	0	1 (12.5)
Medication Error	0	1 (12.5)
Myalgia	0	1 (12.5)
Muscle strain	0	1 (12.5)

	SGA	
OCMQ/GQ Term Preferred Term	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8) n (%)
Pain In Extremity	0	1 (12.5)
Pyrexia	1 (25.0)	0
Tonsillitis	1 (25.0)	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: GQ, grouped query; OCMQ, OND custom medical query; SGA, small for gestational age

Table 139. Adverse Events by OCMQ Analysis, Trial 4469, NS Safety Population

	Noonan Syndrome	
OCMQ/GQ Term Preferred Term	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7) n (%)
Any AE	4 (66.7)	6 (85.7)
Cough	1 (16.7)	2 (28.6)
Ear infection	0	2 (28.6)
Headache	1 (16.7)	1 (14.3)
Nasopharyngitis	1 (16.7)	1 (14.3)
Nasopharyngitis	0	1 (14.3)
Pharyngitis	1 (16.7)	0
Pyrexia	1 (16.7)	1 (14.3)
Abdominal pain	1 (16.7)	0
Abdominal pain upper	1 (16.7)	0
Anemia	1 (16.7)	0
Iron deficiency anemia	1 (16.7)	0
Aortic Valve Incompetence	1 (16.7)	0
Bronchitis	0	1 (14.3)
COVID-19	0	1 (14.3)
Dysuria	0	1 (14.3)
Fall	1 (16.7)	0
Hemorrhage	0	1 (14.3)
Contusion	0	1 (14.3)
Hypothyroidism	1 (16.7)	0
Blood thyroid stimulating hormone increased	1 (16.7)	0
Injection site reaction	0	1 (14.3)
Injection site bruising	0	1 (14.3)
Lipodystrophy acquired	0	1 (14.3)
Oropharyngeal pain	1 (16.7)	0
Respiratory tract infection	1 (16.7)	0
Upper respiratory tract infection	1 (16.7)	0
Rhinorrhea	1 (16.7)	0
Scarlet fever	1 (16.7)	0
Seasonal allergy	0	1 (14.3)

	Noonan Syndrome	
OCMQ/GQ Term Preferred Term	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7) n (%)
Seizure	1 (16.7)	0
Epilepsy	1 (16.7)	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: GQ, grouped query; NS, Noonan syndrome; OCMQ, OND custom medical query

Table 140. Adverse Events by OCMQ Analysis, Trial 4469, ISS Safety Population

	ISS	
OCMQ/GQ Term Preferred Term	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9) n (%)
Any AE	2 (100.0)	8 (88.9)
Respiratory tract infection	0	4 (44.4)
Upper respiratory tract infection	0	2 (22.2)
Pneumonia	0	1 (11.1)
Respiratory syncytial virus infection	0	1 (11.1)
Abdominal pain	1 (50.0)	2 (22.2)
Abdominal pain upper	1 (50.0)	1 (11.1)
Abdominal pain	0	1 (11.1)
Cough	2 (100.0)	1 (11.1)
Cough	2 (100.0)	1 (11.1)
Productive cough	0	1 (11.1)
Arthralgia	2 (100.0)	0
Pyrexia	1 (50.0)	1 (11.1)
Asthma exercise induced	1 (50.0)	0
Chest Pain	1 (50.0)	0
Coccydynia	0	1 (11.1)
Costochondritis	1 (50.0)	0
Diarrhea	0	1 (11.1)
Fracture	1 (50.0)	0
Avulsion fracture	1 (50.0)	0
Fungal infection	1 (50.0)	0
Fungal skin infection	1 (50.0)	0
Groin Pain	0	1 (11.1)
Hemorrhage	0	1 (11.1)
Contusion	0	1 (11.1)
Headache	0	1 (11.1)
Insulin-like growth factor increased	1 (50.0)	0
Ligament sprain	0	1 (11.1)
Myalgia	0	1 (11.1)
Nasopharyngitis	0	1 (11.1)
Odynophagia	0	1 (11.1)
Osteitis	1 (50.0)	0
Overdose	0	1 (11.1)
Accidental overdose	0	1 (11.1)

	ISS	
OCMQ/GQ Term Preferred Term	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9) n (%)
Precocious puberty	0	1 (11.1)
Product administration error	0	1 (11.1)
Seasonal allergy	0	1 (11.1)
Sports injury	0	1 (11.1)
Tendon pain	0	1 (11.1)
Underdose	0	1 (11.1)
Accidental underdose	0	1 (11.1)
Wheezing	1 (50.0)	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: GQ, grouped query; ISS, idiopathic short stature; OCMQ, OND custom medical query

Table 141. Mean (SD) Hematology Parameters After 52 Weeks of Treatment, Trial 4469, SGA Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=4)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Leukocytes (10^9/L)					
Baseline	Mean (SD)	7 (0.9)	-	6 (1.5)	-
	n		4		8
Week 26	Mean (SD)	6.5 (1.8)	-0.5 (2.3)	5.8 (1.2)	-0.3 (0.9)
	n		4		8
Week 52	Mean (SD)	6.3 (-)	-0.8 (-)	5.6 (1.5)	0 (0.5)
	n		1		4
Hematocrit (%)					
Baseline	Mean (SD)	42.5 (2.4)	-	40.9 (2.6)	-
	n		4		8
Week 26	Mean (SD)	41.7 (4.3)	-0.8 (2.4)	41 (2.4)	0.2 (1)
	n		4		8
Week 52	Mean (SD)	37.6 (-)	-4.8 (-)	43.4 (3.6)	1.4 (1.4)
	n		1		4
Thrombocytes (10^9/L)					
Baseline	Mean (SD)	321 (52)	-	281.4 (72.3)	-
	n		4		8
Week 26	Mean (SD)	335 (31.1)	14 (27.6)	285.6 (68)	4.2 (21.7)
	n		4		8
Week 52	Mean (SD)	380 (-)	3 (-)	292 (85.2)	1.8 (24.8)
	n		1		4

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n, number of subjects with available data; SD, standard deviation; SGA, small for gestational age

Table 142. Mean (SD) Hematology Parameters After 52 Weeks of Treatment, Trial 4469, NS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Leukocytes (10^9/L)					
Baseline	Mean (SD)	6 (0.5)	-	6.3 (0.8)	-
	n		6		7
Week 26	Mean (SD)	6.1 (0.9)	0.1 (0.6)	6.5 (1)	0.2 (1.1)
	n		6		7
Week 52	Mean (SD)	-	-	6.5 (1.2)	0.5 (0.6)
	n		0		3
Hematocrit (%)					
Baseline	Mean (SD)	40.8 (2.6)	-	40.9 (2.2)	-
	n		6		7
Week 26	Mean (SD)	40.7 (2)	-0.4 (3.9)	39.1 (1.7)	-1.9 (1.9)
	n		5		7
Week 52	Mean (SD)	-	-	41.7 (2)	-0.8 (1)
	n		0		3
Thrombocytes (10^9/L)					
Baseline	Mean (SD)	222.8 (55)	-	253 (64.4)	-
	n		6		7
Week 26	Mean (SD)	232.3 (63.2)	9.5 (21.1)	245.1 (92.1)	-7.9 (45.4)
	n		6		7
Week 52	Mean (SD)	-	-	243.3 (45.2)	2 (9.5)
	n		0		3

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation

Table 143. Mean (SD) Coagulation Parameters After 39 Weeks of Treatment, Trial 4469, NS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)
Prothrombin time (s)			
Week 4	Mean (SD)	12.1 (0.9)	13.3 (-)
	n	6	1
Week 39	Mean (SD)	11.6 (0.5)	12.6 (0.7)
	n	4	3
Partial thromboplastin time (s)			
Week 4	Mean (SD)	37.3 (3.6)	37.8 (-)
	n	6	1
Week 39	Mean (SD)	34.8 (4.7)	39.9 (4.4)
	n	4	3

Source: Data compiled from the Clinical Trial Report for trial 4469, Table 8.3.5.117, pages 974 and 975.
Per protocol, pretreatment values for coagulation parameters were not evaluated. Week 4 was the first visit where these were assessed.
Abbreviations: n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation

Table 144. Mean (SD) Hematology Parameters After 52 Weeks of Treatment, Trial 4469, ISS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Leukocytes (10^9/L)					
Baseline	Mean (SD)	7.2 (2.6)	-	5.7 (1.5)	-
	n		2		9
Week 26	Mean (SD)	5.1 (1.6)	-2.1 (1)	6.2 (2.3)	0.2 (2.9)
	n		2		8
Week 52	Mean (SD)	6.4 (1)	-0.8 (1.6)	7.8 (1.7)	1.6 (2.4)
	n		2		7
Hematocrit (%)					
Baseline	Mean (SD)	43.4 (5.3)	-	40 (2.7)	-
	n		2		9
Week 26	Mean (SD)	42 (3)	-1.4 (2.3)	39.3 (2.9)	-0.8 (1.3)
	n		2		8
Week 52	Mean (SD)	42.7 (3.7)	-0.7 (1.6)	40.4 (2.6)	0.2 (1.6)
	n		2		7
Thrombocytes (10^9/L)					
Baseline	Mean (SD)	272.5 (21.9)	-	292.6 (36.2)	-
	n		2		9
Week 26	Mean (SD)	250.5 (19.1)	-22 (41)	304.6 (53.3)	14 (27.9)
	n		2		8
Week 52	Mean (SD)	249.5 (40.3)	-23 (62.2)	292.7 (37.4)	4.9 (21.6)
	n		2		7

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; SD, standard deviation

Table 145. Number (%) of Subjects With Hematology Parameters Outside of Normal Range, Trial 4469, SGA Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=8) n (%)
Leukocytes			
Total	n	4	8
	Low (< LLN)	1 (25)	0
	High (> ULN)	0	0
Hematocrit			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	1 (25)	0

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=8) n (%)
Thrombocytes			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; n, number of subjects with available data; SGA, small for gestational age; ULN, upper limit of normal

Table 146. Number (%) of Subjects With Hematology Parameters Outside of Normal Range, Trial 4469, NS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=7) n (%)
Leukocytes			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	0	0
Hematocrit			
Total	n	5	7
	Low (< LLN)	0	0
	High (> ULN)	0	0
Thrombocytes			
Total	n	6	7
	Low (< LLN)	1 (16.7)	0
	High (> ULN)	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; n, number of subjects with available data; NS, Noonan syndrome; ULN, upper limit of normal

Table 147. Number (%) of Subjects With Coagulation Parameters That Shift to Outside of Normal Range, Trial 4469, NS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7) n (%)
Prothrombin time			
Week 4	Low (< LLN)	0	0
	High (> ULN)	0	0
	n	6	1
Week 39	Low (< LLN)	0	0
	High (> ULN)	0	0
	n	4	3
Partial thromboplastin time			
Week 4	Low (< LLN)	0	0
	High (> ULN)	1 (16.7)	0
	n	6	1

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7) n (%)
Week 39	Low (< LLN)	0	0
	High (> ULN)	1 (25)	2 (66.7)
	n	4	3

Source: Data compiled from the Clinical Trial Report for trial 4469, Table 8.3.5.118, page 976 and 977.
Per protocol, pretreatment values for coagulation parameters were not evaluated. Week 4 was the first visit where these were assessed.
Abbreviations: LLN, lower limit of normal; ULN, upper limit of normal; n, number of subjects with available data; NS, Noonan syndrome

Table 148. Number (%) of Subjects With Hematology Parameters Outside of Normal Range, Trial 4469, ISS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=9) n (%)
Leukocytes			
Total	n	2	8
	Low (< LLN)	0	1 (12.5)
	High (> ULN)	0	1 (12.5)
Hematocrit			
Total	n	2	9
	Low (< LLN)	0	1 (11.1)
	High (> ULN)	0	0
Thrombocytes			
Total	n	2	8
	Low (< LLN)	0	0
	High (> ULN)	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: ISS, idiopathic short stature; LLN, lower limit of normal; n, number of subjects with available data; ULN, upper limit of normal

Table 149. Mean (SD) Lipid Parameters After 52 Weeks of Treatment, Trial 4469, SGA Safety Population

Treatment		0.24 mg/kg/week Somapacitan Treatment Naïve (N=4)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Cholesterol (mg/dL)					
Baseline	Mean (SD)	189.3 (33.6)	-	189.5 (20.8)	-
	n		4		8
Week 26	Mean (SD)	180.8 (25.2)	-8.5 (16.5)	188.6 (22.2)	-0.9 (16.2)
	n		4		8
Week 52	Mean (SD)	187.2 (-)	10.1 (-)	171.6 (22.2)	-17.9 (17.2)
	n		1		4
Low density lipoprotein (mg/dL)					
Baseline	Mean (SD)	109.1 (26.9)	-	106.3 (16)	-
	n		4		8

Treatment		0.24 mg/kg/week Somapacitan Treatment Naïve (N=4)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Week 26	Mean (SD)	111.9 (23.3)	2.7 (6.8)	110.5 (18.8)	4.2 (10.4)
	n		4		8
Week 52	Mean (SD)	109 (-)	10.8 (-)	98.3 (19.2)	-5.9 (9.1)
	n		1		4
High density lipoprotein (mg/dL)					
Baseline	Mean (SD)	51.8 (9.4)	-	63.4 (11.3)	-
	n		4		8
Week 26	Mean (SD)	49.1 (8.3)	-2.7 (5.4)	56.7 (15.5)	-6.8 (11.1)
	n		4		8
Week 52	Mean (SD)	63 (-)	10.1 (-)	45.8 (11.2)	-18.5 (1.9)
	n		1		4
Triglycerides (mg/dL)					
Baseline	Mean (SD)	140.2 (46.8)	-	98.8 (33.4)	-
	n		4		8
Week 26	Mean (SD)	99.2 (11.4)	-41 (45.3)	106.8 (48.4)	8.1 (34.3)
	n		4		8
Week 52	Mean (SD)	74.4 (-)	-54.9 (-)	135.7 (43.9)	30.6 (41.5)
	n		1		4

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided cholesterol, lipoproteins, and triglycerides in units of mmol/L.
To provide cholesterol and lipoproteins in mg/dL in this table, this reviewer multiplied the mmol/L value by 38.67.
To provide triglycerides in mg/dL in this table, this reviewer multiplied the mmol/L value by 88.57.
Abbreviations: n, number of subjects with available data; SD, standard deviation; SGA, small for gestational age

Table 150. Mean (SD) Lipid Parameters After 52 Weeks of Treatment, Trial 4469, NS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Cholesterol (mg/dL)					
Baseline	Mean (SD)	167.4 (46.5)	-	141.4 (26.8)	-
	n		6		7
Week 26	Mean (SD)	176.9 (44.2)	9.5 (14.6)	131.5 (11.4)	-9.9 (21.5)
	n		6		7
Week 52	Mean (SD)	-	-	138.2 (7.9)	2.3 (6)
	n		0		3
Low density lipoprotein (mg/dL)					
Baseline	Mean (SD)	102.6 (37.7)	-	74 (14.1)	-
	n		6		7
Week 26	Mean (SD)	106.3 (31)	3.7 (20.2)	67.3 (11.6)	-6.7 (14.4)
	n		6		7
Week 52	Mean (SD)	-	-	78.8 (8.2)	6.3 (4.2)
	n		0		3

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
High density lipoprotein (mg/dL)					
Baseline	Mean (SD)	49.6 (17.1)	-	50.5 (16.7)	-
	n		6		7
Week 26	Mean (SD)	47.8 (12.1)	-1.8 (16.1)	49.8 (9.6)	-0.7 (13.7)
	n		6		7
Week 52	Mean (SD)	-	-	48.5 (1.6)	
	n		0		3
Triglycerides (mg/dL)					
Baseline	Mean (SD)	75 (30.9)	-	83.9 (35.7)	-
	n		6		7
Week 26	Mean (SD)	113.1 (90.5)	38.1 (74.1)	72.5 (28)	-11.4 (39.7)
	n		6		7
Week 52	Mean (SD)	-	-	55.2 (10.3)	-42.8 (53.6)
	n		0		3

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided cholesterol, lipoproteins, and triglycerides in units of mmol/L.
To provide cholesterol and lipoproteins in mg/dL in this table, this reviewer multiplied the mmol/L value by 38.67.
To provide triglycerides in mg/dL in this table, this reviewer multiplied the mmol/L value by 88.57.
Abbreviations: n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation

Table 151. Mean (SD) Lipid Parameters After 52 Weeks of Treatment, Trial 4469, ISS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Cholesterol (mg/dL)					
Baseline	Mean (SD)	129.2 (7.1)	-	159.8 (24.7)	-
	n		2		9
Week 26	Mean (SD)	155.6 (23.2)	26.5 (16.1)	167.3 (22)	7.6 (13.6)
	n		2		9
Week 52	Mean (SD)	153.3 (8.5)	24.2 (1.4)	155.6 (24.1)	-6 (13.2)
	n		2		8
Low density lipoprotein (mg/dL)					
Baseline	Mean (SD)	64 (12.9)	-	86.8 (21.7)	-
	n		2		9
Week 26	Mean (SD)	87.8 (29)	23.8 (16.1)	92.5 (19.4)	5.7 (12.3)
	n		2		9
Week 52	Mean (SD)	88.6 (2.2)	24.6 (10.7)	79.5 (16.6)	-8.6 (10.6)
	n		2		8
High density lipoprotein (mg/dL)					
Baseline	Mean (SD)	51 (0)	-	58.4 (11)	-
	n		2		9
Week 26	Mean (SD)	46 (4.4)	-5 (4.4)	58.9 (10.8)	0.5 (8.3)

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
	n		2		9
Week 52	Mean (SD)	48.5 (9)	-2.5 (9)	56.3 (10.1)	-2.4 (7.8)
	n		2		8
Triglycerides (mg/dL)					
Baseline	Mean (SD)	70.9 (28.8)	-	72.3 (38.6)	-
	n		2		9
Week 26	Mean (SD)	110.7 (47.6)	39.9 (18.8)	80.6 (32.8)	8.3 (22.1)
	n		2		9
Week 52	Mean (SD)	78.8 (15)	8 (13.8)	98.3 (50.2)	23.9 (52.9)
	n		2		8

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided cholesterol, lipoproteins, and triglycerides in units of mmol/L.
To provide cholesterol and lipoproteins in mg/dL in this table, this reviewer multiplied the mmol/L value by 38.67.
To provide triglycerides in mg/dL in this table, this reviewer multiplied the mmol/L value by 88.57.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; SD, standard deviation

Table 152. Number (%) of Subjects With Lipid Parameters Outside of Normal Range, Trial 4469, SGA Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=8) n (%)
Cholesterol			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	3 (75)	6 (75)
Low density lipoprotein			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	2 (50)	4 (50)
High density lipoprotein			
Total	n	4	8
	Low (< LLN)	1 (25)	2 (25)
	High (> ULN)	0	0
Triglycerides			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	3 (75)	5 (62.5)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; n, number of subjects with available data; SGA, small for gestational age; ULN, upper limit of normal

Table 153. Number (%) of Subjects With Lipid Parameters Outside of Normal Range, Trial 4469, NS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=7) n (%)
Cholesterol			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	3 (50)	0
Low density lipoprotein			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	3 (50)	0
High density lipoprotein			
Total	n	6	7
	Low (< LLN)	3 (50)	2 (28.6)
	High (> ULN)	0	0
Triglycerides			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	2 (33.3)	2 (28.6)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; n, number of subjects with available data; NS, Noonan syndrome; ULN, upper limit of normal

Table 154. Number (%) of Subjects With Lipid Parameters Outside of Normal Range, Trial 4469, ISS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=9) n (%)
Cholesterol			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	1 (50)	3 (33.3)
Low density lipoprotein			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	0	2 (22.2)
High density lipoprotein			
Total	n	2	9
	Low (< LLN)	1 (50)	2 (22.2)
	High (> ULN)	0	0
Triglycerides			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	1 (50)	4 (44.4)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: ISS, idiopathic short stature; LLN, lower limit of normal; n, number of subjects with available data; ULN, upper limit of normal

Table 155. Mean (SD) Fasting Glucose, HbA1c, and Insulin Values, Trial 4469, SGA Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=4)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Fasting glucose (mg/dL)					
Baseline	Mean (SD)	90 (4.9)	-	89.1 (5.5)	-
	n		4		8
Week 26	Mean (SD)	90 (10.6)	0 (10.9)	87.5 (7.2)	-1.6 (7.2)
	n		4		8
Week 52	Mean (SD)	91.8 (-)	-5.4 (-)	90.9 (5.6)	2.7 (5.4)
	n		1		4
Week 78	Mean (SD)	-	-	90 (-)	3.6 (-)
	n		0		1
HbA1c (%)					
Baseline	Mean (SD)	5.3 (0.3)	-	5.2 (0.4)	-
	n		4		8
Week 26	Mean (SD)	5.5 (0.4)	0.3 (0.2)	5.2 (0.4)	0 (0.1)
	n		4		8
Week 52	Mean (SD)	5.4 (-)	0.1 (-)	5.2 (0.4)	0 (0.2)
	n		1		4
Week 78	Mean (SD)	-	-	5.7 (-)	0.2 (-)
	n		0		1
Fasting insulin (uIU/L)					
Baseline	Mean (SD)	9.4 (2.7)	-	10.6 (2.9)	-
	n		4		7
Week 26	Mean (SD)	1637 (7.3)	7.3 (7.9)	13.6 (7.6)	3.5 (6.5)
	n		4		8
Week 52	Mean (SD)	11.3 (-)	0.2 (-)	18.8 (13.9)	11.8 (12.8)
	n		1		4

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided glucose in units of mmol/L. To provide glucose in mg/dL in this table, this reviewer multiplied the mmol/L value by 18.
The Applicant provided insulin in units of pmol/L. To provide insulin in uIU/L in this table, this reviewer divided the pmol/L value by 6.
Abbreviations: n, number of subjects with available data; SD, standard deviation; SGA, small for gestational age

Table 156. Mean (SD) Fasting Glucose, HbA1c, and Insulin Values, Trial 4469, NS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Fasting glucose (mg/dL)					
Baseline	Mean (SD)	85.5 (9.2)	-	89.7 (4.8)	-
	n		6		7
Week 26	Mean (SD)	88.5 (2.1)	3 (8.3)	93.6 (9.2)	3.9 (11.8)
	n		6		7
Week 52	Mean (SD)	-	-	91.8 (3.6)	0.6 (3.8)
	n		0		3
Week 78	Mean (SD)	-	-	84.6 (-)	-3.6 (-)
	n		0		1
HbA1c (%)					
Baseline	Mean (SD)	5 (0.3)	-	5 (0.1)	-
	n		6		7
Week 26	Mean (SD)	5.1 (0.2)	0.2 (0.2)	5.1 (0.2)	0.1 (0.2)
	n		6		7
Week 52	Mean (SD)	-	-	5 (0.2)	0 (0.2)
	n		0		3
Week 78	Mean (SD)	-	-	4.9 (-)	-0.1 (-)
	n		0		1
Fasting insulin (uIU/L)					
Baseline	Mean (SD)	13.9 (8.1)	-	13.3 (7.2)	-
	n		6		7
Week 26	Mean (SD)	14.2 (5)	0.3 (9.8)	23.8 (27)	10.5 (25.6)
	n		6		7
Week 52	Mean (SD)	-	-	11.7 (1.5)	-0.2 (3.3)
	n		0		3
Week 78	Mean (SD)	-	-	12 (-)	-5.4 (-)
	n		0		1

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided glucose in units of mmol/L. To provide glucose in mg/dL in this table, this reviewer multiplied the mmol/L value by 18.
The Applicant provided insulin in units of pmol/L. To provide insulin in uIU/L in this table, this reviewer divided the pmol/L value by 6.
Abbreviations: n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation

Table 157. Mean (SD) Fasting Glucose, HbA1c, and Insulin Values, Trial 4469, ISS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Fasting glucose (mg/dL)					
Baseline	Mean (SD)	99 (5.1)	-	91.6 (5.1)	-
	n		2		9

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Week 26	Mean (SD)	100.8 (5.1)	1.8 (0)	88.6 (5.5)	-3 (5)
	n		2		9
Week 52	Mean (SD)	94.5 (24.2)	-4.5 (19.1)	90.7 (7.6)	-0.2 (4.2)
	n		2		8
Week 78	Mean (SD)	95.4 (-)	-7.2 (-)	84.6 (2.6)	-6.3 (3.8)
	n		1		2
HbA1c (%)					
Baseline	Mean (SD)	5.3 (0.1)	-	5.4 (0.3)	-
	n		2		9
Week 26	Mean (SD)	5.4 (0.1)	0.1 (0)	5.4 (0.3)	0.1 (0.2)
	n		2		9
Week 52	Mean (SD)	5.3 (0.1)	0 (0.1)	5.4 (0.3)	0 (0.2)
	n		2		8
Week 78	Mean (SD)	5.7 (-)	0.3 (-)	5.4 (0)	0 (0.1)
	n		1		2
Fasting insulin (uIU/L)					
Baseline	Mean (SD)	13.4 (3.9)	-	12.4 (5)	-
	n		2		9
Week 26	Mean (SD)	21.7 (6.8)	8.3 (10.6)	15.1 (3.1)	2.6 (4.7)
	n		2		9
Week 52	Mean (SD)	13.3 (0.5)	-0.1 (4.3)	19.4 (9)	6.5 (9.2)
	n		2		8
Week 78	Mean (SD)	17.9 (-)	7.3 (-)	17 (13.3)	1.4 (12.5)
	n		1		2

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided glucose in units of mmol/L. To provide glucose in mg/dL in this table, this reviewer multiplied the mmol/L value by 18.
The Applicant provided insulin in units of pmol/L. To provide insulin in uIU/L in this table, this reviewer divided the pmol/L value by 6.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; SD, standard deviation

Table 158. Number (%) of Subjects With Glucose Parameters Outside of Normal Range, Trial 4469, SGA Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=8) n (%)
Fasting glucose			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	0	1 (12.5)
HbA1c			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	0	0

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=8) n (%)
Fasting insulin			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; n, number of subjects with available data; SGA, small for gestational age; ULN, upper limit of normal

Table 159. Number (%) of Subjects With Glucose Parameters Outside of Normal Range, Trial 4469, NS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=7) n (%)
Fasting glucose			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	0	2 (28.6)
HbA1c			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	0	0
Fasting insulin			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	0	1 (14.3)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; n, number of subjects with available data; NS, Noonan syndrome; ULN, upper limit of normal

Table 160. Number (%) of Subjects With Glucose Parameters Outside of Normal Range, Trial 4469, ISS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=9) n (%)
Fasting glucose			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	1 (50)	1 (11.1)
HbA1c			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	0	0

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=9) n (%)
Fasting insulin			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	0	0

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: ISS, idiopathic short stature; LLN, lower limit of normal; n, number of subjects with available data; ULN, upper limit of normal

Table 161. Mean (SD) Alkaline Phosphatase Values, Trial 4469, SGA Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=4)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Alkaline phosphatase (U/L)					
Baseline	Mean (SD)	301.2 (84.5)	-	285.9 (54.5)	-
	n		4		8
Week 26	Mean (SD)	432.2 (107.9)	131 (37.4)	336.4 (71.8)	50.5 (47.8)
	n		4		8
Week 52	Mean (SD)	485 (-)	91 (-)	311 (70.4)	22 (71.8)
	n		1		50
Week 78	Mean (SD)	-	-	239 (-)	24 (-)
	n		0		1

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n, number of subjects with available data; SD, standard deviation; SGA, small for gestational age

Table 162. Mean (SD) Alkaline Phosphatase Values, Trial 4469, NS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Alkaline phosphatase (U/L)					
Baseline	Mean (SD)	174.7 (44.3)	-	195.7 (46.7)	-
	n		6		7
Week 26	Mean (SD)	247.3 (29.6)	72.7 (25.4)	195.7 (61.4)	0 (30.5)
	n		6		7
Week 52	Mean (SD)	-	-	224.7 (130.1)	28.3 (68.7)
	n		0		3
Week 78	Mean (SD)	-	-	189 (-)	-12 (-)
	n		0		1

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation

Table 163. Mean (SD) Alkaline Phosphatase Values, Trial 4469, ISS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Alkaline phosphatase (U/L)					
Baseline	Mean (SD)	277.5 (30.4)	-	270.7 (119.7)	-
	n		2		9
Week 26	Mean (SD)	349.5 (44.6)	72 (75)	275.8 (92.9)	5.1 (51.7)
	n		2		9
Week 52	Mean (SD)	336.5 (46)	59 (76.4)	265.9 (97.8)	0.6 (69)
	n		2		8
Week 78	Mean (SD)	350 (-)	94 (-)	224 (21.2)	3 (1.4)
	n		1		2

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; SD, standard deviation

Table 164. Mean (SD) Phosphate Values, Trial 4469, SGA Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=4)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=8)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Phosphate (mg/dL)					
Baseline	Mean (SD)	5 (0.3)	-	5.1 (0.5)	-
	n		4		8
Week 26	Mean (SD)	5.4 (0.3)	0.4 (0.1)	6.1 (0.7)	0.9 (0.7)
	n		4		8
Week 52	Mean (SD)	5.6 (-)	0.2 (-)	5.8 (0.8)	0.8 (0.4)
	n		1		4
Week 78	Mean (SD)	-	-	5 (-)	0.6 (-)
	n		0		1

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided phosphate in units of mmol/L. To provide phosphate in mg/dL in this table, this reviewer multiplied the mmol/L value by 3.1.
Abbreviations: n, number of subjects with available data; SD, standard deviation; SGA, small for gestational age

Table 165. Mean (SD) Phosphate Values, Trial 4469, NS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Phosphate (mg/dL)					
Baseline	Mean (SD)	4.4 (0.5)	-	4.6 (0.5)	-
	n		6		7
Week 26	Mean (SD)	5.4 (0.5)	1 (0.6)	5.1 (0.5)	0.5 (0.4)
	n		6		7
Week 52	Mean (SD)	-	-	5.6 (0.5)	1 (0.6)

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
	n		0		3
Week 78	Mean (SD)	-	-	4.9 (-)	0.2 (-)
	n		0		1

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided phosphate in units of mmol/L. To provide phosphate in mg/dL in this table, this reviewer multiplied the mmol/L value by 3.1.
Abbreviations: n, number of subjects with available data; NS, Noonan syndrome; SD, standard deviation

Table 166. Mean (SD) Phosphate Values, Trial 4469, ISS Safety Population

Treatment		0.24 mg/kg/Week Somapacitan Treatment Naïve (N=2)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=9)	
Evaluation		Value	Change From Baseline	Value	Change From Baseline
Phosphate (mg/dL)					
Baseline	Mean (SD)	4.9 (0.4)	-	5.1 (0.7)	-
	n		2		9
Week 26	Mean (SD)	5.6 (0.7)	0.7 (0.4)	5.5 (0.7)	0.4 (0.5)
	n		2		9
Week 52	Mean (SD)	6 (0.9)	1.2 (0.6)	5.3 (0.7)	0.2 (0.9)
	n		2		8
Week 78	Mean (SD)	5.6 (-)	0.5 (-)	5.9 (0.6)	0.1 (0.7)
	n		1		2

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
The Applicant provided phosphate in units of mmol/L. To provide phosphate in mg/dL in this table, this reviewer multiplied the mmol/L value by 3.1.
Abbreviations: ISS, idiopathic short stature; n, number of subjects with available data; SD, standard deviation

Table 167. Number (%) of Subjects With Alkaline Phosphatase or Phosphate Levels Outside of Normal Range, Trial 4469, SGA Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=4) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=8) n (%)
Alkaline phosphatase			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	4 (100)	5 (62.5)
Phosphate			
Total	n	4	8
	Low (< LLN)	0	0
	High (> ULN)	3 (75)	7 (87.5)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; NS, Noonan syndrome; n, number of subjects with available data; SGA, small for gestational age; ULN, upper limit of normal

Table 168. Number (%) of Subjects With Alkaline Phosphatase or Phosphate Levels Outside of Normal Range, Trial 4469, NS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=6) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=7) n (%)
Alkaline phosphatase			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	2 (33.3)	0
Phosphate			
Total	n	6	7
	Low (< LLN)	0	0
	High (> ULN)	4 (66.7)	4 (57.1)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: LLN, lower limit of normal; n, number of subjects with available data; NS, Noonan syndrome; ULN, upper limit of normal

Table 169. Number (%) of Subjects With Alkaline Phosphatase or Phosphate Levels Outside of Normal Range, Trial 4469, ISS Safety Population

Parameter		0.24 mg/kg/Week Somapacitan Treatment Naive (N=2) n (%)	0.24 mg/kg/Week Somapacitan Treatment Non-Naive (N=9) n (%)
Alkaline phosphatase			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	0	3 (33.3)
Phosphate			
Total	n	2	9
	Low (< LLN)	0	0
	High (> ULN)	2 (100)	8 (88.9)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: ISS, idiopathic short stature; LLN, lower limit of normal; n, number of subjects with available data; ULN, upper limit of normal

Table 170. Mean (SD) IGF-1 SDS, Weeks 0 to 52, Trial 4469

Treatment		0.24 mg/kg/Week Somapacitan							
Population		SGA		NS		ISS		TS	
Treatment Status		Naïve N = 4	Non-Naïve N = 8	Naïve N = 6	Non-Naïve N = 7	Naïve N = 2	Non-Naïve N = 9	Naïve N = 3	Non-Naïve N = 8
IGF-1 SDS									
Baseline	Mean (SD)	-0.1 (1.3)	0.5 (1)	-0.7 (1.2)	-1 (1.7)	0.4 (0.4)	0.4 (1.4)		(b) (4)
	n	4	8	6	7	2	9		
Week 4	Mean (SD)	1.5 (0.3)	1.7 (0.7)	0.3 (1.1)	0.7 (1.2)	2.5 (0)	1.3 ().8)		
	n	4	8	6	7	2	9		
Week 8	Mean (SD)	0.4 (0.8)	0.9 (0.9)	-0.2 (1.3)	0.2 (0.9)	2.6 (0.5)	1.1 (0.7)		
	n	4	8	6	7	2	9		
Week 13	Mean (SD)	1.9 (0.3)	2.8 (0.6)	0.4 (1.8)	1 (1)	2.5 (0.4)	2.4 (0.6)		
	n	4	8	6	7	2	9		

Treatment		0.24 mg/kg/Week Somapacitan							
Population		SGA		NS		ISS		TS	
Treatment Status		Naïve N = 4	Non-Naïve N = 8	Naïve N = 6	Non-Naïve N = 7	Naïve N = 2	Non-Naïve N = 9	Naïve N = 3	Non-Naïve N = 8
Week 20	Mean (SD)	0.5 (1)	1 (0.9)	0 (0.9)	-0.2 (0.8)	2.9 (0.7)	1.1 (0.8)		(b) (4)
	n	4	8	5	7	2	9		
Week 26	Mean (SD)	1.5 (0.9)	1.9 (1.1)	0.3 (1.3)	1.3 (0.7)	3.2 (0.9)	2.1 (0.6)		
	n	4	8	6	7	2	9		
Week 39	Mean (SD)	1.4 (1.3)	1.6 (0.9)	0.2 (1.2)	0.8 (0.5)	3.2 (0.7)	1.2 (0.7)		
	n	3	8	5	5	2	9		
Week 52	Mean (SD)	0.4 (-)	2.9 (0.3)	-	1.1 (1)	3.3 (1)	1.8 (1.2)		
	n	1	4	0	3	2	8		

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
Abbreviations: n, number of subjects with available data; ISS, idiopathic short stature; NS, Noonan syndrome; SGA, small for gestational age; TS, Turner syndrome

Table 171. Mean (SD) Annualized Height Velocity (cm/Year) in Subjects Who Were Antibody Positive or Negative, Trial 4469, NS Population

	0.24 mg/kg/Week Somapacitan Treatment Naïve (N=6)		0.24 mg/kg/Week Somapacitan Treatment Non-Naïve (N=7)
Antibody Status	Subjects With Negative ADA n = 5 (83.3%)	Subjects With ≥ 1 Positive ADA n = 1 (16.7%)	Subjects With Negative ADA n = 7 (100%)
Baseline	4.4 (2.5)	3.2 (-)	6.2 (1.5)
Week 13	10 (2.7)	8.7 (-)	5.3 (1.8)
Week 26	9.2 (2.6)	8.4 (-)	6.4 (2)
Week 39*	9.7 (1.4)	8.1 (-)	5.7 (2)

Source: Clinical reviewer generated report using OCS Analysis Studio, Custom Table Tool and JMP clinical.
* For the one subject with positive ADA, the Week 39 visit is the most recent visit for which this subject has data as of the database lock date of the original sBLA submission.
Abbreviations: ADA, antidrug antibody; NS, Noonan syndrome; SD, standard deviation

15.4.4. Additional Information From Adverse Events

15.4.4.1. Narratives From SAEs Reported in the Pivotal Phase 3 Trial 4467

SGA

Main Period

Somapacitan Arm

- Choking

  This case involves a 32-month-old female who had an episode of choking (graded as severe) on a mint in the parking lot about 30 minutes after the first dose of study drug in this trial. The mother brought her to the emergency department (ED) where she received a Heimlich maneuver and breathing recovered. However, she was noted to be hypoglycemic secondary

to the subsequent prolonged fasting, received IV dextrose, and the hypoglycemia resolved. She was admitted for observation and discharged the next day having fully recovered. The SAE of choking was most likely related to the mint and hypoglycemia was most likely secondary to having fasted for the trial visit, then prolonged secondary to concern of choking on food. Therefore, this SAE is unlikely to be related to somapacitan.

- Pneumonia mycoplasmal; melanocytic nevus

  The SAE of melanocytic nevus was reported in a 4-year-old male with a history of allergic rhinitis. The parent first noticed a nevus on the left sole about 3 months after starting study drug. It was small at the time and was otherwise unremarkable. After an unspecified amount of time, it was noted to grow rapidly and be conical in shape. About a month and a half after first being noticed, he was hospitalized for excision of the nevus and later pathology diagnosed it as melanosis of epidermal basal layer and nevus cell hyperplasia (graded as mild). The SAE was reported as recovered. Somapacitan was temporarily discontinued. While IGF-1 is a growth promoting factor and it is theorized that chronically elevated IGF-1 levels may play a role in tumorigenesis, there is no conclusive evidence regarding an increased risk of neoplasm in patients with GHD treated with hGH products or analogs and, also given the level of progression of the tumor at diagnosis, and it is unlikely that the relatively short duration of time on treatment would have led to this finding. Thus, while a causal association may not be able to be ruled out entirely, it is unlikely. Further, malignancies are already a labeled contraindication to GH product and analog therapy.

  This same subject had an SAE of pneumonia mycoplasmal (graded as severe) about 5 months after starting study drug. His symptoms started with recurrent fever and cough. Two days after onset of symptoms he had chest x-ray done which showed a lower left pneumonia and he was hospitalized four days after the x-ray. He was treated with antibiotics, antipyretics, inhaled steroids, and decongestants (it is unclear if treatment started prior to or after hospital admission). After 4 days in the hospital, he was discharged from the hospital and his SAE was recovered. While somapacitan therapy was temporarily discontinued, there has been no known relationship between growth hormone therapy and infections, and the subject recovered with appropriate therapy.

Norditropin 0.067 mg/kg/day Arm

- Bronchiolitis

  This case concerned a 7-year-old male who, in addition to a history of being SGA, also has a history of bronchopulmonary dysplasia and hypermetropia. Approximately 7 months after starting study treatment, the subject had cough, runny nose, and fever. Home treatment (not specified) was unsuccessful and 3 days after symptom onset he was admitted to the hospital where he was treated with antibiotics and corticosteroids for bronchiolitis (mild severity). Approximately 5 days after hospitalization his condition resolved, and he was discharged. Norditropin therapy was not interrupted or changed, the subject has a history of bronchopulmonary dysplasia which may put him at risk for bronchiolitis, and as the

subject recovered with appropriate therapy, it is unlikely that bronchiolitis was related to Norditropin therapy.

- Viral infection

  This case involved a 5-year-old male with a history of strabismus, reflux nephropathy, and vesicular lithiasis. About 5 months after starting study drug, he was drowsy, and experienced vomiting and abdominal pain, and he was admitted to the hospital for presumed viral infection (mild severity). He was treated with ondansetron and discharged the same day after recovery. Norditropin therapy was not interrupted or changed, and as the subject recovered with appropriate therapy, it is unlikely that the SAE was related to Norditropin therapy.

- Metapneumovirus infection; tonsillar hypertrophy and adenoidal hypertrophy

  The SAE of metapneumovirus infection (graded as severe) was reported in a 4-year-old male with a history of retinopathy of prematurity, cerebral palsy, constipation, eczema, and allergic conjunctivitis, about 6 months after starting therapy with 0.067 mg/kg/day Norditropin in the trial. The diagnosis was made after an onset of fevers and febrile convulsions and subsequent hospitalization for dehydration related to inability to take oral fluids. After approximately 4 days in the hospital, the subject was discharged, and the SAE was reported as recovered. Norditropin therapy was not interrupted or changed, and as the subject recovered with appropriate therapy, it is unlikely that the SAE was related to Norditropin therapy.

  SAEs of tonsillar and adenoidal hypertrophy (both of moderate severity) were also reported in this same subject. About a month after the SAE of metapneumovirus infection and seven months after starting Norditropin, he visited a doctor who noted adenoid hypertrophy and enlarged tonsils. About two months later he visited an otolaryngologist who confirmed these findings, and diagnosed moderate obstructive sleep apnea, and about five months after that (about sixteen months after starting study drug), he had adenoidectomy and tonsillectomy. Norditropin dosing was not interrupted or changed and both SAEs resolved. Adenoidal and tonsillar hypertrophy are not uncommon findings in pediatric patients and may be related to previous or concurrent viral infections (such as the previous SAE of metapneumovirus infection), however given the temporal association, a causal relationship between Norditropin and these SAEs cannot be completely ruled out.

- Tonsillar hypertrophy

  This case involved a 3-year-old male with a history of impetigo contagious, eczema, and dermatitis atopic. About 3 months after starting Norditropin, he was noted to have nasal congestion and snoring. A month later he was recommended for surgery due to tonsillar hypertrophy (graded as severe), which occurred approximately 9 months after onset of Norditropin therapy. Norditropin dosing was not interrupted or changed and both SAEs resolved. Tonsillar hypertrophy is not an uncommon finding in pediatric patients, and despite decades of use, however given the temporal association, a causal relationship between Norditropin and this SAE cannot be completely ruled out.

Norditropin 0.035 mg/kg/day Arm

- Upper respiratory tract infection

  This case relates to a 4-year-old male with a history of bronchopulmonary dysplasia and umbilical hernia who reported symptoms of fever, cough, rhinorrhea, otitis media, and throat and ear pain about 3 months after starting study drug, diagnosed as a severe SAE of upper respiratory tract infection. He received antibiotics, tantum verde, furotalgin, and saline inhalations outpatient, but six days after onset of symptoms was hospitalized for worsening condition. While hospitalized he received ceftriazone after which fevers stopped and five days after admission his symptoms improved, and he was discharged on outpatient antibiotics. While Norditropin was temporarily interrupted, after decades of use, no known relationship between somatropin therapy and infection exists. Further, the subject has a history of bronchopulmonary dysplasia, and the subject recovered with appropriate therapy. It is therefore unlikely that the upper respiratory tract infection was related to Norditropin therapy.

- Influenza; pneumonia streptococcal and pneumonia Hemophilus

  The case of influenza (graded as severe) involved a 6-year-old female with a history of patent foramen ovale, dyslipidemia, and alpha thalassemia. About 5 months after starting 0.035 mg/kg/day Norditropin, she had onset of dizziness and fever. After receiving ibuprofen that did not improve the fever, Norditropin therapy was temporarily discontinued. The subject was also prescribed unclear Chinese medications, taken to an emergency department the next day, and was subsequently hospitalized. At the hospital, she received antibiotics IV glucose, and IV dextrose, as well as analgesics. She was diagnosed with influenza A and also received oseltamivir. While in the hospital, she was also diagnosed with acute tonsillitis, though it was not an SAE. Three days after admission she was discharged from the hospital and the SAE was recovered. While Norditropin was temporarily interrupted, there is no known relationship between somatropin therapy and infection, the subject recovered with appropriate therapy, and it is therefore unlikely that the influenza was related to Norditropin therapy.

  One year after starting Norditropin, this same subject reported fever and cough and was hospitalized and diagnosed with pneumonia and tested positive for streptococcus pneumonia and Hemophilus influenza (both of moderate severity), both of which were SAEs. The narrative reports a positive test for mycoplasma pneumonia as well, but this is not listed as an adverse event. She received multiple treatments, including “traditional” medicines and antibiotics, though the timing in the narrative is not specific. About a week and a half after admission to the hospital, she was discharged, and her SAEs are reported as recovered. Somapacitan was temporarily interrupted during the SAEs. As has been discussed, it is unlikely that growth hormone therapy is related to a risk of infection, and the SAEs of pneumonia resolved with antibiotic therapy. Somapacitan is therefore unlikely to be related to these SAEs.

- Tonsillar hypertrophy

  This case relates to a 5-year-old female with a history of vitamin D deficiency and hypertrophia tonsillae palatinae. Prior to consenting to the trial, she had already been noted to have tonsillar hypertrophy (graded as severe), which was observed without other treatment at the time. Approximately twelve months after starting study therapy, she was found to have grade III hypertrophia tonsillae palatinae and about two weeks later underwent tonsillectomy. Norditropin therapy was not interrupted or changed, and the SAE recovered. Tonsillar hypertrophy is not an uncommon finding in pediatric patients, this subject's tonsillar hypertrophy predated onset of treatment, however given the temporal association, a causal relationship between Norditropin and this SAE cannot be completely ruled out.

Extension Period

- Pneumonia

  This case involves a 5-year-old female with a history of cerebral palsy, intermittent alternating exotropia, and developmental delay. She was originally randomized to the somapacitan group and began having symptoms of fever and vomiting 14 months after starting treatment. She was admitted the hospital the next day and was diagnosed with, and treated for, pneumonia of moderate severity. The narrative does not report treatment for pneumonia but does note that somapacitan dosing was not interrupted or changed. After two days in the hospital, she was discharged, and the SAE is reported as recovered. As the somapacitan was not changed and the subject recovered following treatment, it is unlikely that the SAE of pneumonia was related to somapacitan therapy.

- Pneumonia

  This other case of pneumonia (of moderate severity) involves a 4-year-old male without significant medical history who was originally randomized to the 0.35 mg/kg/day Norditropin arm. Approximately 3 months after transitioning to somapacitan, he was hospitalized for pneumonia and treated with antibiotics, inhaled steroids, and decongestants. About 5 days after admission to the hospital, he was considered recovered enough to continue with outpatient oral medications. The SAE of pneumonia was listed as recovered and there was no change to somapacitan dosing. As the somapacitan was not changed and the subject recovered following treatment, it is unlikely that the SAE of pneumonia was related to somapacitan therapy.

- Tonsillitis bacterial

  This case concerns a 6-year-old female with a history of refractive errors in the eyes and hyperlipidemia. She was originally randomized to somapacitan and 13 months after starting therapy reported fever and a non-serious AE of upper respiratory tract infection (adenovirus). The next day she was diagnosed with acute suppurative tonsillitis of moderate severity and then hospitalized. She was treated with antibiotics, fluids, and analgesics, and was discharged about five days after hospitalization. Her tonsillitis bacterial is reported as

recovered. Her somapacitan dosing was not changed or interrupted, and as the subject recovered with appropriate therapy, it is unlikely that the SAE was related to somapacitan therapy.

- Tonsillitis; mesenteric lymphadenitis

  This is the same subject that reported SAEs of influenza, pneumonia streptococcal, and pneumonia Hemophilus in the 0.035 mg/kg/day Norditropin group in the Main Period of trial 4467.

  During the Extension Period, about one month after starting somapacitan, the subject began to have abdominal pain and fever. She was admitted to the hospital and diagnosed with acute tonsillitis and acute mesenteric lymphadenitis, both of moderate severity, and both of which were SAEs. She was also diagnosed with a non-serious AE of tracheitis. She received antibiotics and cimetidine and was discharged after 5 days in the hospital. The SAEs were reported as recovered. Her somapacitan dosing was not changed or interrupted, and as the subject recovered with appropriate therapy, it is unlikely that the SAEs were related to somapacitan therapy.

NS

Main Period

Somapacitan Arm

- Pneumonia and asthma

  These moderate SAEs were reported in an 8-year-old female with a history of asthma who started experiencing runny nose, cough, fatigue, and fever within a day of starting somapacitan therapy. She was brought to an emergency department where she was diagnosed with pneumonia decompensation of asthma decompensation. She was treated with respiratory physiotherapy, antibiotics, and salbutamol. About a week and a half after onset of symptoms, she was discharged from the hospital and the SAEs were reported as recovered. She missed one dose of somapacitan during her hospitalization. While somapacitan was temporarily interrupted, there is no known relationship between growth hormone therapy and infection, the subject has a history of asthma, the subject recovered with appropriate therapy, and it is therefore unlikely that these SAEs were related to somapacitan therapy.

- Cholesteatoma

  This case involved a 7-year-old female with a history of nasosinusitis who developed fluid and pus in the left ear canal about 1 month after starting somapacitan therapy. About three weeks after onset of symptoms, she received unspecified drug therapy for her symptoms, with some relief, though symptoms persisted. Therefore, on the same day she went to the hospital where a CT was done that demonstrated left middle ear mastoiditis, bacterial external auditory canal elements, and bilateral maxillary sinus and ethmoid sinusitis. About

2 weeks later she was admitted to the hospital, diagnosed with a moderate cholesteatoma of the external auditory canal, and underwent external auditory canal mass resection. Four days later she was discharged, and the SAE is listed as recovered. Somapacitan dosing was not interrupted or changed, and as the subject recovered with appropriate therapy, it is unlikely that cholesteatoma was related to somapacitan therapy.

- Febrile convulsion

  This case concerns a 4-year-old male with a history of dermatitis atopic. Nine months after starting somapacitan therapy, this subject developed spasms with bilateral supination and asymmetrical flexion of both upper limbs. He was brought to the emergency department where he was found to be febrile. He received fosphenytoin, diazepam, and midazolam, which resolved the convulsions. However, the fever persisted, and he was diagnosed with convulsions (graded as severe) secondary to fever of unknown source (screening tests for infectious causes were negative). After 5 days in the hospital, convulsions and fever had resolved, and he was discharged. Somapacitan dosing was not changed or interrupted. Seizures associated with fever are not uncommon in this this age group, and given resolution with appropriate therapy and no changes to somapacitan dosing, a causal association between this SAE and somapacitan is unlikely.

- Gastroenteritis

  This mild SAE was reported in a 5-year-old female with a history of pulmonary artery stenosis and insomnia. The narrative notes that about 10 after starting therapy, on (b) (6), she was admitted to the hospital for a planned stent placement, and 3 days later her hospitalization was extended due to gastroenteritis. She received antibiotics, and a day later gastroenteritis symptoms resolved, and she was discharged with antibiotic therapy. Somapacitan dosing was unchanged. Gastroenteritis is not infrequent in this patient population and recovered with no changes to somapacitan dosing. Somapacitan is thus unlikely to be related to this SAE.

Norditropin Arm

- Lower respiratory tract infection

  This moderate SAE was reported in a 4-year-old male with a history of hearing loss, dysplastic pulmonary valve with severe supravalvular pulmonary stenosis, and muscular ventricular septal defect. Approximately 2 months after starting Norditropin therapy, he was admitted to the hospital for a lower respiratory tract infection where he was treated with antibiotics, IV fluids, and respiratory therapy. Two days later he was discharged on oral antibiotics and the SAE was reported as recovered. Norditropin dosing was unchanged, and as the subject recovered with appropriate therapy, it is unlikely the SAE was related to Norditropin therapy.

- Obstructive sleep apnea syndrome

  This case concerns a 3-year-old male with a history of atrial ectopic tachycardia, bilateral ptosis, snoring, allergic rhinitis, hypertrophic cardiomyopathy without left ventricular outflow obstruction, and small patent foramen ovale. The severe SAE of obstructive sleep apnea syndrome was first reported 7 months after starting Norditropin therapy, and about 2 months after onset he underwent tonsillectomy and adenoidectomy. However, the SAE was not noted to recover, and a follow up polysomnography study was recommended. Norditropin dosing was temporarily discontinued. The labels for somatropin products and their analogs do include language related to reports of fatalities after initiating therapy with somatropin in pediatric patients with a history of upper airway obstruction or sleep apnea, under contraindications and under warnings and precautions. Therefore, it is possible that somatropin therapy could contribute to obstructive sleep apnea syndromes and we cannot exclude a causal relationship between Norditropin therapy and this SAE.

- Adenoidal hypertrophy

  This severe SAE was reported in a 6-year-old male without reported medical history who first noted sleep apnea about 11 months after starting Norditropin therapy. About a month later he was diagnosed with adenoid vegetations, this was reported as an SAE, he and referred for adenoidectomy. The adenoidectomy occurred seventeen months after starting Norditropin therapy (about five months after switching to somapacitan in the Extension Period). Study drug therapy was unchanged, and the outcome of the SAE was reported as recovered. Adenoidal hypertrophy is not an uncommon finding in pediatric patients, however given the temporal association, a causal relationship between Norditropin and these SAEs cannot be completely ruled out.

<u>Extension Period</u>

- Bone cell giant tumor

  This case involves a 6-year-old male with a history of autism, tympanostomy tubes, mild pectus excavatum, and seasonal allergies. He was originally randomized to the Norditropin group. On an unknown date, an unspecified incidental finding was reported by the subject's dentist after a routine dental x-ray. The subject was referred for a follow up CT scan, which occurred about two months after switching to somapacitan therapy in the Extension Period and found a giant cell tumor (location not specified, though the narrative notes that on the same day, large expansile cysts bilaterally on mandible were reported). The AE of bone cell giant tumor resulted in permanent early discontinuation of somapacitan therapy. The outcome of the SAE is reported as recovered, though treatment was not specified and the narrative notes that the family was pursuing options to have the tumor surgically removed. While IGF-1 is a growth promoting factor and it is theorized that chronically elevated IGF-1 levels may play a role in tumorigenesis, there is no conclusive evidence regarding an increased risk of neoplasm in patients with GHD treated with hGH products or analogs and there is little evidence to suggest that somapacitan therapy contributed to the bone cell giant tumor; it is unclear when the tumor originated relative to the finding on dental x-ray,

the timing of the CT that discovered the tumor, or to initiation of Norditropin or somapacitan therapy. Malignancies are a contraindication to GH product and analog therapy.

- Pneumonia

  This SAE was reported in a 7-year-old male without significant past medical history who was originally randomized to somapacitan in the Main Period of the trial. After approximately 15 months of somapacitan therapy he developed fever and cough and was diagnosed with, and hospitalized for, moderate pneumonia. He received antibiotic and antipyretic therapy and there was no change to somapacitan dosing. About a week and a half after admission he was discharged from the hospital and the pneumonia was reported as recovered. Following no changes in study drug dosing and recovery with appropriate therapy, it is unlikely that there is a causal relationship between somapacitan and the SAE of pneumonia.

- Diarrhea and nasopharyngitis

  These SAEs were reported in the same subject with an SAE of gastroenteritis in the somapacitan arm of the Main Period of the trial. About 12 months after starting trial therapy (and 1 month after the SAE of gastroenteritis), she had frequent diarrhea (of mild severity) which led to dehydration, dizziness, and tachycardia and was subsequently hospitalized. At the hospital, she was also noted to have symptoms consistent with a common cold (nasopharyngitis; of mild severity) for which antibiotics were prescribed. The next day, her diarrhea improved, and she was discharged on outpatient antibiotic therapy for her nasopharyngitis. Both SAEs were reported as recovered and somapacitan therapy was not interrupted or changed. Gastroenteritis and nasopharyngitis are not infrequent in this patient population, and both recovered with appropriate therapy and no changes to somapacitan dosing. Somapacitan is thus unlikely to be related to these SAEs.

- Pneumonia aspiration

  This case involves a 9-year-old male without significant reported medical history and who was originally randomized to somapacitan in the Main Period of the trial. Approximately 15 months after initiation of therapy he was admitted to the hospital for a scheduled bilateral otoplasty. After surgery, he vomited, causing reactive laryngospasm and bronchoaspiration, resulting in admission to the intensive care unit for pneumonia aspiration of moderate severity requiring non-invasive mechanical ventilation and fluid therapy. Two days after admission for the surgery he was discharged, and the SAE was reported as recovered. Somapacitan dosing was not changed or interrupted. Somapacitan therapy is most likely not related to the aspiration pneumonia, but rather to the vomiting following surgery.

ISS

Main Period

Somapacitan Arm

- Influenza

  This case involves a 5-year-old female without significant past medical history who reported a mild SAE of influenza about 7 months after starting somapacitan therapy, when she presented to the emergency department for fever. She was found to be positive for influenza B and subsequently hospitalized. The narrative for this case also notes that she was positive for respiratory syncytial virus, though this does not appear to be reported as an adverse event. She as treated with oseltamivir, pseudoephedrine, and ebastine, and was discharged about 5 days after admission and the SAE was reported as recovered. There was no change or interruption with somapacitan dosing and there is no known relationship between growth hormone therapy and infections, the subject recovered with appropriate therapy, and it is therefore unlikely that the influenza was related to somapacitan therapy.

- Inguinal hernia

  This case concerns an 8-year-old female subject without significant past medical history. Approximately 11 months after starting therapy a palpable mass was noted, confirmed by ultrasound 1 month later to be bilateral inguinal hernias, graded as severe. About 3 weeks after the ultrasound, she was hospitalized for surgical repair of the inguinal hernias and discharged the same day. The SAE was reported as recovered. Somapacitan dosing was never changed, and there are no known associations between growth hormone therapy and inguinal hernias, and the SAE recovered with appropriate therapy. Therefore, a causal relationship between somapacitan and this SAE is unlikely.

Norditropin Arm

No SAEs were reported by subjects with ISS when treated with Norditropin in the Main Period of trial 4467.

Extension Period

- Pneumonia bacterial

  This case involves a 10-year-old female subject originally randomized to Norditropin in the Main Period of the pivotal phase 3 trial 4467 who has a history of congenital heart valve dysplasia, rickets, and compensated hypothyroidism. Approximately 2 months after switching to somapacitan therapy in the Extension Period of the trial, she was evaluated for fever. She received outpatient antibiotic therapy which lasted a week, but at the end of the week she had persistent fever and cough, and due to concern for pneumonia (of moderate severity), she was admitted to the hospital. After receiving additional inpatient antibiotics,

about 5 days after admission, her pneumonia was reported as recovered and she was discharged. Her somapacitan dosing was unchanged, there has been no known relationship between growth hormone therapy and infections, and the subject recovered with appropriate therapy. Thus, it is unlikely that there is a causal relationship between the SAE and somapacitan.

15.4.4.2. Narratives From SAEs Reported in the Phase 2 Dose Finding Trial 4245

Main Period and Extension Period I

Norditropin 0.035 mg/kg/day arm

- Inguinal hernia

  This case involves a 6-year-old female with a history of iron deficiency anemia. Approximately 6 months after starting Norditropin therapy, a mild left inguinal hernia was found, which underwent surgical repair approximately one year after diagnosis. She was discharged from the hospital on the same day of surgery. Norditropin dosing was unchanged, and the SAE was reported as recovered. There are no known associations between growth hormone therapy and inguinal hernias, Norditropin dosing continued, and the SAE recovered with appropriate therapy. Therefore, a causal relationship between Norditropin and this SAE is unlikely.

No SAEs were reported in the 0.16, 0.2, or 0.24 mg/kg/week somapacitan arms, or the 0.067 mg/kg/day Norditropin arm, during the first 52 weeks of the trial.

Extension Period II

- Asthma

  This case involves a 4-year-old female subject originally randomized to the 0.035 mg/kg/day Norditropin arm who had a history of dermatitis atopic. Approximately 18 months after starting Norditropin therapy in the trial, and on which she continued when this SAE was reported, the subject had onset of non-serious asthmatic bronchitis, which has not yet recovered. Approximately 1 month later, she had cough, runny nose, and fever, resulting in admission to the hospital for a severe SAE of asthmatic bronchitis. She was treated with steroid injections, salbutamol, a mucolytic, and administration of supplemental oxygen, and after 6 days in the hospital she was discharged, and the SAE was later reported as recovered. Norditropin therapy was not interrupted or changed, and as the subject recovered with appropriate therapy. Thus, it is unlikely that asthma was related to Norditropin therapy.

- Developmental hip dysplasia

  This moderate SAE was reported in a 12-year-old female with a history of vitamin D deficiency, congenital hip dislocation, and devalgizing subtrochanteric osteotomy of the left

femur with metalosteosynthesis reconstructive plate who was originally randomized to 0.24 mg/kg/week somapacitan in the phase 2 trial. Approximately 26 months after starting therapy in this trial, she first experienced a worsening of the congenital hip dislocation, for which she was hospitalized approximately 6 months later. Following MRI, which showed multilane deformation of the acetabulum and proximal femur, with coxarthrosis of the 3rd degree, she did not receive any other therapy while inpatient and was discharged after approximately 2 days in the hospital with the SAE reported as recovered. Somapacitan therapy was not interrupted or changed. This subject had a history of congenital hip dislocation, which likely contributed to this SAE. However, as the SAE recovered without any changes to somapacitan dosing, it is unlikely that there is a causal relationship between developmental hip dysplasia and somapacitan therapy.

15.4.4.3. Narratives From SAEs Reported in the Phase 3 Trial 4469

SGA

Main Period

- Constipation; gastrointestinal microorganism overgrowth and gastroesophageal reflux disease

  The mild SAE of constipation was reported in an 11-year-old, treatment non-naïve male with a history of aberration of chromosome 16p (benign variant), osteopenia, vision impairment, vitamin D3 deficiency, heart functional murmurs, autism, pollen allergy, mutism, and Tourette syndrome. Approximately 13 months after starting somapacitan therapy he reported abdominal pain, eventually leading to hospitalization about 1 month later. Work up included normal chest x-ray and an abdominal x-ray which indicated dilation of the rectal ampulla. Esophageal pH was not fully diagnostic but may have indicated gastroesophageal reflux disease. He was diagnosed with functional bowel movement impairment (constipation), treated with laxatives and omeprazole, and discharged after about 6 days in the hospital. The SAE was reported as recovered. There was no interruption or change in somapacitan dosing, and as the event recovered with appropriate therapy, it is unlikely that somapacitan therapy was related to this SAE.

  Approximately one month after discharge (about 15 months after starting somapacitan) the subject again reported abdominal pain and was admitted to a gastroenterology clinic. At this clinic, his workup included a positive hydrogen breath test, and he was diagnosed with mild gastrointestinal microorganism overgrowth and mild gastroesophageal reflux disease, both reported as SAEs. He was treated with rifaximin, probiotics, and chondroitin sulfate. Two days after admission, he was discharged and both SAEs were later reported as recovered. There was no interruption or change in somapacitan dosing, and as the events recovered with appropriate therapy, it is unlikely that somapacitan therapy was related to these SAEs.

Extension Period I

No subjects born SGA reported SAEs in the Extension Period.

ISS

Main Period

- Pneumonia

  This case relates to a 10-year-old, treatment non-naïve female without significant past medical history who began to have cough with sputum about 5 months after starting somapacitan therapy. The next day she was hospitalized and diagnosed with moderate pneumonia, where she received unspecified treatment. She was discharged from the hospital after about 4 days and her pneumonia was recovered. The SAE recovered without interruption or change in somapacitan dosing, and it is unlikely that growth hormone therapy is related to a risk of infection. Somapacitan is therefore unlikely to be related to the SAE of pneumonia in this case.

Extension Period I

No subjects with ISS reported SAEs in the Extension Period

As of the database lock date, no subjects with NS reported SAEs at in the trial.

15.4.4.4. Summary of Clinically Significant ECG Findings

Pivotal Phase 3 Trial 4467

SGA

There were no clinically significant ECG findings, or AEs related to ECG findings, in any subject in the SGA population enrolled in trial 4467.

NS

A total of 3/49 (6.1%) subjects originally randomized to somapacitan, and no subjects treated with Norditropin, demonstrated abnormal ECG findings, including right atrial enlargement, accelerated escape heart rate, and sinus tachycardia. The subject with the accelerated escape heart rate was found to have a similar finding with the screening ECG, leaving relatively few subjects with abnormal ECG findings that were not present prior to treatment.

A comparable proportion of subjects in each treatment arm reported AEs related to ECG findings: 2/49 (4.1%) subjects in the somapacitan arm (atrial escape rhythm [in the same subject with the ECG finding of accelerated escape heart rate, above] and sinus tachycardia) and 1/28 (3.6%) subject in the Norditropin arm (tachycardia). These AEs were all mild and non-serious, and neither somapacitan nor Norditropin doses were interrupted or changed in

response. With the exception of the AE of atrial escape rhythm, which is not recovered, the other AEs have recovered.

ISS

During the Main and Extension Periods of trial 4467, only 1 subject, originally randomized to somapacitan (1/59 subject; 1.7%), reported an abnormal ECG finding during the trial: 1st degree AV block with possible ventricular hypertrophy. This same subject also had an AE of "electrocardiogram abnormal" reported at the same time that was mild and non-serious and resolved without any changes or interruption of somapacitan dosing.
This was the only subject in the ISS population of trial 4467 with an ECG-related AE.

Dose Finding Phase 2 Trial 4245

Throughout all periods of the phase 2 dose finding trial 4245, only 2 subjects reported clinically significant ECG findings. Information related to the description of these ECG findings is not available, other than that the findings were "abnormal". The abnormal ECG findings occurred in 1/12 [8.3%] subject originally randomized to the 0.16 mg/kg/week somapacitan group and 1/13 [7.7%] subject originally randomized to the 0.2 mg/kg/week somapacitan group, and both findings occurred after transition to 0.24 mg/kg/week somapacitan in Extension Period II, at Weeks 156 and 208, respectively. For the subject originally randomized to 0.16 mg/kg/week somapacitan, the follow up ECG at Week 208 was not noted to have a clinically significant abnormal finding. For the other subject, the abnormal ECG at Week 208 is the most recently documented ECG. Both subjects had normal baseline ECGs.

During trial 4245, only 2 subjects with AEs related to ECG findings were reported, with PTs of arrhythmia (in the subject randomized to 0.2 mg/kg/week somapacitan who had an abnormal ECG at Week 208 and the AE was reported the same month as the abnormal ECG) and ventricular extrasystoles (in a subject originally randomized to 0.16 mg/kg/week somapacitan [not the subject in this treatment arm reporting an abnormal ECG, above], prior to transition to 0.24 mg/kg/week somapacitan). Both these AEs were mild, non-serious, and the dose of somapacitan was not changed or interrupted, though neither AE has resolved.

Phase 3 Trial 4469

No subject in any patient population had clinically significant abnormal ECG findings in the phase 3 trial 4469.

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/s/

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02/26/2026 11:36:52 AM

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