Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04970654
Sponsor trial ID:	NN8640-4468
Official title of study:	A trial comparing the efficacy and safety of once weekly dosing of somapacitan with daily Norditropin® in Chinese children with growth hormone deficiency
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Protocol

Protocol title: A trial comparing the efficacy and safety of once weekly dosing of somapacitan with daily Norditropin® in Chinese children with growth hormone deficiency

Substance: Somapacitan

Universal Trial Number: U1111-1250-7530

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Trial phase: IIIa

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
NA	NA	NA

Protocol version X (DD Month YYYY)

Overall rationale for preparing protocol, version X:

Section # and name	**Description of change**	**Brief rationale**
NA	NA	NA

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Protocol attachment I Global list of key staff and relevant departments and suppliers

Protocol attachment II Country list of key staff and relevant departments

1 Protocol summary

1.1 Synopsis

Rationale:

The purpose of the phase 3 trial in China is to confirm non-inferiority of efficacy and investigate safety of once weekly subcutaneous treatment of somapacitan compared to daily subcutaneous growth hormone (GH) (Norditropin®) treatment in Chinese prepubertal children with growth hormone deficiency (GHD).

Objectives and endpoints:

Primary endpoint

Efficacy endpoint

- Height velocity (HV, annualised) at week 52

Secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline (week 0) to week 52 in:

- Height Standard Deviation Score (SDS)
- Height Velocity Standard Deviation Score

Change from Visit 1 to Week 52 in:

- Bone age

Supportive secondary safety endpoints

Change from baseline (week 0) to week 52 in:

- Fasting plasma glucose
- Glycated haemoglobin (HbA1c)

Supportive secondary pharmacodynamics endpoints

Change from baseline (week 0) to week 52

- Insulin-like growth factor I (IGF-I) Standard Deviation Score
- Insulin-like growth factor binding protein 3 (IGFBP-3) Standard Deviation Score

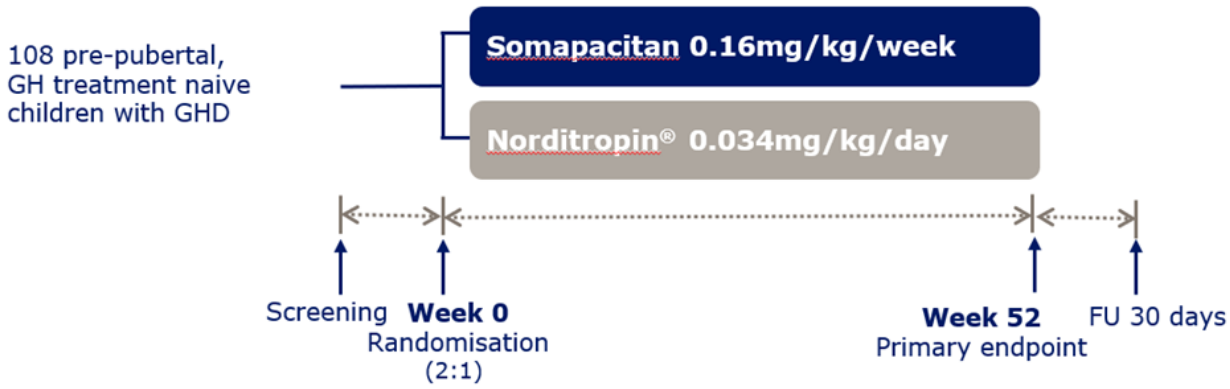
Overall design:

A randomised open-labelled two arm trial designed to confirm non-inferiority of efficacy and investigate safety of once weekly subcutaneous treatment of somapacitan compared to daily subcutaneous growth hormone (Norditropin®) treatment in Chinese prepubertal children with growth hormone deficiency.

The total trial duration for a subject will be 58 to 70 weeks approximately.
The trial duration includes a 2 to 14 weeks screening period, a 52 weeks treatment period and a minimum of 30 days follow up period.

Eligible subjects will be randomised in a 2:1 manner to receive either somapacitan or Norditropin®
A non-inferiority margin of -2.0 cm/year is used in the trial. The randomisation will be stratified by age (<6 versus ≥6 years), gender (boys versus girls) and GH peak (< 7 versus ≥ 7 ng/ml) ensure equal distribution of these factor levels across treatment.

Figure 1 Trial design



The trial will be a single country (China) trial to compare the results obtained to data observed in subjects with different demographic characteristics, including Asian population(s) obtained in the pivotal global phase 3 trial.

Approximately 108 subjects will be randomised in a 2:1 ratio to receive either somapacitan (0.16 mg/kg/week) or Norditropin® (0.034 mg/kg/day) during a 52-week period, with a primary endpoint at week 52.

Inclusion criteria

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.
   - The parent or legally acceptable representative of the child must sign and date the Informed Consent Form (according to local requirements).
   - The child must sign and date the child assent form or provide oral assent (if required according to local requirements)
2. Pre-pubertal children:

- Boys:
  - Testis volume < 4 ml[1]
  - Age ≥ 2 years and 26 weeks and ≤ 11.0 years at the time of signing informed consent.
- Girls:
  - Tanner stage 1, for breast development (no palpable glandular breast tissue)[1]
  - Age ≥ 2 years and 26 weeks and ≤ 10.0 years at the time of signing informed consent.

3. Confirmed diagnosis of growth hormone deficiency determined by two different GH stimulation tests performed within 12 months prior to screening, defined as a peak growth hormone level of ≤ 10.0 ng/ml using the WHO International Somatropin 98/574 standard.
   - If only one GH stimulation test is available before screening, then confirmation of GHD by second and different GH stimulation test must be done.
   - For children with at least 2 additional pituitary hormone deficiencies (other than GHD) only one GH stimulation test is needed.
4. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and gender according to Chinese general population standards at screening [2].
5. Impaired height velocity defined as annualised height velocity at screening less than 7 cm/year for subjects between 2.5 and 3 years old and less than 5 cm/year for subjects from 3 years and above calculated over a time span of minimum 3 months and maximum 18 months prior to screening according to Chinese guideline and expert consensus on children with short stature and GH therapy[3].
6. No prior exposure to GH therapy or IGF-I treatment
7. Bone age less than chronological age at screening.
8. Body Mass Index >5th and <95th percentile, body mass index for age growth charts according to the Chinese general population standards[4].
9. IGF-I < -1.0 SDS at screening, compared to age and gender normalized range measured at central laboratory
10. No intracranial tumour confirmed by magnetic resonance imaging or computer tomography scan. An image or scan taken within 9 months prior to screening can be used as screening data if the medical evaluation and conclusion is available.

Exclusion Criteria

1. Known or suspected hypersensitivity to trial products or related products.
2. Previous participation in this trial. Participation is defined as randomisation.
3. Receipt of any investigational medicinal product within 3 months prior to screening or participation in another clinical trial before randomisation
4. Any suspected or known clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements:
   - Turner syndrome (including mosaicisms)
   - 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.
   - Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
   - Congenital abnormalities (causing skeletal abnormalities), including but not limited to Russell-Silver syndrome or skeletal dysplasia.
   - Family history of skeletal dysplasia
5. Children born small for gestational age (birth weight 10th percentile of the recommended gender-specific birth weight for gestational age according to national standards in China)[5].
6. Children diagnosed with diabetes mellitus or screening values from central laboratory of
   - fasting plasma glucose ≥126 mg/dl (7.0 mmol/L) or
   - 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 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 presence of malignancy including intracranial tumors.
12. Prior history or 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 clinically significant abnormal laboratory screening tests, as judged by the investigator
14. Any disorder which, in the opinion of the investigator, might jeopardize subject's safety or compliance with the protocol.
15. The subject or the parent/legally acceptable representative (LAR) is likely to be non-compliant in respect to trial conduct, as judged by the investigator.
16. Children with hypothyroidism and/or adrenal insufficiency not on adequate and stable replacement therapy for at least 90 days prior to randomisation.

Primary estimand

- Hypothetical strategy - ancillary therapy not available*:* The treatment difference between somapacitan and Norditropin® in mean annualised HV at week 52 if ancillary therapy had not been available prior to week 52 (i.e. assuming no initiation of ancillary therapy) in children with GHD.

The use of ancillary therapy may lead to attenuation of the treatment effect of interest or even exaggerate the treatment effect and the estimand thus aims to reflect the treatment difference attributable to the initially randomised treatments.

The sample size calculation is based on the primary estimand. It is expected based on phase 2 trial data (NN8640-4172) that the proportion of subjects with no landmark visit data or who discontinued randomised treatment before landmark visit is 10% with similar withdrawal reasons in the two treatment arms. It is expected that subjects discontinuing their randomised treatment will start on ancillary treatment, if no medical reasons prohibit this. Thus data assessed after discontinuation of the randomised treatment will not be used for the primary analysis of the primary endpoint based on the primary estimand. Assuming the same proportions of subjects with no landmark visit and subjects discontinuing randomised treatment but have landmark visit data in the two arms leads to the following sample size calculation.

The sample size is determined using a non-inferiority margin of -2.0 cm/year and a one sided two-group t-test with a significance level of 2.5% for a 2:1 randomisation ratio between somapacitan and Norditropin®.

Based on data from NN8640-4172, a standard deviation for HV at week 52 was chosen (SD=2.6 cm/year) for the sample size calculation giving a sample size of 108 subjects. Different SD scenarios with power calculation for the primary analysis are presented in the table below under the assumption of a true difference in annualized HV of 0 cm/year between the two treatment arms

Table 1 Calculated power with 108 subjects randomised 2:1

SD	2.5 cm/year	2.6 cm/year	2.7 cm/year	2.8 cm/year
	95%	**94%**	**92%**	**90%**

The SD candidates are based on reported SD values from clinical trials: Valtropin phase 3 trial[6], 52 weeks (SD=2.8, 3.0), OPKO phase 2 trial[4], 52 weeks (SD=2.1, 2.3, 2.6, 3.5), and NN8640-4172, phase 2 trial, 52 weeks (SD=2.3, 2.6).

Number of subjects:

Approximately 270 subjects will be screened to achieve 108 subjects randomly assigned (2:1 ratio) to either Somapacitan or Norditropin® trial products.

Treatment groups and duration:

The total trial duration for a subject will be 58 to 70 weeks approximately.

The trial duration includes a 2 to 14 weeks screening period, A 52 weeks treatment period and a minimum of 30 days of follow up period.

The trial products comprise the Investigational Medicinal Product (IMP) somapacitan and the active comparator Norditropin®. Both trial products will be supplied by Novo Nordisk A/S, Denmark.

The somapacitan trial product and Norditropin® will be delivered in prefilled pen-injectors of the PDS290 pen-injector family developed by Novo Nordisk A/S. The PDS290 family of pen-injectors has been approved for use in China with Novo Nordisk insulins (e.g. NovoRapid® FlexTouch®, Tresiba® FlexTouch®, Ryzodeg® FlexTouch®). Norditropin® in PDS290 pen-injector is approved in many countries including EU, USA and Japan etc, as Norditropin® FlexPro®. The somapacitan PDS290 pen-injector has been developed to be in compliance with the European Medical Device Directive.

Data monitoring committee: Not applicable

1.2 Flowchart

	Protocol section	Screening		Randomisation	Treatment period				End of Treatment	Discontinuation of trial product	Follow-up
Visit		**Visit 1a[d]**	**Visit 1b**	**Visit 2[c]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[a]**	**Visit 7A**	**Visit 8[b]**
Timing of Visit (Weeks)		-14W	-2W	0	4W+1D	13W	26W+1D	39W	52W+5D		30D
Visit Window (Days)		minimum 1 day prior to visit 1b	±7	0	+3	±7	+3	±7	±1		+5
SUBJECT RELATED INFORMATION AND ASSESSMENTS											
Informed Consent and Demography	10.1.3	X									
Informed Consent Obtain by Child Assent	10.1.3	X									
Eligibility Criteria	5.2	X	X	X							
Medical History/Concomitant Illness	8.2	X									
Concomitant medication	6.5	X	X	X	X	X	X	X	X	X	
Randomisation				X							
Pubertal Status	8.1.2		X	X			X		X	X	
Discontinuation/Withdrawal criteria	7.1, 7.2				X	X	X	X	X	X	
EFFICACY											

	Protocol section	Screening		Randomisation	Treatment period				End of Treatment	Discontinuation of trial product	Follow-up
Visit		**Visit 1a[d]**	**Visit 1b**	**Visit 2[c]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[a]**	**Visit 7A**	**Visit 8[b]**
Timing of Visit (Weeks)		-14W	-2W	0	4W+1D	13W	26W+1D	39W	52W+5D		30D
Visit Window (Days)		minimum 1 day prior to visit 1b	±7	0	+3	±7	+3	±7	±1		+5
X-ray for bone age assessment	8.1.4		X						X	X	
BODY MEASUREMENT											
Height	8.1.1.1	X	X	X	X	X	X	X	X	X	
Body Weight	8.1.1.2		X	X	X	X	X	X	X	X	
Pharmacodynamics	8.6	X		X	X	X	X	X	X	X	
PK	8.5			X	X	X	X	X	X	X	
SAFETY											
Physical examination	8.2.1	X	X				X		X	X	
Vital signs	8.2.2	X	X				X		X	X	
ECG	8.2.3		X						X	X	
Haematology	8.2.5			X			X		X	X	
Biochemistry	8.2.5			X			X		X	X	

	Protocol section	Screening		Randomisation	Treatment period				End of Treatment	Discontinuation of trial product	Follow-up
Visit		**Visit 1a[d]**	**Visit 1b**	**Visit 2[c]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[a]**	**Visit 7A**	**Visit 8[b]**
Timing of Visit (Weeks)		-14W	-2W	0	4W+1D	13W	26W+1D	39W	52W+5D		30D
Visit Window (Days)		minimum 1 day prior to visit 1b	±7	0	+3	±7	+3	±7	±1		+5
Glucose metabolism	8.2.5		X				X		X	X	
Hormones	8.2.5		X				X		X	X	
Lipids	8.2.5			X			X		X	X	
Antibodies	8.2.5			X			X		X	X	
Adverse event	8.3			X	X	X	X	X	X	X	X
Injection site reaction	8.3			X	X	X	X	X	X	X	
Technical complaint	8.3.6			X	X	X	X	X	X	X	
Medication Error, Misuse and Abuse	8.4			X	X	X	X	X	X	X	
PRO QUESTIONNAIRES											
GHD-CIM	8.8			X			X		X	X	
GHD-CTB	8.8						X		X	X	
GHD-PTB	8.8						X		X	X	

	Protocol section	Screening		Randomisation	Treatment period				End of Treatment	Discontinuation of trial product	Follow-up
Visit		**Visit 1a[d]**	**Visit 1b**	**Visit 2[c]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[a]**	**Visit 7A**	**Visit 8[b]**
Timing of Visit (Weeks)		-14W	-2W	0	4W+1D	13W	26W+1D	39W	52W+5D		30D
Visit Window (Days)		minimum 1 day prior to visit 1b	±7	0	+3	±7	+3	±7	±1		+5
TRIAL MATERIAL											
Drug dispensing	6.2			X	X	X	X	X			
Drug accountability	6.2			X	X	X	X	X	X	X	
IWRS session	6.2	X		X	X	X	X	X	X	X	
REMINDERS											
Ensure that MRI/CT scan is available	8.2.4		X								
Attend visit fasting	5.3.1		X				X		X	X	
Hand out ID card	8	X									
Training in devices	6.1.1			X							
Hand out directions for use	6.1			X							
Collect diary	6.4, 8.9				X	X	X	X	X	X	

	Protocol section	Screening		Randomisation	Treatment period				End of Treatment	Discontinuation of trial product	Follow-up
Visit		**Visit 1a[d]**	**Visit 1b**	**Visit 2[c]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[a]**	**Visit 7A**	**Visit 8[b]**
Timing of Visit (Weeks)		-14W	-2W	0	4W+1D	13W	26W+1D	39W	52W+5D		30D
Visit Window (Days)		minimum 1 day prior to visit 1b	±7	0	+3	±7	+3	±7	±1		+5
End of treatment	6.7, 7.1								X	X	
End of trial	4.4, 7.2										X
Screening failure	5.4		X								

a	Primary endpoint visit
b	Follow up visit should also be performed after visit 7A for subjects who discontinue treatment. The follow up visit can be performed as phone visit
c	All screening assessments must be completed before randomising the subject.
d	Visit 1a and 1b must not be combined.

2 Introduction

The trial will be conducted in compliance with this protocol, ICH-GCP[7] and applicable regulatory requirements, and in accordance to declaration of Helsinki[8].

Throughout the protocol, the term subject refers to the subject and the parent or legally acceptable representative (LAR) as a whole if applicable, depending on the age and the capability of the subject to perform the required trial procedures.

2.1 Trial rationale

The trial is a randomised, China only, multicentre, open labelled and active controlled- parallel group design with a once weekly somapacitan dose regimen.

The purpose of this phase 3 trial is to confirm non-inferiority of efficacy and investigate safety of once weekly subcutaneous (s.c) treatment with somapacitan compared to daily s.c growth hormone (GH) (Norditropin®) treatment in prepubertal children with growth hormone deficiency (GHD). This confirmatory trial in children with GHD will serve as the basis for market authorisation application within this indication in China.

Dosing somapacitan once weekly can potentially provide greater convenience, and thus potentially better adherence, compared to standard GH treatment which must be administered daily. Treatment with GH in children with GHD aims to induce growth, increase HV and improve final adult height.

2.2 Background

2.2.1 Growth hormone deficiency

GH is essential for normal longitudinal growth in children and acts partly by direct action on the growth plates and partly by stimulation of insulin like growth factor-I(IGF-1) release [9]. Besides, the importance of GH and IGF-I for facilitating the growth in children, both proteins are also involved in various metabolic processes in children as well as in adults.[10]

Rapid proteolysis and ligand-receptor internalization result in a short half-life for human growth hormone (hGH). Consequently, hGH is given as daily injections. Children and adults with GHD currently require many years or lifelong treatment with a daily s.c injection regimen. Studies investigating treatment adherence have shown approximately one fourth of children on GH treatment miss more than two of the seven injections per week[11-13].

GHD may occur as an isolated hormonal deficiency or in combination with multiple pituitary hormone deficiencies. It may result from congenital, genetic, acquired (by tumours in the central nervous system, cranial irradiation, head trauma or other organic causes) or idiopathic causes.

Idiopathic GHD is the most common form, accounting for approximately 75% of diagnosed patients[14].

GHD in children is characterised by a reduced HV and a markedly reduced final adult height compared to the predicted height based on mid-parental height. Normal growth can be restored with GH replacement therapy[14-16]. The treatment for GHD in children is the same whether the cause is congenital, genetic, acquired or idiopathic. GHD may be present already at birth but is generally first discovered within the first years of childhood.

Experience gained during the last 15-20 years shows that GH treatment is also effective in restoring normal growth in children with other forms of growth retardation, including Turner and Noonan syndromes, children with chronic renal failure and children born small for gestational age with insufficient catch up growth[16, 17]

2.2.2 Somapacitan

Somapacitan is a long acting hGH derivative, with a single amino acid substitution in the growth hormone backbone to which a non-covalent albumin binding moiety has been attached. The albumin binder is attached to position 101 of the hGH backbone through a hydrophilic spacer. Somapacitan is intended for once weekly subcutaneous administration with the aim of reducing treatment burden for patients by reducing injection frequency and improving treatment adherence[18]. The molecular weight of somapacitan is 23.2 kDa which is similar to somatropin Norditropin® 22 kDa. As for hGH, the mechanism of action of somapacitan is via IGF-I. The receptor potency and pharmacokinetics (PK) profile of somapacitan is evaluated as suitable for once weekly administration in humans and it is anticipated that once weekly treatment with somapacitan will be as safe and effective as daily GH treatment[19]

2.2.3 Somapacitan non-clinical data

No safety issues were identified during the non-clinical development of somapacitan which would prevent further administration of the compound in humans. Non-clinical data supports once weekly administration in humans and further development in phase 3.

Further details on the non-clinical findings are described in the Investigator Brochure (IB)[19]

2.2.4 Somapacitan clinical data

No safety issues have been identified during the clinical development of somapacitan. Clinical data obtained from both adults and children continue to support the further development of somapacitan into phase 3 in children[19]

2.2.5 Norditropin®

For information please refer to the summary of product characteristics (SmPC).

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections:

2.3.1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
• Adrenocortical insufficiency Hyperglycaemia	Patients receiving growth hormone therapy who have or are at risk for pituitary hormone deficiency(s) may experience reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of growth hormone treatment Treatment with growth hormone may decrease insulin sensitivity, particularly at higher doses in susceptible patients, and consequently hyperglycemia may occur in subjects with inadequate insulin secretory capacity. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during growth hormone treatment	Only physicians trained within pediatric endocrinology and therefor knowledge of these identified risks for all growth hormone products will be chosen as investigators in the trial. Additionally, subjects with diabetes mellitus or increase fasting plasma glucose or HbA1c will not be included in the trial. Lastly both identified risks are mentioned under the warning and precautions in the investigator's brochure[19].
Trial treatment(s)		
• Subcutaneous injections	Can occasionally lead to undesired local side effects, such as redness, swelling,	It is highlighted in the protocol that the injection site should be rotated with each injection.

	itching, and tenderness of the skin at the point of injection.	This to minimize the risk for injection site reactions
Trial procedures		
• Physical examination, body measurements and Tanner pubertal staging	• No risks are expected to be associated with standard physical examination. Burden (embarrassment, discomfort, distress) associated with examinations that are related to sexual development (e.g., Tanner staging) can be expected.	• As this assessment is performed by pediatricians familiar with the population the burden is expected to be low.
• Computerised tomography (CT) scan	• Risks are related to the total dose of radiation received from the scan (possibly contributing to tissue damage, mutations and cancer) and to allergy / anaphylaxis with contrast agents. Burdens may include discomfort, fear, pain in case of contrast agent injection and need for specialised setting.	• The burden of this assessment is reduced by the possibility of using CT scans performed up to nine months prior to screening as part of local clinical practice. The investigator will decide if a CT scan or MRI will be performed.
• Magnetic resonance imaging (MRI)	• Risks include those related to contrast agents, such as nausea, hypersensitivity reactions and accumulation and functional impact of contrast agents in several organs. Burdens may include discomfort, claustrophobia, fear, pain from venepuncture and heat sensation in case of contrast agent injection and need for specialised setting.	• The burden of this assessment is reduced by the possibility of using an MRI performed up to nine months prior to screening as part of local clinical practice. The investigator will decide if a CT scan or MRI will be performed.
• X-Ray for bone age assessment	• No risks are expected to be associated with the procedure. The risks are	• The burden of this assessment is reduced by the possibility of using an

	related to the total dose of radiation received.	X-Ray performed up to 13 weeks prior to screening. The frequency of the X-Ray examination is similar to normal clinical practise to limit the total dose of radiation received.
• Electrocardiogram (ECG)	• The procedure involves placing adhesive skin surface electrodes on the body. This procedure does not incur any risks. Burdens may include discomfort and fear	• Electrocardiograms (ECGs) are collected at screening and end of treatment during the trial.
• Fasting prior to blood sampling	• Risks may include modest to moderate hypoglycemia (usually subclinical). Burdens may include hunger and distress, increasing with duration of fasting and generally with younger age	• In this trial the number of fasting visits and length of the fasting period are reduced to the extent possible.
• Peripheral venipuncture	• Peripheral venous access is widely used for taking blood samples. Risks include vasovagal reactions, minor bleeding and vessel damage. Burdens include moderate pain and possibly fear and distress.	• In this trial investigators are encouraged to use numbing cream according to local practice.
• GH stimulation tests	• Risks are related to peripheral venepuncture, fasting prior to blood sampling and reactions to the stimulating agent.	• To reduce the burden the investigator should select the stimulation test most suitable for the subject's age. Results of prior stimulation tests performed as part of clinical practice can be used as screening data and do not need to be repeated.

Other		
• Risk of COVID-19 infection in relation to participation in the trial.	• Patients/ LAR may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the country.	• The risk of COVID-19 transmission in relation to site visits is overall considered to be low. To minimize the risk as much as possible, the following measures have been taken: o On-site visits will be well-prepared and as short as possible. Physical contact between patients and site staff will be limited to the extent possible, and protective measures will be implemented such as masks sanitizers etc.
	• If a patient is tested positive for COVID-19	• The risk of COVID-19 transmission in relation to site visits is over all considered to be low considering patient population participating in the trial, however if a subject is tested positive for COVID-19 then the investigator must ensure proper medical care and if possible site visits can be converted to telephone visits and if the subject recovers in time for the primary endpoint visit then the investigator should encourage the subject to visit the site for the primary

		endpoint visit. All necessary precautions must be taken for the site visit.

2.3.2 Benefit assessment

All subjects will receive GH trial treatment and auxiliary supplies free of charge until the end of trial. Subjects randomised to somapacitan will receive fewer injections than standard practice.

2.3.3 Overall benefit-risk conclusion

No important identified or important potential safety risks have been recognised from treatment with somapacitan neither in non-clinical studies nor in completed or ongoing clinical trials in both adults and children. There are well known risks associated with administration of injectable medication[19] as well as procedural risks. In this trial the risks associated with administration of trial product as well as the risks associated with the trial procedures are expected to be comparable to what is seen in routine clinical practice. Therefore, it is expected that the benefits of participation in this trial outweigh the risks.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of somapacitan and Norditropin® may be found in the investigator's brochure of somapacitan[19] and summary of product characteristics of Norditropin®[20]

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objective(s) and estimand(s)

Primary objective:

To compare efficacy of somapacitan vs Norditropin® on longitudinal growth in Chinese children with GHD.

Secondary objective:

To compare safety of somapacitan vs Norditropin® in Chinese children with GHD

Primary estimand

Hypothetical strategy - ancillary therapy not available*:* The treatment difference between somapacitan and Norditropin® in mean annualised HV at week 52 if ancillary therapy had not been available prior to week 52 (i.e. assuming no initiation of ancillary therapy) in children with GHD.

The use of ancillary therapy may lead to attenuation of the treatment effect of interest or even exaggerate the treatment effect and the estimand thus aims to reflect the treatment difference attributable to the initially randomised treatments.

3.2 Primary, secondary and exploratory endpoint(s)

3.2.1 Primary endpoint

Table 2 Primary endpoint

Endpoint title	Time frame	Unit
Height Velocity	Height velocity (annualised) at week 52	cm / year

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoints

Not Applicable

3.2.2.2 Supportive secondary endpoints

Table 3 Efficacy

Endpoint title	Time frame	Unit
Change in bone age	From visit 1 to week 52	Years
Change in Height Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
Change in Height Velocity Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10

Table 4 Safety

Endpoint title	Time frame	Unit
Change in fasting plasma glucose	From baseline (week 0) to week 52	mmol/l
Change in $HbA1_c$	From baseline (week 0) to week 52	%

Table 5 Pharmacodynamics

Endpoint title	Time frame	Unit
Change in IGF-I Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
Change in IGFBP-3 Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10

3.2.3 Exploratory endpoint(s)

Not Applicable

4 Trial design

4.1 Overall design

A randomised open-labelled two arm trial designed to confirm non-inferiority of efficacy and investigate safety of once weekly subcutaneous treatment of somapacitan compared to daily subcutaneous growth hormone (Norditropin®) treatment in Chinese prepubertal children with growth hormone deficiency.

The total trial duration for a subject will be up to70 weeks approximately.

The trial duration includes a variable 14 weeks of screening period, a 52 weeks of treatment period and a minimum 30 days of follow up period.

Eligible subjects will be randomised in a 2:1 manner to receive either somapacitan or Norditropin®

The non-inferiority margin of -2.0 cm/year is used in the trial. The randomisation will be stratified by age (<6 versus ≥6 years), gender (boys versus girls) and GH peak (< 7 versus ≥ 7 ng/ml) to minimize bias on the primary endpoint.

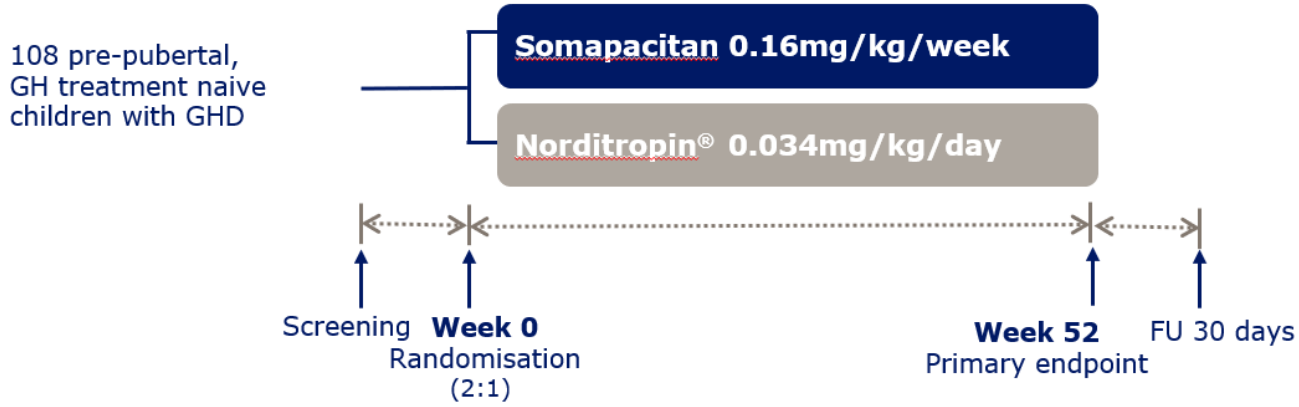


Figure 2 Trial design

Approximately 108 subjects will be randomly assigned to the trial product. For sample size determination please see section 9.2

4.2 Scientific rationale for trial design

Sensitivity to GH treatment is higher in GH deficient than non-GH deficient conditions, therefore treatment-naïve children with GHD are considered a sensitive population and are also a well-known model for evaluating the primary endpoint; HV (cm/year) during first 52-weeks [21]. Only pre-pubertal children will be enrolled to minimize interference of the pubertal growth spurt with the treatment effect of GH. Some of the subjects may enter puberty during the trial however age and gender stratification will ensure that children who enter puberty during the trial will be randomly distributed between the two arms.

Both boys and girls will be enrolled in this trial in order to obtain information on efficacy and safety of somapacitan in both genders.

No placebo controlled GHD trial results are available to be used for supporting the choice of a non-inferiority margin for this GHD trial.

It has therefore been necessary to look for results in a related indication: paediatric patients with small for gestational age (SGA).

In a Norditropin® trial in paediatric patients with SGA (GHLIQUID-1424)[22], the estimated treatment effect in delta height (change from baseline) for Norditropin® vs no treatment at 1 year was 3.3 cm [2.9; 3.7] for 0.033 mg/kg/day and 6.5 cm [6.0; 6.9] for 0.100 mg/kg/day of Norditropin®, respectively. This gives some indication that the expected effect of Norditropin® versus placebo would be well approximated by the 3.3 cm/year observed in trial GHLIQUID-1424 for SGA.

The observed mean values (SD) from the daily rhGH comparator in a pivotal phase 3 GHD trial[22] were 2.93 (1.09) cm/year at baseline and 11.97 (3.09) cm/year after 1 year. This large difference between baseline and 1 year HV data makes a hypothesized difference in HV after 1 year between a GH treatment arm and a no treatment arm of 4 cm/year in GHD not unreasonable in a pre-pubertal population as spontaneous HV as a function of age is expected to be approximately constant until the start of the pubertal growth spurt, while still allowing for a substantial trial effect impacting the change from baseline result. The 3.3 cm/year may therefore be viewed as a conservative approximation of the treatment effect vs no treatment in GHD. By using a non-inferiority margin of -2.0 cm/year, an improvement of at least 1.3 cm against no GH treatment would be expected to be preserved after the first year.

4.3 Justification for dose

The somapacitan dose is selected upon available evidence and supported by modelling and simulation. The dose level of somapacitan in this phase 3 trial in GHD is 0.16 mg/kg/week. This is supported by the results from the phase 2 dose-finding trial (NN8640-4172) that showed somapacitan doses of 0.08 mg/kg/week and 0.16 mg/kg/week were not statistically different from Norditropin® (0.034 mg/kg/day) in HV at 26 weeks while displaying an acceptable tolerability profile. The efficacy of the 0.16 mg/kg/week dose was also supported by exposure-response modelling of HV, height based supportive endpoints and IGF-I SDS compared to 0.034 mg/kg/day Norditropin®. The mean IGF-I SDS levels of the somapacitan 0.16 mg/kg/week dose were comparable to the mean IGF-I SDS level of Norditropin® (0.034 mg/kg/ day), and for the somapacitan 0.16 mg/kg/week dose the population mean for the IGF-I average was 0.5 SDS with a 90% range below 2.0 SDS.

Somapacitan will be administered once weekly and Norditropin® will be administered once daily. A fixed body weight-based regimen is chosen as it is standard practise for GH treatment in China. Dosing of daily Norditropin® in this trial design is similar to the dosing used in the phase 2 dose finding trial and ongoing global phase 3 trial in pre-pubertal, GH treatment naïve children with GHD. The dose used for Norditropin® in the trial is 0.034 mg/kg/day, which is within label. The ongoing phase 3a trials use similar dosage regimen as proposed in this trial.

Both treatments will be administered s.c as this is the approved administration route for Norditropin® and is the intended route of administration for somapacitan. The Phase 2 trials did not include Chinese subjects but Japanese subjects.

4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed all visits of the trial including the last visit. The end of the trial is defined as the date of the last visit of the last subject in the trial.

5 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

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 child assent form or provide oral assent (if required according to local requirements)
2. Prepubertal children:
    a. Boys:
        i. Age ≥ 2 years and 26 weeks and ≤ 11.0 years at the time of signing informed consent.
        ii. Testis volume < 4 ml[1]
    b. Girls:
        i. Age ≥ 2 years and 26 weeks and ≤ 10.0 years at the time of signing informed consent.
        ii. Tanner stage 1 for breast development (no palpable glandular breast tissue)[1]
3. Confirmed diagnosis of growth hormone deficiency determined by two different growth hormone stimulation tests performed within 12 months prior to randomisation, defined as a peak growth hormone level of ≤ 10.0 ng/ml using the WHO International Somatropin 98/574 standard
    a. If only one growth hormone stimulation test is available before screening, then confirmation of growth hormone deficiency by second and different growth hormone stimulation test must be done
    b. For children with at least 2 additional pituitary hormone deficiencies (other than growth hormone deficiency) only one growth hormone stimulation test is needed
4. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and gender according to Chinese general population standards at screening[2]
5. Impaired height velocity defined as annualised height velocity at screening less than 7cm/year for subjects between 2.5 and 3 years old and less than 5 cm/year for subjects from 3 years and above calculated over a time span of minimum 3 months and maximum 18 months prior to screening according to Chinese guideline and expert consensus on children with short stature and GH therapy[3]
6. No prior exposure to growth hormone therapy or IGF-I treatment

7. Bone age less than chronological age at screening
8. Body Mass Index >5th and <95th percentile, Body Mass Index-for-age growth charts according to Chinese general population standards.[4]
9. IGF-I < -1.0 SDS at screening, compared to age and gender normalized range measured at central laboratory
10. No intracranial tumour confirmed by magnetic resonance imaging or computer tomography scan. An image or scan taken within 9 months prior to screening can be used as screening data if the medical evaluation and conclusion is available[19]

5.2 Exclusion criteria

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 before 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
5. Children born small for gestational age (birth weight 10^{th} percentile of the recommended gender-specific birth weight for gestational age according to national standards in China[5]
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 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 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 clinically significant abnormal laboratory screening tests, as judged by the investigator
14. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
15. The subject or the parent/legally acceptable representative is likely to be non-compliant in respect to trial conduct, as judged by the investigator.
16. Children with hypothyroidism and/or adrenal insufficiency not on adequate and stable replacement therapy for at least 90 days prior to randomisation.

The following criteria will be assessed at the following visits:

Table 6

Visit 1a	Visit 1b
Inclusion criteria: 3, 9	Inclusion criteria: 4, 5,7, 8, 10
	Exclusion criteria: 6,7,8

All eligibility criteria must be assessed before randomising the subject.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

Subjects should be fasting (only water is allowed) for 6 hours prior to blood sampling for fasting plasma glucose and for GH stimulation test at screening visit, please see flowchart 1.2.

5.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, any serious adverse event (SAE), laboratory results.

A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. If the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

6 Treatments

6.1 Treatments administered

The trial products comprise of the investigational medicinal product (IMP) somapacitan and the active comparator Norditropin®. Both the trial products will be supplied by Novo Nordisk A/S.

The investigator should train the subject on use of pen device and must document that directions for use are given to the subject verbally and in writing at the first dispensing visit (Visit 2) (as specified in the flowchart). Furthermore the investigator must communicate in-use time to the subject while dispensing trial product.

Investigational medicinal products (IMP)

Table 7 Investigational and comparator medicinal product provided by Novo Nordisk A/S

Trial product name:	Somapacitan 5mg/ 1.5ml Somapacitan 10mg/ 1.5ml Somapacitan 15mg/1.5ml	Norditropin® Flex Pro® 10mg/1.5 ml
Dosage form:	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Dosing instructions	Once weekly	Daily
Packaging	Somapacitan PDS290 pen-injector	Norditropin® FlexPro® pen-injector

Three different strengths of somapacitan will be used as stated above in the Table 7. The strength used is dependent on the subject's current weight.

Time of injection of somapacitan

- Somapacitan can be injected subcutaneously any time during the dosing day (Once weekly).
- If a dose is not administered on the planned dosing day, the dose must then be administered as soon as possible after the missed planned dosing day.
- If the dose cannot be administered within 3 days after planned dosing day, the dose should be skipped. The next dose afterwards should be taken on the originally planned weekday as per randomisation schedule.
- In case it is known that dose cannot be administered on the planned dosing day, the dose can be given the day before the planned dosing date.

Time of injection of Norditropin®

- Subjects randomised to Norditropin® should inject subcutaneous daily in the evening (to reflect standard treatment practice) throughout the trial.
- Injections with Norditropin® the night before blood sampling for anti-hGH antibodies must occur at least 12 hours prior to planned blood sampling.
- If a subject randomised to Norditropin® forgets or is unable to inject the dose in the evening, the dose should be skipped. The subject should take the next dose on the following evening as scheduled.

Auxiliary supplies

- Only needles provided or approved by Novo Nordisk must be used for administration of trial product. Maximum needle length should be 6 mm.
- Direction for use (DFU) for somapacitan and Norditropin®.

6.1.1 Medical devices

Information about the pre-filled somapacitan PDS290 pen-injector can be found in the IB for somapacitan and any updates hereof[23]
Information about the use of pre-filled PDS290 pen-injector for somapacitan can be found in the DFU.
Information about the use of pre-filled Norditropin® FlexPro® can be found in the DFU.
Information about Norditropin® FlexPro® can be found in the IB of Norditropin.

Training in the PDS290 somapacitan pen-injector and Norditropin® FlexPro®

The subjects (and parent/LAR) must be trained according to the DFU in how to handle the Somapacitan PDS290 pen-injector or Norditropin® FlexPro® when handed out the first time. Training must be documented and repeated during the trial at regular intervals in order to ensure correct use of the Somapacitan PDS290 pen-injector or Norditropin® FlexPro® as judged by the investigator.

6.1.1.1 Non-investigational medical device(s)

Non-investigational medical devices are listed in Section 6.1.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply or administer trial product.

Trial product storage, in-use conditions and in-use time will be available on the label and in the trial materials manual (TMM).

- Investigator must clearly instruct the in-use time to the subject as described in the DFU of each trial product. When the subject returns the trial product, the in-use time of each pen needs to be discussed and documented in the subject medical record. Subjects must be retrained as required.
- Acceptable temperature ranges and conditions for storage and handling of each trial product when not in use and when in use are described in the TMM.
- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial product will be distributed to the sites according to screening and randomisation.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.
- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- Drug accountability for somapacitan and Norditropin® is performed on a dispensing unit number (DUN) level using the IWRS drug accountability module to account for the status of each pen for each DUN.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor in IWRS.
- All returned, unused, expired or damaged trial products (for technical complaint samples, see Section 10.4) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

All screened patients will receive a unique patient number at the screening visit (1a), which will be assigned to the patient throughout the trial.

Trial using IWRS	All subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarized in the flowchart.

- This is an open-label trial

Novo Nordisk staff involved in interpretation of data will be kept blinded until database lock for primary endpoint

For blinding of site staff performing the height measurements please refer to Section (8.1.1.1)

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to encourage subject compliance.

When subjects are dosed at the site, they will receive trial product directly from the investigator or designee, under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents.

When subjects self-administer trial product(s) at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available. Any missed dose should be discussed with the subject and followed up to ensure subject is compliant to trial product and trial procedures. If any suspicion of non-compliance arises i.e, 30% of the missed doses of somapacitan or Norditropin® between two visits the site must enter into a dialogue with the patient, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned trial product, visual inspection of pens
- Review of dosing diaries
- Questioning of subjects

Treatment start dates, stop dates and all doses will be recorded in the electronic case report form (eCRF).

6.5 Concomitant medication

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) other than the trial product(s) that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates
- Total daily dose

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE/SAE, then this must be reported according to section 8.3

During the trial, initiation of any treatment that may affect growth (primary endpoint) is not allowed, however investigator can prescribe methylphenidate for treatment of ADHD during the trial, but it is not recommended to do so as it would affect the primary endpoint of the trial. Medical judgement should always be according to investigator's discretion.

6.5.1 Ancillary therapy

Ancillary therapy is defined as any GH treatment (other than trial product) and IGF-I medication that the subject is receiving. Ancillary therapy is not allowed but subjects who discontinue trial product can start treatment with a marketed GH product as stated in Section 6.7

Any ancillary therapy must be recorded along with:

- Trade name or generic name
- Start and stop dates

6.6 Dose modification

The dose will be calculated based on the subject's current body weight. The investigator will communicate the dose to the subject at each visit.

Modification to the calculated dose should only be performed as described in section 6.6.1

6.6.1 Dose reduction criteria

If adverse events with a probable relationship to the trial product are persistent but allow continuation in the trial, as judged by the investigator, dose reduction in consecutive steps of 25% of the current dose can be considered at the investigator's discretion. If after consecutive dose reduction steps AEs still persist, the subject's treatment may be discontinued according to treatment discontinuation (See section 7.1) or withdrawal criteria (See section 7.2). When the AE is resolved the dose can be resumed to the original planned dose at the investigator's discretion.

If IGF-I SDS exceeds +2.5 SDS at two consecutive visits the investigator will be informed by Novo Nordisk. Dose reduction must then be done by a 25% of the current dose.

6.7 Treatment after end of trial

When discontinuing trial products, the subject should be transferred to a suitable marketed product, at the discretion of the investigator or treating physician.

If a subject discontinues trial product during the trial and is transferred to a marketed product this should be recorded as ancillary therapy.

7 Discontinuation of trial treatment and subject discontinuation/withdrawal

Treatment of a subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have the subjects, who discontinue trial product, attend the planned visit schedule until visit 7 to collect the required data for the analysis. Only subjects who withdraw consent will be considered as withdrawn from the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product.

7.1 Discontinuation of trial treatment

A subject who does not fulfil the eligibility criteria (inclusion/exclusion criteria) must not be randomised. Randomisation in violation of any of the eligibility criteria is a Good Clinical Practice (GCP) non-compliance and must be reported to the sponsor without delay. This will be handled as an important protocol deviation, and the independent ethics committee (IEC)/ institutional review board (IRB) and regulatory authorities must be notified according to local requirements. If there are no safety concerns, trial treatment may be continued or resumed at the discretion of the investigator after agreement with the sponsor´s global medical expert.

The trial product must be discontinued, if any of the following applies for the subject:

1. Safety concern related to trial product or unacceptable intolerability
2. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial
3. Tumour development

See the flowchart 1.2 for data to be collected at the time of treatment discontinuation (early discontinuation visit) and follow-up and for any further evaluations that need to be completed.

The purpose of the follow-up visit is to collect information about adverse events. For convenience of the subject the follow up visit can be performed as a telephone contact. The follow up visit should be performed as a site visit for subjects with an ongoing injection site reaction at visit 8.

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the CRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

If a subject discontinues treatment prior to visit 7, Visit 7A should be performed at least 7 days after the last dose of trial product and prior to starting treatment with marketed product. The follow up visit should be performed 30 days after the last dose of trial product.

Although the treatment has been discontinued, the subject will continue to follow the planned visit schedule until visit 7 (52 weeks).

If the subject or family refuse to attend planned visit schedule, then efforts should be made for the subject to attend visit 7 as it is the primary endpoint visit.

After visit 7A the following assessments are not applicable for subjects who discontinue trial product:

- Trial drug administration
- Drug accountability
- PK and Antibody sampling
- Collection of technical complaints
- Injection site reaction
- Medication errors
- PRO's

7.1.1 Temporary discontinuation of trial treatment

Temporary discontinuation of trial treatment is not allowed in the trial.

7.2 Subject discontinuation/withdrawal from the trial

A subject may withdraw consent at any time at his/her own request or at the request of the subject's parent(s)/subject's LAR.

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to visit 7A. See the flowchart for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the site.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

Although a subject is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end-of-trial form in the eCRF.

7.2.1 Replacement of subjects

Subjects who discontinue trial product or withdraw from trial will not be replaced.

7.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a subject fails to return to the site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of `lost to follow-up'.

8 Trial assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart 1.2.

Informed consent must be obtained before any trial related activity, see Section 10.1.3.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening (1a visit), subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.

Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.

Review of diaries, PRO questionnaire, ECG, laboratory reports etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary or PRO questionnaire is needed, the subject must be questioned, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
The maximum amount of blood collected from each subject over the duration of the trial will not exceed 72 ml.

Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart.

8.1.1 Body Measurement

Body measurements will be assessed according to the flowchart 1.2

8.1.1.1 Height

For height measurements, European Medicines Agency (EMA) guideline should be followed.
A manual for height measurement prepared by Novo Nordisk A/S will be provided to the sites.

Standing height should be measured

- by a trained person blinded to treatment allocation (preferably the same person throughout the trial)
- preferably by using the same calibrated stadiometer
- at the same time (± 2 hours, compare to baseline-visit 2)
- without shoes
- with 3 consecutive measurements
- in centimetres with one decimal to the nearest 1 mm with one decimal

Confirmation that height measurements have been performed by a trained person blinded to treatment allocation should be documented.

For pre-trial height measurement guidance please see section 8.2 under GHD history.

8.1.1.2 Body weight

Body weight will be measured in kilos (kg) with one decimal without shoes and wearing only light clothing.
Body weight should be measured preferably at the same time of the day and by using the same scale throughout the trial, if possible.

8.1.1.3 Body Mass Index

Body Mass Index will be calculated by the investigator at the screening visit (Visit 1b) and documented in subject medical record.

8.1.2 Pubertal Status

Pubertal status according to Tanner staging will be assessed[1]. Please refer to protocol flow chart 1.2 for the frequency of the assessment.

8.1.3 GH Stimulation test

Subjects with two additional pituitary deficiencies other than GHD need one GH stimulation test to confirm GHD. All other subjects need two different GH stimulation tests to confirm GHD. As a minimum the first test should have been performed as part of clinical practice and the result must be available prior to screening and fulfil inclusion criterion 3 (see Section 5.1). The second stimulation test can be performed according to local practice in the screening period and before randomisation. The result(s) must be available prior to randomisation in order to evaluate eligibility. The WHO International Somatropin 98/574 standard should be used to evaluate inclusion criterion 3 (see

Section 5.1). If other standards similar to WHO International Somatropin 98/574 standard are used locally, this is acceptable.

8.1.4 X-ray for bone age assessment

X-rays of left hand and wrist for bone age assessment according to the Greulich and Pyle atlas [24] will be taken.

The X-ray images will be sent to a central imaging laboratory for evaluation. An X-ray taken within 13 weeks prior to screening (visit 1a) can be used as screening data if the image is acquired according to the required standards defined by the central imaging laboratory and available to be sent to the central imaging laboratory.

The overall process for imaging is described in a manual prepared by the central imaging laboratory.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart section 1.2

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the subject experienced prior to the time point from which AEs are collected.

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/ Concomitant Illness form.

GHD history

- Type of GH stimulation tests and result of peak GH values
- Standing height measured minimum 3 months and maximum 18 months prior to screening (Visit 1b). Standing height should be reported in centimetres with one decimal to the nearest 1 mm with one decimal. The pre-trial height assessment is collected to be used when evaluating inclusion criterion 5 and for baseline HV derivation. If more than two height measurement measured 3-18 months prior to screening are available the most recent should be used.
- If pre-trial height is not measured, then height must to be measured at visit 1a and the subject will have to wait for 3 months before attending visit 1b to complete screening procedures.

- If pre-trial height is measured but is less than 3 months before screening (visit 1b), then the patient, after signing the informed consent and completing visit 1a, will have to wait to complete 3-month period to attend visit 1b.
- If pre-trial height is measured at least 3 months prior to visit 1a then the subject can attend visit 1b. Note, there has to be at least 1 day between visit 1a and 1b.
- Parental height: Standing height for both biological parents in centimetres with one decimal to the nearest 1 mm with one decimal.

8.2.1 Physical examinations

A physical examination will include assessments of the Cardiovascular, Respiratory, Gastrointestinal, Musculoskeletal, Central and Peripheral Nervous system and Skin systems, head, ears, eyes, nose, throat, neck and lymphnode palpation.
Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

Pulse rate as well as systolic and diastolic blood pressure will be assessed.

8.2.3 Electrocardiograms

12-lead ECG will be obtained as outlined in the flowchart.

The investigator will evaluate the ECG recordings and classify them as either: “normal”, “abnormal, not clinically significant” or “abnormal, clinically significant”.

If the ECG is evaluated as “abnormal, clinically significant” at screening, and judged by the investigator not to be relevant for exclusion of the trial, the finding will be recorded as a concomitant illness.
The ECG results must be dated and signed by the investigator to verify that the data have been reviewed.

8.2.4 MRI and CT scans

An MRI or CT scan of the brain performed according to standard practice at site must be available before randomisation, to confirm eligibility in relation to inclusion criterion 11. A scan or imaging performed within 9 months prior to screening (visit 1b) can be used as screening data if medical evaluation and conclusion is available.
The only information collected in the eCRF is subject eligibility for trial participation.

8.2.5 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual and the protocol flowchart 1.2.

8.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE
The definition of AEs and SAEs can be found in Appendix 3, along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant event(s) are listed below in Table 8

Table 8 AEs requiring additional data collection (serious and non-serious AEs),

Event type	AE requiring additional data collection
Injection site reaction	X
Medication error	X
Misuse and abuse	X

In subjects with severe headache, a fundoscopy should be performed at the investigators discretion.

A detailed description of the events mentioned in the above table can be found in Appendix 3, section 10.3.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the first trial-related activity after obtaining informed consent and until the follow up visit/the end of trial visit at the time points specified in the flowchart 1.2.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix3, section 10.3. All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk or designee within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the trial product or related to trial participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3, section 10.3. Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the subject is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3, section 10.3.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

The patient population included in the trial is pre-pubertal thus this section is not applicable for the trial.

8.3.6 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in section 10.4.

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Treatment of overdose

There is no antidote for overdose of somapacitan or Norditropin®. In the event of an overdose, appropriate supportive treatment should be initiated according to local practice.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 for further details.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities until resolved.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

For more information on overdose, also consult the current version of the somapacitan and Norditropin® investigator's brochure[19].

8.5 Pharmacokinetics

Samples will be used to evaluate the pharmacokinetics of somapacitan and Norditropin®.

All samples must be drawn prior to trial product administration if this is planned on a sampling day. The bioanalysis of somapacitan and Norditropin® PK samples will be performed by a special laboratory.

8.6 Pharmacodynamics

All protocol-required laboratory assessments, as defined in 10.2, must be conducted in accordance with the flowchart and the laboratory manual.
IGF-I and IGFBP-3 will be used to evaluate the pharmacodynamics (PD) of somapacitan and Norditropin®.
All samples must be drawn prior to trial product administration if this is planned on a sampling day.

8.7 Immunogenicity assessments

All anti-drug antibody (ADA) samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day see Appendix 2, section 10.2.

A tiered approach includes screening of samples, confirmation of anti-drug antibodies as well as characterisation of cross-reactivity towards endogenous hGH.

The investigator will not be able to review the results of the antibody measurements in relations to AEs as the results will not be available to the investigator.

All subjects who have had two consecutive positive antibody test results with impact on safety/PK or PD will be offered an appropriate follow-up period until the antibody clinical manifestation has resolved, the subjects at the investigators discretion may be requested to have additional blood samples collected for follow-up analyses.

The results may be reported as an amendment to the clinical trial report (CTR).

8.7.1.1 Anti somapacitan antibodies

Determination of antibodies against somapacitan in subjects randomised to somapacitan will be performed by a special laboratory using a validated binding antibody assay. Confirmed anti-somapacitan antibody positive samples will be further tested for cross-reactivity to hGH.

8.7.1.2 Anti hGH antibodies

Anti-hGH antibodies in subjects randomised to Norditropin® will be analysed by a special laboratory using a validated binding antibody assay.

8.8 Patient reported Outcomes

The following Patient reported outcome questionnaires would be collected in the trial:

- GHD-CIM (Growth Hormone Deficiency – Child Impact Measure)
- GHD-CTB (Growth Hormone Deficiency – Child Treatment Burden)
- GHD-PTB (Growth Hormone Deficiency – Parent Treatment Burden)

Title	Time frame	Unit
Change in GHD-CIM (domain and total scores)	From Baseline (Week 0) to visit 5 (Week 26), Baseline (Week 0) to Week 52	-100 to 100
GHD – CTB (domain and total scores)	At visit 5 (Week 26) At visit 7(Week 52)	0 to 100
GHD – PTB (domain and total scores)	At visit 5 (Week 26) At visit 7(Week 52)	0 to 100

Data from paper PRO's should be transcribed into eCRF. Please refer to protocol flow chart 1.2 for frequency of the assessments. Investigator must review the PRO's and discuss with the subject if there are any discrepancies observed and must document the discussion in the subject medical records.

8.9 Diary

Paper diaries will be used in the trial and diary will be dispensed for the first time at randomisation, Investigator / delegated site staff must train the subject/LAR on diary completion and should instruct the subject to return the diary at the next site visit. Last diary will be dispensed at visit 6 and must be collected at visit 7.

Entries in the diaries are only to be made by the subject/LAR/Parent, unless otherwise specified. Any discrepancy must be discussed with the subject and documented in the subject medical records.

9 Statistical considerations

9.1 Statistical hypotheses

Hypothesis testing for the primary endpoint will be done by testing H0: D≤ -2 cm/year vs HA: D>-2 cm/year, where D is the mean treatment difference (somapacitan – Norditropin®). Non-inferiority of somapacitan will be considered confirmed if the lower boundary of the two-sided 95% confidence interval is above -2 cm/year. As only one confirmatory hypothesis is to be tested, no further control for multiplicity is needed.

9.2 Sample size determination

Approximately 108 subjects will be randomly assigned to trial product.

The sample size calculation is based on the primary estimand. It is expected based on phase 2 trial data (NN8640-4172) that the proportion of subjects with no landmark visit data or who discontinued randomised treatment before landmark visit is 10% with similar withdrawal reasons in the two treatment arms. NN8640-4172 is a global trial, including Japanese subjects, and therefore trial information from 4172 is expected to also be of use when planning for a somapacitan phase 3 trial in China. It is expected that subjects discontinuing their randomised treatment will start on ancillary treatment, if no medical reasons prohibit this. Thus, data assessed after discontinuation of the randomised treatment will not be used for the primary analysis of the primary endpoint based on the primary estimand. Assuming the same proportions of subjects with no landmark visit and subjects discontinuing randomised treatment but have landmark visit data in the two arms leads to the following sample size calculation.

The sample size is determined using a non-inferiority margin of -2.0 cm/year and a one sided two-group t-test with a significance level of 2.5% for a 2:1 randomisation ratio between somapacitan and Norditropin®.

Based on data from NN8640-4172, a standard deviation for HV at week 52 was chosen (SD=2.6 cm/year) for the sample size calculation giving a sample size of 108 subjects. Different SD scenarios with power calculation for the primary analysis are presented in the table below under the assumption of a true difference in annualized HV of 0 cm/year between the two treatment arms.

Table 9 Calculated power with 108 subjects randomised 2:1

SD	2.5 cm/year	2.6 cm/year	2.7 cm/year	2.8 cm/year
	95%	**94%**	**92%**	**90%**

The SD candidates are based on reported SD values from clinical trials: Valtropin phase 3 trial[6], 52 weeks (SD=2.8, 3.0), OPKO phase 2 trial, 52 weeks (SD=2.1, 2.3, 2.6, 3.5), and NN8640-4172, phase 2 trial, 52 weeks (SD=2.3, 2.6).

For sensitivity analysis, a one-way tipping point analysis is planned. Based on a penalty of 2 cm/year for subjects in the somapacitan arm who have missing landmark visit data or discontinue randomised treatment before landmark visit, this gives a power of ~92% (adjusted treatment effect 0.9*0 – 0.1*2 = -0.2).

If the per protocol analysis set (PP) is assumed to consist of ~85% of the trial subjects (same proportion across treatment groups), giving 60 subjects in the somapacitan arm and 30 subjects in the Norditropin® arm, then repeating the primary analysis based on the primary estimand on the PP should result in a power of 92% for confirming non-inferiority of somapacitan compared to Norditropin®, under the assumption of no true treatment difference between the two treatments.

9.3 Populations for analyses

The following population*s* are defined:

Population	Description
Full analysis set	Full analysis set (FAS): All subjects randomised. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. Subjects will be analysed according to the randomised treatment
Safety analysis set	Safety analysis set (SAS): All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received.
Per protocol analysis set	PP: Subjects from FAS who have not violated any inclusion/exclusion criteria and have used the randomised treatment for at least 47 weeks (for subjects receiving somapacitan) or 329 days (for subjects receiving Norditropin) corresponding to 90% of the planned exposure. Subjects are analysed according to the treatment they actually received.

The subjects or observations to be excluded, and the reasons for their exclusion must be documented before unblinding. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CTR. Two observation periods are defined:

- on-treatment: from first administration and up until last trial contact, visit 7 or 14 days after last administration, whichever comes first
- in-trial: from first administration and up until last trial contact or visit 8, whichever comes first

Analysis based on the 'in-trial' observation period is to be viewed as supplemental analysis to the analysis based on the 'on-treatment' analysis.

9.4 Statistical analyses

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol. The SAP will be finalised prior to first subject first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary endpoint.

9.4.1 General considerations

The one-sided test used for the primary endpoint is based on an alpha level of 2.5%. All other statistical tests conducted will be two-sided on the 5% significance level.

Two factors are defined as follows:

- Age group: Age at randomisation (<6 versus ≥6 years)
- GH peak group: Growth hormone peak level (< 7 versus ≥ 7 ng/ml)

All efficacy endpoints will be analysed using FAS and all safety endpoints will be analysed using SAS. The primary endpoint will additionally be analysed using PP as a support to the results achieved using FAS under the hypothetical strategy.

9.4.2 Primary endpoint*(s)*

The primary endpoint:

- Height velocity (cm/year) at week 52

will be derived from height measurements taken at baseline and the week 52 visit (landmark visit) in the following way:

HV = (height at 52 weeks visit - height at baseline)/(time from baseline to 52 weeks visit in years).

Annualized HV at the intermediate visits: Week 13, 26 and 39, will be derived analogously to the week 52 HV: HV = (height at j weeks visit - height at baseline)/(time from baseline to j weeks visit in years), j=13, 26, 39.

The primary analysis of the primary endpoint addressing the primary estimand described in section 3.1 is based on the FAS but data assessed after discontinuation of randomised treatment will be disregarded in the analysis.

In order to estimate the primary estimand, a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix is conducted on HV data (annualized HV at planned visits at week 13 ,week 26, week 39 and week 52) up to discontinuation of randomised treatment for each treatment arm using all randomised subjects and assuming missing at random (MAR) for both treatment arms. The MMRM will include sex, age group, GH peak group and sex by age group interaction term as factors and baseline height as a covariate, all nested within week as a factor. From this analysis an estimate of the treatment difference at week 52 with corresponding 95% CI will be presented.

Non-inferiority of somapacitan will be considered confirmed if the lower boundary of the two-sided 95% confidence interval is above -2 cm/year.

A tipping point analysis will be conducted as a sensitivity analysis for the analysis of the primary endpoint for the primary estimand. For this analysis, the missing data are expected to be mainly due to subjects that are withdrawn from the trial or discontinue randomised treatment. The sensitivity analyses described below will be used to investigate whether the results from the primary analysis are robust against departures from the assumption of MAR.

Let δ be defined as the difference between the mean of the observed data and the mean of the unobserved data μ_{obs}-μ_{unobs}, adjusted for other observed data. Under an MAR analysis, δ is assumed to be 0. Positive values of δ indicate that subjects with missing endpoint values have smaller HV than subjects with observed endpoint values. If subjects primarily withdraw or discontinue randomised treatment/start ancillary therapy due to a perceived lack of efficacy, then this could be the most likely direction of departure from MAR. Let f_1 and f_0 be the fractions of subjects with unobserved endpoint data in the somapacitan and Norditropin® arms, respectively. The sensitivity analysis is done by subtracting a quantity Δ from the treatment effect estimate under the MAR assumption, where $\Delta = f_1\delta$ if data depart from MAR in the somapacitan arm only, $\Delta = -f_0\delta$ if data depart from MAR in the Norditropin® arm only, and $\Delta = (f_1-f_0)\delta$ if data depart from MAR in the same way in both arms. The calculations for the 3 scenarios will use a range of δ values increasing from 0 until the resulting 95% CI no longer is completely above -2cm/year for the most conservative evaluation (data depart from MAR in the somapacitan arm only) and the approximation that the standard error of the treatment difference is unaffected by the sensitivity analysis[25]. All subjects from the FAS can be viewed as included in this analysis as subjects with missing endpoint data will be contributing to one of the fraction values f_1 and f_0.

An analysis of the primary endpoint using the same analysis model as was used for the primary analysis under the primary estimand but based on PP instead of FAS will be conducted as a supplementary analysis.

9.4.3 Secondary endpoint(s)

9.4.3.1 Confirmatory secondary endpoint(s)

NA

9.4.3.2 Supportive secondary endpoints

Table 10 Efficacy

Endpoint title	Time frame	Unit
Change in bone age	From visit 1 to week 52	Years
Change in Height Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
Change in Height Velocity Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10

The efficacy endpoints will be analysed based on the 'on-treatment' observation period and the 'in-trial' observation period within the trial period (52 weeks of treatment).

Height SDS will be derived using Chinese general population standards and HV SDS will be derived using Prader standards[26] as reference data.

Change in height SDS and HV SDS will be analysed using the same analysis model as was used for analysing the primary endpoint for the primary estimand except for using baseline height SDS and baseline HV SDS, respectively, as a covariate in the model instead of baseline height. The estimate for the treatment difference at week 52 will be reported with corresponding 95% CI and p-value.

Bone age will be analysed using an ANCOVA model on bone age/chronological age assessed at week 52 and the model will include treatment, sex, age group, GH peak group and sex by age group interaction term as factors and baseline bone age/chronological age as a covariate. The treatment difference estimate will be reported with corresponding 95% CI and p-value.

Table 11 Safety

Endpoint title	Time frame	Unit
Change in fasting plasma glucose	From baseline (week 0) to week 52	mmol/l
Change in $HbA1_c$	From baseline (week 0) to week 52	%

The safety endpoints will be analysed using descriptive statistics based on the 'on –treatment' observation period and the 'in-trial' observation period.

Table 12 Pharmacodynamics

Endpoint title	Time frame	Unit
Change in IGF-I Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
Change in IGFBP-3 Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10

The PD endpoints will be analysed based on the 'on –treatment' observation period and the 'in-trial' observation period.

Change in IGF-I SDS and IGFBP-3 SDS will be analysed using an MMRM with an unstructured covariance matrix on all relevant post-baseline change from baseline values as dependant variables. The model will include treatment, sex, age group, region, GH peak group and sex by age group interaction term as factors and baseline value as a covariate, all nested within week as a factor. From the MMRM, the treatment difference at Week 52 will be estimated and the corresponding 95% CI and p-value will be reported for each endpoint.

9.4.4 Other safety analyse*(s)*

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be analysed using descriptive statistics based on the 'on –treatment' observation period. Additionally, AEs will also be analysed using descriptive statistics based on the 'in-trial' observation period.

9.4.5 Other analyse(s)

PRO analysis

The PRO data will be analysed based on the 'on –treatment' observation period.

GHD – CTB scores and GHD – PTB scores will be analysed using an MMRM with an unstructured covariance matrix on all relevant post-baseline values as dependant variables. The model will include treatment, sex, age group, GH peak group and sex by age group interaction term as factors, all nested within week as a factor. From the MMRM, the treatment differences will be estimated and the corresponding 95% CI and p-values will be reported for week 26 and week 52, respectively.

Changes from baseline to week 26 and week 52 in GHD-CIM scores will be analysed using an MMRM with an unstructured covariance matrix. The model will include treatment, sex, age group, GH peak group and sex by age group interaction term as factors and baseline value as a covariate, all nested within week as a factor. From the MMRM, the treatment differences will be estimated and the corresponding 95% CI and p-values will be reported for week 26 and week 52, respectively.

In addition, the following questions of the physical domain of the GHD-CTB PRO will be analysed using Wilcoxon rank sum tests:

- In the past week, how much did your child's injections hurt
- In the past week, how much did your child's injections sting
- In the past week, how much bruising did your child have from their injections
- In the past week, how much soreness did your child have at their injection site

9.4.6 Pharmacokinetic and/or pharmacodynamic modelling

Somapacitan and IGF-I serum concentration data may be used for population PK, population PK/PD and exposure-response modelling, potentially as a joint analysis of data from multiple trials. Other exploratory PK/PD and exposure-response analyses for this trial may be performed if deemed relevant. If conducted, a more technical and detailed elaboration of the population PK, population PK/PD and exposure-response analyses will be given in a prospective modelling analysis plan.

9.5 Interim analyses

Not applicable for the trial.

9.6 Data monitoring committee

Not applicable for the trial.

9.7 Reporting of the trial

The database lock is planned shortly after last subject last visit. The results will thereafter be reported.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[8] and applicable ICH GCP Guideline[27]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.

- Any amendments to the protocol will require local health authority and IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
  - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - providing oversight of the conduct of the trial at the site and adherence to requirements of International Council for Harmonisation (ICH) guidelines, the IRB/IEC, and all other applicable local regulations
  - ensuring submission of the CTR synopsis to the IRB/IEC
  - reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.

10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and/or the subject's parent(s)/subject's LAR and answer all questions regarding the trial. This includes the use of an impartial witness where required according to local requirements.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects or their parent(s)/LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[27], Declaration of Helsinki[8] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.

- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects and/or their parent(s)/LAR must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject or the subject's parent(s)/subject´s LAR.
- During the trial, the investigator should reassess the assent of a child in recognition of their advancing age, evolving maturity and competency.

10.1.4 Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a "thank you for your participation letter" after completion of the trial. Further, the subject may receive other written information during the trial.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed about his/her privacy rights, including that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at chinadrugtrials.org.cn, clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[28], the Food and Drug Administration Amendment Act (FDAAA)[29], European Commission Requirements[30-32] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last subject first treatment (LSFT) + 52 weeks corresponding to visit 7. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 7 The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the CRF is temporarily unavailable:
  - Safety information forms
  - Technical complaint forms
  - AE forms
- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and

reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

- The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the subject's medical records and other source data, e.g. the diaries and PROs, to ensure consistency and/or identify omissions compared to the CRF.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the CRF or via listings from the trial database.

10.1.9 Source documents

- All data entered in the eCRF/ paper CRF must be verifiable in source documentation other than the CRF,
- If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the trial staff making the entry.
- All data entered in the eCRF must be verifiable in source documentation other than the CRF.
- The original of the completed diaries and/or PROs must not be removed from the site, unless they form part of the CRF and a copy is kept at the site
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents, such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must

inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon trial completion. A site is considered closed when all required documents and trial supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of subjects by the investigator
- discontinuation of further trial product development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

10.1.14 Publication policy

The information obtained during the conduct of this trial is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.

The information obtained during this trial may be made available to other investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted CTR for this trial.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[33]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 Site-specific publication(s) by investigator(s)

For a multicentre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

10.1.14.4 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 13 and Table 14 will be performed by the central and special laboratories.

The use of topical anaesthetics (e.g. numbing cream) for blood sampling should be according to local practice.

At visits where it is not possible to perform blood sampling on the actual visit day (e.g. if the child does not cooperate during blood sampling) the samples can be taken within a week from the actual visit. The sample conditions (fasting or non-fasting) and timing of sampling in relation to study drug administration should always be followed.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

The central lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.

The investigator must review all laboratory results for concomitant illnesses and AEs.

Laboratory samples will be destroyed no later than at finalisation of the CTR.

The antibody samples will be stored at a central laboratory after end of trial and until marketing authorisation approval or until the research project terminates, after which they will be destroyed.

Blood sampling volume

The investigator should follow local guidelines or the European guideline if applicable for blood sampling and volume of blood at each visit in relation to the subject's body weight and age.

For subjects with a lower body weight
At visits where blood sampling requiring a higher blood volume than allowed, the blood sampling can be split into two different occasions with maximum one week apart. The sampling conditions (fasting or non-fasting) and timing of sampling in relation to study drug administration should always be followed.

Blood sampling can be prioritised as described in the laboratory manual.

Table 13 Protocol-required efficacy laboratory assessments

Laboratory assessments	**Parameters**
PD	IGF-I IGFBP-3
PK	Somapacitan Norditropin®
NOTES: IGF-I and IGFBP-3 will be blinded to site staff during the trial. At visit 1a IGF-I SDS will be reported to sites in order to evaluate eligibility. Novo Nordisk will monitor IGF-I throughout the trial. PK will not be reported to the sites.	

Table 14 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	Haematocrit Haemoglobin Leucocytes Thrombocytes
Biochemistry	Alanine Aminotransferase (ALT) Alkaline phosphatase (AP) Bilirubin Aspartate Aminotransferase (AST) Creatine Kinase Creatinine Potassium Sodium
Glucose metabolism	Fasting insulin Fasting plasma glucose HbA_{1c} Homeostatic model assessment (HOMA) will be calculated
Lipids	Total Cholesterol High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Triglycerides
Hormones	Cortisol serum Serum free T3 Serum free T4 Thyroid stimulating hormone (TSH)
Antibodies	Anti somapacitan antibodies Anti hGH antibodies

Timing of visits and blood sampling

At the randomisation visit (Visit 2) blood samples should be collected prior to first trial product administration. In order to ensure correct timing of PK and antibody sampling in relation to trial product administration, the visits after randomisation should be scheduled within the allowed visit window according to the flowchart 1.2 and Table 15. Blood sample should always be collected prior to trial product administration (irrespective of if patients are randomised to somapacitan or Norditropin®) if the visit is planned on a dosing day.

For subjects randomised to somapacitan:

Table 15 Timing of visits and blood sampling

Visit	Timing of visit
3	1 to 4 days after dosing
4	On a planned dosing day
5	1 to 4 days after dosing
6	On a planned dosing day
7	4 to 6 days after dosing
8	No blood sampling

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

For trials with investigational medical device(s), please refer to Appendix 7.

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

An AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected • Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected • Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent A "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE. Also, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
• Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP. • Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history. • Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE. • Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE. Note: ◦ Hospitalisations for administrative, trial related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. ◦ Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical event: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion. • The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable: ◦ Suspicion of transmission of infectious agents via the IMP

- Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

Description of AEs requiring additional data collection (on specific event form)

Adverse events requiring additional data collection

Injection site reactions:

An injection site reaction is defined as: An injection site reaction considered clinically significant by the investigator.

An injection site reaction form should be filled in, in addition to the AE form (and safety information form (SIF) for SAE).

Medication error

A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the subject, such as:

- administration of wrong drug
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g. overdose to maximize effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycemia or other), this must be reported on an additional AE form.

10.3.4 Recording and follow-up of AE and/or SAE

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms, refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess severity for each event reported during the trial and assign it to one of the following 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.
  Note: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
- Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  - Probable - Good reason and sufficient documentation to assume a causal relationship.
  - Possible - A causal relationship is conceivable and cannot be dismissed.
  - Unlikely - The event is most likely related to aetiology other than the IMP.

- Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator should use the investigator's brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**
- The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.
  Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

SAE reporting via electronic CRF
• Relevant forms (AE and safety information form) must be completed in the CRF. • For reporting and sign-off timelines, see Figure 3 below. • If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available. • After the trial is completed, the trial database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF

• Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.
• For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting timelines (as illustrated in the figure below):
  • AE form within 24 hours
  • Safety information form within 5 calendar days
  • Both forms must be signed within 7 calendar days after first knowledge by the investigator.
• The specific event form for AEs requiring additional data collection within 14 calendar days

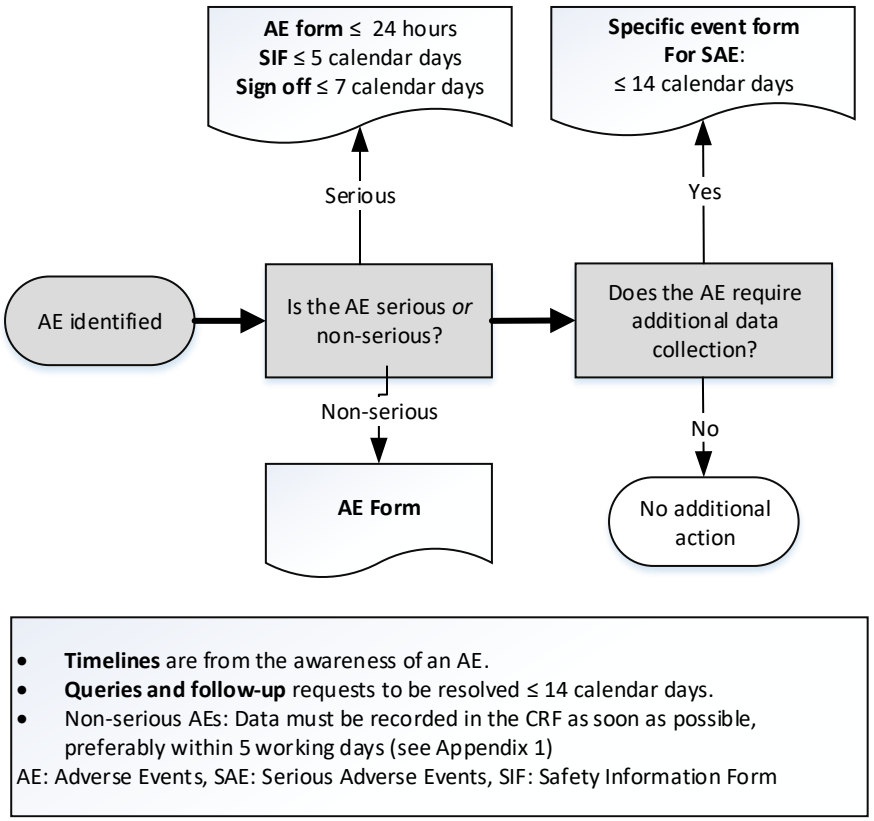


Figure 3 Decision tree for determining the event type and the respective forms to complete with associated timelines

Contact details for SAE reporting can be found in the investigator trial master file.

10.4 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.4.1 Definition of technical complaint

Technical complaint definition
• A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle)

Time period for detecting technical complaints
All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.4.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk
Contact details (fax, e-mail and address) for Customer Complaint Center – refer to Attachment I Technical complaints must be reported on a separate technical complaint form: • One technical complaint form must be completed for each affected DUN • If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within: • 24 hours if related to an SAE (or could have led to an SAE) • 5 days calendar for all other technical complaints If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject , the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

10.4.3 Reporting of technical complaints

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

10.5 Appendix 12: Country-specific requirements

item	Section	Section title	Local requirement
1	5.1 and 5.2	Inclusion/Exclusion criteria	The criteria will be assessed at the investigator's discretion unless otherwise stated.
2	10.1	Appendix 1: Regulatory, ethical, and trial oversight considerations	Any trial procedure conducted in China mainland should comply with "Regulations on management of Human Genetic Resources of People's Republic of China" and relative guideline. http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm
3	10.1.10	Retention of clinical trial documentation	Site specific data should only be stored at site. Long term storage of Chinese Patients' Trial Data is not allowed in other entities.
4	10.5	Appendix 12: Country-specific requirements	The samples which are tested at sites will be destroyed as biological waste according to local regulation, if applicable. The samples which are tested at central lab will be destroyed as biological waste according to local regulation and lab manual. The laboratory samples for Chinese subjects will be destroyed no later than the finalization of the clinical trial report, or according to local regulatory requirement. The antibody samples will be stored at a central laboratory after end of trial and until marketing authorization approval or until the research project terminates, after which they will be destroyed

Note: The following appendices are not applicable for the trial and have been removed.

Appendix4 Contraceptive guidance and collection of pregnancy information, Appendix 6 Genetics, Appendix 7 Medical device adverse events, adverse device effects, serious adverse events and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting, Appendix 8 Retention of human bio-samples, Appendix 9 Hypoglycaemic episodes, Appendix 10 Hyperglycaemic episodes, Appendix11 Titration guidelines

10.6 Appendix 13: Abbreviations

ADHD	attention deficit hyperactivity disorder
AE	adverse event
AESI	adverse event of special interest
CRF	case report form
CT	computerised tomography
CTR	clinical trial report
DFU	directions for use
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDAAA	the Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
$HbA1_c$	glycated haemoglobin
hGH	human growth hormone
HV	height velocity
IB	Investigator Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IGF-I	insulin-like growth factor I
IGF BP-3	insulin-like growth factor binding protein 3
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
LAR	legally acceptable representative
MAR	missing at random

MMRM	mixed model for repeated measurements
MRI	magnetic resonance imaging
PCD	primary completion date
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol analysis set
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c	subcutaneous
SDS	standard deviation score
SGA	small for gestational age
SMPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TMM	trial materials manual

10.7 Appendix 14: Dose tables for Norditropin® and somapacitan

Norditropin® FlexPro®:

0.034 mg/kg Norditropin® FlexPro® 10 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
5.0-5.1	0.15
5.2-6.6	0.20
6.7-8.0	0.25
8.1-9.5	0.30
9.6-11.0	0.35
11.1-12.4	0.40
12.5-13.9	0.45
14.0-15.4	0.50
15.5-16.9	0.55
17.0-18.3	0.60
18.4-19.8	0.65
19.9-21.3	0.70
21.4-22.7	0.75
22.8-24.2	0.80
24.3-25.7	0.85
25.8-27.2	0.90
27.3-28.6	0.95
28.7-30.1	1.00
30.2-31.6	1.05
31.7-33.0	1.10
33.1-34.5	1.15
34.6-36.0	1.20
36.1-37.4	1.25
37.5-38.9	1.30
39.0-40.4	1.35
40.5-41.9	1.40
42.0-43.3	1.45
43.4-44.8	1.50
44.9-46.3	1.55

0.034 mg/kg Norditropin® FlexPro® 10 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
46.4-47.7	1.60
47.8-49.2	1.65
49.3-50.7	1.70
50.8-52.2	1.75
52.3-53.6	1.80
53.7-55.1	1.85
55.2-56.6	1.90
56.7-58.0	1.95
58.1-59.5	2.00
59.6-61.0	2.05
61.1-62.4	2.10
62.5-63.9	2.15
64.0-65.4	2.20
65.5-66.9	2.25
67.0-68.3	2.30
68.4-69.8	2.35
69.9-70.0	2.40

Somapacitan:

0.16 mg/kg Somapacitan 5 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
5.0-5.1	0.80
5.2-5.4	0.85
5.5-5.7	0.90
5.8-6.0	0.95
6.1-6.4	1.00
6.5-6.7	1.05
6.8-7.0	1.10
7.1-7.3	1.15
7.4-7.6	1.20
7.7-7.9	1.25
8.0-8.2	1.30
8.3-8.5	1.35
8.6-8.9	1.40
9.0-9.2	1.45
9.3-9.5	1.50
9.6-9.8	1.55
9.9-10.1	1.60
10.2-10.4	1.65
10.5-10.7	1.70
10.8-11.0	1.75
11.1-11.4	1.80
11.5-11.7	1.85
11.8-12.0	1.90
12.1-12.3	1.95
12.4-12.5	2.00

0.16 mg/kg Somapacitan 10 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
10.5-10.7	1.70
10.8-11.0	1.75
11.1-11.4	1.80
11.5-11.7	1.85
11.8-12.0	1.90
12.1-12.3	1.95
12.4-12.6	2.00
12.7-12.9	2.05
13.0-13.2	2.10
13.3-13.5	2.15
13.6-13.9	2.20
14.0-14.2	2.25
14.3-14.5	2.30
14.6-14.8	2.35
14.9-15.1	2.40
15.2-15.4	2.45
15.5-15.7	2.50
15.8-16.0	2.55
16.1-16.4	2.60
16.5-16.7	2.65
16.8-17.0	2.70
17.1-17.3	2.75
17.4-17.6	2.80
17.7-17.9	2.85
18.0-18.2	2.90
18.3-18.5	2.95
18.6-18.9	3.00
19.0-19.2	3.05
19.3-19.5	3.10
19.6-19.8	3.15
19.9-20.1	3.20
20.2-20.4	3.25
20.5-20.7	3.30
20.8-21.0	3.35

0.16 mg/kg Somapacitan 10 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
21.1-21.4	3.40
21.5-21.7	3.45
21.8-22.0	3.50
22.1-22.3	3.55
22.4-22.6	3.60
22.7-22.9	3.65
23.0-23.2	3.70
23.3-23.5	3.75
23.6-23.9	3.80
24.0-24.2	3.85
24.3-24.5	3.90
24.6-24.8	3.95
24.9-25.0	4.00

0.16 mg/kg Somapacitan 15 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
16.0-16.5	2.6
16.6-17.1	2.7
17.2-17.8	2.8
17.9-18.4	2.9
18.5-19.0	3.0
19.1-19.6	3.1
19.7-20.3	3.2
20.4-20.9	3.3
21.0-21.5	3.4
21.6-22.1	3.5
22.2-22.8	3.6
22.9-23.4	3.7
23.5-24.0	3.8
24.1-24.6	3.9
24.7-25.3	4.0
25.4-25.9	4.1
26.0-26.5	4.2
26.6-27.1	4.3
27.2-27.8	4.4
27.9-28.4	4.5
28.5-29.0	4.6
29.1-29.6	4.7
29.7-30.3	4.8
30.4-30.9	4.9
31.0-31.5	5.0
31.6-32.1	5.1
32.2-32.8	5.2
32.9-33.4	5.3
33.5-34.0	5.4
34.1-34.6	5.5
34.7-35.3	5.6
35.4-35.9	5.7
36.0-36.5	5.8
36.6-37.1	5.9

0.16 mg/kg Somapacitan 15 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
37.2-37.8	6.0
37.9-38.4	6.1
38.5-39.0	6.2
39.1-39.6	6.3
39.7-40.3	6.4
40.4-40.9	6.5
41.0-41.5	6.6
41.6-42.1	6.7
42.2-42.8	6.8
42.9-43.4	6.9
43.5-44.0	7.0
44.1-44.6	7.1
44.7-45.3	7.2
45.4-45.9	7.3
46.0-46.5	7.4
46.6-47.1	7.5
47.2-47.8	7.6
47.9-48.4	7.7
48.5-49.0	7.8
49.1-49.6	7.9
49.7-50.3	8.0
Split dose	Split dose
50.4-50.9	8.1
51.0-51.5	8.2
51.6-52.1	8.3
52.2-52.8	8.4
52.9-53.4	8.5
53.5-54.0	8.6
54.1-54.6	8.7
54.7-55.3	8.8
55.4-55.9	8.9
56.0-56.5	9.0
56.6-57.1	9.1
57.2-57.8	9.2

0.16 mg/kg Somapacitan 15 mg/1.5 ml	
Weight interval (kg)	**Dose (mg)**
57.9-58.4	9.3
58.5-59.0	9.4
59.1-59.6	9.5
59.7-60.3	9.6
60.4-60.9	9.7
61.0-61.5	9.8
61.6-62.1	9.9
62.2-62.8	10.0
62.9-63.4	10.1
63.5-64.0	10.2
64.1-64.6	10.3
64.7-65.3	10.4
65.4-65.9	10.5
66.0-66.5	10.6
66.6-67.1	10.7
67.2-67.8	10.8
67.9-68.4	10.9
68.5-69.0	11.0
69.1-69.6	11.1
69.7-70.0	11.2

10.8 Appendix 15: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version X, including version(s) Y and Z: (date), global/country

Overall rationale for preparing protocol version X

Section # and name	Description of change	Brief rationale

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