Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03878446
Sponsor trial ID:	NN8640-4245
Official title of study:	A dose-finding trial evaluating the effect and safety of once-weekly treatment of somapacitan compared to daily Norditropin® in children with short stature born small for gestational age with no catch-up growth by 2 years of age or older
Document date*:	12 June 2020

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header from Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
includes redaction of company confidential information.

Protocol

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

Substance: somapacitan

Universal Trial Number: U1111-1207-9741

EUdraCT Number: **2018-000232-10**

Trial phase: 2

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in countries
Protocol version 7.0	12-Jun-2020	Denmark
Protocol version 6.0	06-Apr-2020	Israel, Italy, Spain
Protocol version 5.0	09-Mar-2020	India
Protocol version 4.0	12-Dec-2019	All
Protocol version 3.0	17-Jul-2019	All
Protocol version 2.0	04-Jan-2019	All
Original protocol version 1.0	29-Jun-2018	All

Protocol version 7.0 (12-Jun-2020)

CCI [redacted]

Section # and name	Description of change	Brief rationale
Appendix 5 Contraceptive guidance and collection of pregnancy information	Reference to Appendix 9 for country-specific requirements added for Denmark.	CCI [redacted]
Appendix 9 Country specific requirements	CCI [redacted]	CCI [redacted]

Table of Contents

1 Synopsis

Rationale

The purpose of this phase 2 dose-finding trial is to evaluate effect, safety and tolerability of once-weekly subcutaneous treatment of somapacitan compared to daily subcutaneous growth hormone (Norditropin®) treatment in children with short stature born small for gestational age with no catch-up growth by 2 years of age or older. CCI [redacted].

The trial is a dose-finding, randomised, multinational, multi-centre, open-labelled active-controlled, parallel group design with a once weekly somapacitan dose regimen. Dosing somapacitan once weekly can potentially provide greater convenience, and thus potentially better adherence, compared to standard growth hormone treatment which must be administered daily. Treatment with growth hormone of children with short stature born small for gestational age with no catch-up growth by 2 years of age or older aims to induce growth, increase height velocity and improve final height.

Objectives and endpoints

Primary objective

To evaluate the effect of somapacitan versus Norditropin® on longitudinal growth in children with short stature born small for gestational age with no catch-up growth by 2 years of age or older.

Primary endpoint

Endpoint title	Time frame	Unit
Height velocity	From baseline (week 0) to visit 6 (week 26)	cm/year

Secondary objective

To evaluate the effect and safety of somapacitan versus Norditropin® in children born small for gestational age with no catch-up growth by 2 years or older.

Key secondary endpoints

Effect

Endpoint title	Time frame	Unit
Change in bone age	From baseline (week 0) to visit 8 (week 52)	Years
Change in height Standard Deviation Score	From baseline (week 0) to visit 6 (week 26)	-10 to +10
Change in Height velocity Standard Deviation Score	From baseline (week 0) to visit 6 (week 26)	-10 to +10

Safety

Endpoint title	Time frame	Unit
Change in fasting plasma glucose	From screening (visit 1) to visit 6 (week 26)	mmol/l
Change in homeostatic model assessment	From screening (visit 1) to visit 6 (week 26)	%
Change in Glycated haemoglobin (HbA1c)	From screening (visit 1) to visit 6 (week 26)	% point

Pharmacodynamics

Endpoint title	Time frame	Unit
Change in Insulin-like growth factor I (IGF-I) SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10
Change in Insulin-like growth factor binding protein 3 (IGFBP-3) SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10

Primary estimand

Not applicable

Overall design:

A dose-finding, randomised, multinational, multicentre, open-label, 5 arm design, active controlled, parallel group trial designed to evaluate effect and safety of once-weekly somapacitan treatment compared to daily GH treatment (Norditropin®) in growth hormone treatment naïve pre-pubertal children with short stature born small for gestational age with no catch-up growth by 2 years of age or older.

The trial will consist of a 26 week main period, a 26 week extension period (extension I), a 208 week additional extension period (extension II) and a 30 day follow up period. In the main period and extension I period, the trial is designed as a 5 arm parallel group trial with 3 dose levels of once-weekly somapacitan treatment and 2 active control arms of once daily Norditropin®. Subjects will be randomised 1:1:1:1:1 into the 3 doses of somapacitan (0.16, 0.20 or 0.24 mg/kg/week) or into one of the 2 doses of Norditropin® (CCI or CCI mg/kg/day).

In the extension II period, all subjects will receive somapacitan once weekly. The dose will be within the tested range of 0.16-0.24 mg/kg/week and will be decided upon once all subjects have completed the main trial period and the data has been analysed and evaluated by Novo Nordisk.

If a subject enters the extension II period before the main phase results are available, the subject will start the extension II period on their initially allocated treatment.

This switch to somapacitan will occur at visit 8 or later once the dose for the extension II period has been decided. Thus, depending on when a subject is enrolled into the trial, the timing of this switch will vary from subject to subject.

The randomisation will be stratified by region (Japan versus rest-of-the-world). The randomisation will additionally be stratified by age (< 6 versus ≥ 6 years) and by gender (boys versus girls) within the rest of the world to ensure equal distribution of these factor levels across treatments.

Key Inclusion criteria

- Pre-pubertal children:
  a) Boys:
     - Age ≥ 2 years and 26 weeks and < 11.0 years at screening.
     - Testes volume < 4 ml.
     -
  b) Girls:
     - Age ≥ 2 years and 26 weeks and < 10.0 years at screening.
     - Tanner stage 1 for breast development (no palpable glandular breast tissue).
- Born small for gestational age (birth length and/or weight < -2 standard deviation scores) (according to national standards).
- Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and gender at screening according to the standards of Centers for Disease Control and Prevention at screening.
- Impaired height velocity defined as annualised height velocity below the 50th percentile for chronological age and gender according to the standards of Prader calculated over a time span of minimum 6 months and maximum 18 months prior to screening.
- No prior exposure to growth hormone therapy or Insulin-like Growth Factor-I (IGF-I) treatment.

Key exclusion criteria

- Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements.
- Children with hormonal deficiencies including suspected or confirmed growth hormone deficiency according to local practise.
- Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.
- Children requiring inhaled glucocorticoid therapy at a dose of greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks within the last 12 months prior to screening.
- 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.
- Diagnosis of attention deficit hyperactivity disorder.
- Prior history or presence of malignancy including intracranial tumours.

Number of subjects:
Approximately 60 subjects will be randomly assigned to trial product.

Treatment groups and duration:
Duration of treatment will be up to 260 weeks (up to 5 years). The follow-up period is a minimum of 30 days.
The following trial products will be supplied by Novo Nordisk A/S:

- somapacitan 5 mg/1.5 ml in prefilled CCI pen-injector
- somapacitan 10 mg/1.5 ml in prefilled CCI pen-injector
- somapacitan 15 mg/1.5 ml in prefilled CCI pen-injector
- Norditropin® FlexPro® 10 mg/1.5 ml pen-injector

The trial products will be administered subcutaneously.

2 Flowchart

Table 1 Flowchart for main and extension I period

	Protocol section	Information	Screening	Randomisation	Treatment[b]					
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6[a]	Visit 7	Visit 8
CCI										
SUBJECT RELATED INFORMATION AND ASSESSMENTS										
Informed consent	6.1	X								
Child assent	6.1	X								
CCI										
Inclusion/Exclusion criteria	6.1 6.2		X	X						
Discontinuation/Withdrawal criteria	8.1 8.2				X	X	X	X	X	X
Medical history	9.4		X							
Concomitant illness	9.4		X							
Concomitant medication	7.7		X	X	X	X	X	X	X	X
Demography[c]	2		X							
Randomisation	7.3			X						
Pubertal Status	9.1.2		X	X			X	X		X
Date of menarche[b]	9.1.2				(X)	(X)	(X)	(X)	(X)	(X)
Pregnancy test[b]	Appendix 5 Appendix 2				(X)	(X)	(X)	(X)	(X)	(X)
EFFICACY										
X-Ray for bone age assessment	9.1.3			X						X
Body measurements	9.1.1		X	X	X		X	X	X	X
Height	9.1.1		X	X			X	X	X	X
Body Weight	9.1.1		X	X	X		X	X	X	X
Body composition	9.1.1		X					X		X
Pharmacodynamics	9.6									
IGFBP-3	9.6			X	X	X	X	X	X	X
IGF-I	9.6			X	X	X	X	X	X	X
PK	9.5			X	X	X	X	X	X	X
Patient reported outcome questionnaire[f]	9.1.4									(X)
SAFETY										

	Protocol section	Information	Screening	Randomisation	Treatment[b]					
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6[a]	Visit 7	Visit 8
CCI										
Physical examination	9 4 1		X		X		X	X		X
Vital signs	9 4 2		X		X		X	X		X
ECG	9 4 3		X							X
Haematology	Appendix 2		X				X	X		X
Biochemistry	Appendix 2		X		X	X	X	X	X	
Glucose metabolism	Appendix 2		X		X[e]		X	X		X
Lipids	Appendix 2			X			X	X	X	
Hormones	Appendix 2		X						X	
Antibodies	9 4 5 Appendix 2			X	X					X
Adverse event	9 2 1 Appendix 4		X	X	X	X	X	X	X	X
Injection site reaction	9 2 1 Appendix 4			X	X	X	X	X	X	X
Technical complaint	9 2 9			X	X	X	X	X	X	X
Medication errors	9 2				X	X	X	X	X	X
TRIAL MATERIAL										
Drug accountability	7 5			X	X		X	X	X	X
Dispensing of trial product	7 3			X	X		X	X	X	X
IWRS session	7 3		X	X	X		X	X	X	X
REMINDERS										
CCI										
Attend visit fasting	6 3 1		X		X		X	X		X
Handout ID card			X							
Training in trial product and pen handling	7 1 1			X	X			X		X[g]
Hand out directions for use	7 1			X						X[g]
Handout and instruct in e-diary	7 2 2			X						
Diary review	7 6				X	X	X	X	X	X
Return e-diary										
End of treatment	8 1 8 2									
End of trial	8 1 8 2									

[a]Landmark visit (collection of primary endpoint data)

[b]If applicable, section 9.1.2and Appendix 5

[c]Demography consists of date of birth, sex, ethnicity and race (according to local regulation for Spain please refer to Appendix 9)

CCI [redacted]

[e]HbA_{1C} not collected at V3

[f]Only applicable for subjects switching from Norditropin® to somapacitan. To be handed out at the visit where subject is switched to somapacitan. Site staff to inform parent/LAR to complete GH-PPQ at 4 weeks after switching

[g]Applicable for subjects switching from Norditropin® to somapacitan from visit 8. Can be repeated if deemed necessary by the investigator

[h]If a subject discontinues treatment prior to visit 8, see section 8.1

Table 2 Flowchart for extension II period

	Protocol section	Treatment															End of treatment	Discontinuation of trial product	Follow-up
		Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 24A	Visit 25[e]
CCI																			
SUBJECT RELATED INFORMATION AND ASSESSMENTS																			
Discontinuation/Withdrawal criteria	8.1, 8.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	7.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pubertal Status	9.1.2		X		X		X		X		X		X		X		X	X	
Date of menarche[a]	9.1.2	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Pregnancy test[a]	Appendix 5 Appendix 2	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
EFFICACY																			
X-Ray for bone age assessment	9.1.3				X				X				X				X	X[c]	
Body measurements	9.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	9.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Weight	9.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body composition	9.1.1				X				X				X				X	X[c]	
Pharmacodynamics	9.6																		
IGFBP-3	9.6		X		X		X		X		X		X		X		X	X	
IGF-I	9.6		X		X		X		X		X		X		X		X	X	

	Protocol section	Treatment															End of treatment	Discontinuation of trial product	Follow-up
		Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 24A	Visit 25[e]
CCI																			
PK	9 5		X		X		X		X		X		X		X		X	X	
Patient reported outcome questionnaire[b]	9 1 4	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			
SAFETY																			
Physical examination	9 4 1		X		X		X		X		X		X		X		X	X	
Vital signs	9 4 2		X		X		X		X		X		X		X		X	X	
ECG	9 4 3				X				X				X				X	X[c]	
Haematology	Appendix 2		X		X		X		X		X		X		X		X	X	
Biochemistry	Appendix 2		X		X		X		X		X		X		X		X	X	
Glucose metabolism	Appendix 2		X		X		X		X		X		X		X		X	X	
Lipids	Appendix 2				X				X				X				X	X	
Hormones	Appendix 2				X				X				X				X	X	
Antibodies	9 4 5 Appendix 2	(X)[d]	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	(X)[d]	X	(X)[d]	(X)[d]	(X)[d]	X	X	
Adverse events	9 2 Appendix 4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions	9 2 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints	9 2 9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication errors	9 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TRIAL MATERIAL																			

	Protocol section	Treatment															End of treatment	Discontinuation of trial product	Follow-up
		Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 24A	Visit 25[e]
CCI																			
Drug accountability	7.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispensing of trial product	7.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
IWRS session	7.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																			
Attend visit fasting	6.3.1		X		X		X		X		X		X		X		X	X	
Diary review	7.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Return diary																	X	X	
End of treatment	8.1, 8.2																X	X	
End of trial	8.1, 8.2																		X

[a]If applicable, see section 9.1.2 and Appendix 5

[b]Only applicable for subjects switching from Norditropin® to somapacitan. To be handed out at the visit where subject is switched to somapacitan. Site staff to inform parent/LAR to complete GH-PPQ at 4 weeks after switching

[c]Not to be done if performed within the last 6 months

[d]Applicable one time for subjects switching from Norditropin® to somapacitan. To be collected at the visit where the subject switches treatment

[e]The follow-up visit should also be performed after Visit 24A for subjects who discontinue treatment. The follow-up visit can be performed as a phone visit

3 Introduction

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.

3.1 Trial rationale

The purpose of this phase 2 dose-finding trial is to evaluate effect, safety and tolerability of once weekly subcutaneous (s.c) treatment of somapacitan compared to daily s.c growth hormone (GH) (Norditropin®) treatment in children with short stature born small for gestational age (SGA) with no catch-up growth by 2 years of age or older. CCI [redacted] CCI [redacted] CCI [redacted].

The trial is a dose-finding, randomised, multinational, multi-centre, open-labelled active-controlled, parallel group design with a once weekly somapacitan dose regimen. 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 short stature born SGA with no catch-up growth by 2 years of age or older will potentially improves growth, increase height velocity (HV) and improve final height.

3.2 Background

3.2.1 Children with short stature born SGA with no catch-up growth by 2 years of age or older

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-I) release[1]. Besides, the importance of GH and IGF-I for facilitating growth in children, both proteins are also involved in various metabolic processes in children as well as in adults[2]. Rapid proteolysis and ligand-receptor internalisation result in a short half-life for human growth hormone (hGH).

Consequently, GH is given as daily injections and children treated with GH often require many years of treatment. Studies investigating treatment adherence have shown that approximately one-fourth of children on GH treatment misses more than 2 of 7 injections per week[3-5] which may impact final adult height.

Children with short stature born SGA with no catch-up growth by 2 years of age or older accounts for approximately 20% of all cases[6]. SGA is a heterogeneous condition which is a result of impaired foetal growth due to environmental as well as genetic factors, not yet clearly identified. SGA refers to the size of an infant at birth and is defined as a birth length and/or weight of at least 2 Standard Deviation Scores (SDS) below the mean for gestational age and gender[7]. Most children born SGA

have sufficient GH secretion and IGF-I levels and show spontaneous catch-up growth to a normal weight and height above 2 SDS by 2 years of age, however, 10% of the children do not catch-up despite sufficient GH and IGF-I levels and do therefore have a markedly reduced final adult height compared to the predicted height[8, 9].

Experience gained during the last 15-20 years shows that GH treatment is effective in restoring normal growth in children with other forms of growth retardation than GHD, including SGA, Turner, Noonan, Prader-Willi syndromes, idiopathic short stature and children with chronic renal failure[10, 11].

3.2.2 Somapacitan

Somapacitan is a long acting hGH derivative, with a single point mutation in the amino acid 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 improving convenience for patients by reducing injection frequency and improving treatment adherence[12]. The molecular weight of somapacitan is 23.3 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 pharmacokinetic (PK) profile of somapacitan has been assessed to be suitable for once weekly administration in humans and it is anticipated that once weekly therapy with somapacitan will be as safe and effective as daily GH treatment[13].

3.2.3 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 Investigators Brochure (IB)[13].

3.2.4 Somapacitan clinical data

No safety issues have been identified during the clinical development of somapacitan. Clinical data obtained from both adult and children continue to support the further development of somapacitan into phase 3 in children with GHD[13] as well as initiating a phase 2 trial in children with short stature born SGA with no catch-up growth by 2 years of age or older .

3.2.5 Norditropin®

For information please refer to the IB[14].

3.3 Benefit-risk assessment

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[13] 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.

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 because of weekly instead of daily administration. All subjects continuing into the extension II period will be switched to weekly treatment with somapacitan.

Subcutaneous injections: Can occasionally lead to undesired local side effects, such as redness, swelling, itching, and tenderness of the skin at the point of injection.

Physical examination 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 paediatricians familiar with the population the burden is expected to be low.

X-Ray for bone age assessment: No risks are expected to be associated with the procedure. The risks are related to the total dose of radiation received. The burden of this assessment is reduced by the possibility of using an 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. ECGs are collected at screening and every 12 month during the trial.

Fasting prior to blood sampling: Risks may include modest to moderate hypoglycaemia (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 venepuncture: Peripheral venous access is widely used for taking blood samples. Pain can be reduced with use of local anaesthetic agents. In this trial investigators are encouraged to use numbing cream according to local practice. Risks include vasovagal reactions, minor bleeding and vessel damage. Burdens include moderate pain and possibly fear and distress.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AE) of somapacitan and Norditropin® may be found in the investigator's brochures[13, 14].

4 Objectives and endpoints

4.1 Primary and secondary objective(s)

4.1.1 Primary objective

To evaluate the effect of somapacitan versus Norditropin® on longitudinal growth in children with short stature born SGA with no catch-up growth by 2 years of age or older.

4.1.2 Secondary objective

To evaluate the effect and safety of somapacitan versus Norditropin® in children with short stature born SGA with no catch-up growth by 2 years of age or older.

4.2 Estimands

Not applicable

4.3 Primary, secondary endpoints

4.3.1 Primary endpoint

Endpoint title	Time frame	Unit
Height velocity	From baseline (week 0) to visit 6 (week 26)	cm/year

4.3.2 Secondary endpoints

4.3.2.1 Confirmatory secondary endpoints

Not Applicable

4.3.2.2 Supportive secondary endpoints

4.3.2.3 Effect

Endpoint title	Time frame	Unit
Change in bone age	From baseline (week 0) to visit 8 (week 52)	Years
Change in height SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10
Change in Height velocity SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10

4.3.2.4 Safety

Endpoint title	Time frame	Unit
Change in fasting plasma glucose	From screening (visit 1) to visit 6 (week 26)	mmol/l
Change in homeostatic model assessment (HOMA)	From screening (visit 1) to visit 6 (week 26)	%
Change in Glycated haemoglobin (HbA1c)	From screening (visit 1) to visit 6 (week 26)	% point

4.3.2.5 Pharmacodynamics

Endpoint title	Time frame	Unit
Change in IGF-I SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10
Change in IGFBP-3 SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10

4.3.3 Exploratory endpoints

- For subjects switching from Norditropin® to somapacitan
  -

• Endpoint title	• Time frame	• Unit
• Growth Hormone Patient Preference Questionnaire (GH-PPQ)	• At 4 weeks after switching from Norditropin® to somapacitan	• Count of subjects choosing the individual response category.

5 Trial design

5.1 Overall design

- A dose-finding, randomised, multinational, multicentre, open-label, five arm design, active controlled, parallel group trial designed to evaluate effect and safety of once-weekly somapacitan treatment compared to daily GH treatment (Norditropin®) in GH treatment naïve pre-pubertal children with short stature born SGA with no catch-up growth by 2 years of age or older.

- The trial will consist of a 26 week main period, a 26 week extension period (extension I), a 208 week additional extension period (extension II) and a 30 day follow up period. In the main period and extension I period, the trial is designed as a 5 arm parallel group trial with 3 dose levels of once-weekly somapacitan treatment and 2 active control arms of once daily Norditropin®. Subjects will be randomised 1:1:1:1:1 into the three doses of somapacitan (0.16, 0.20 or 0.24 mg/kg/week) or to one of the 2 doses of Norditropin® (CCI or CCI mg/kg/day).
- In the extension II period, all subjects will receive somapacitan once weekly. The dose will be within the tested range of 0.16-0.24 mg/kg/week and will be decided upon once all subjects have completed the main trial period and the data has been analysed and evaluated by Novo Nordisk.
- If a subject enters the extension II period before the main phase results are available, the subject will start the extension II period on their initially allocated treatment.
- This switch to somapacitan will occur at visit 8 or later once the dose for the extension II period has been decided. Thus, depending on when a subject is enrolled into the trial, the timing of this switch will vary from subject to subject.

- The randomisation will be stratified by region (Japan versus rest-of-the-world). The randomisation will additionally be stratified by age (< 6 versus ≥ 6 years) and by gender (boys versus girls) within the rest of the world to ensure equal distribution of these factor levels across treatments.

- Data from the main trial will be analysed when all subjects have completed the 26 weeks treatment. Final analysis will take place when all subjects have completed the trial .

- The total trial duration for a subject will be up to 5 years. The follow-up period is a minimum of 30 days.

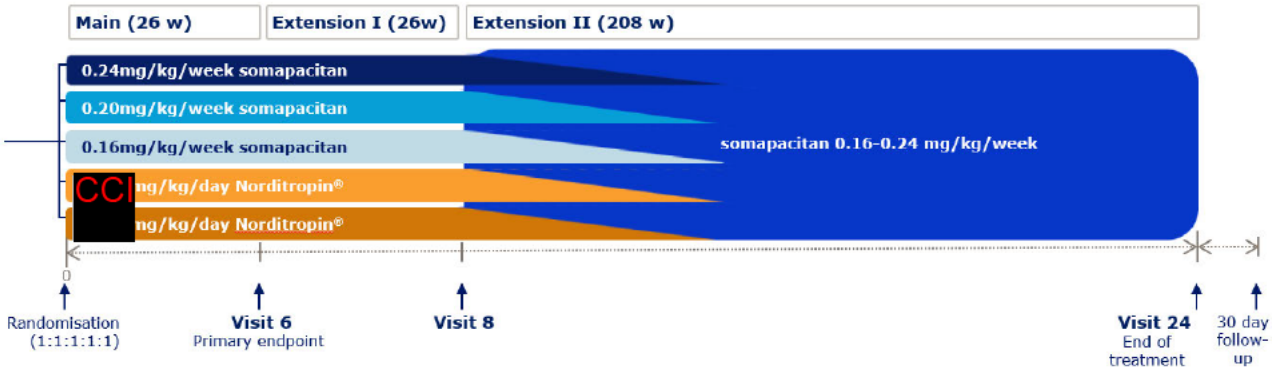

Figure 1 Trial design

5.2 Subject and trial completion

Approximately 60 subjects will be randomly assigned to trial product. Trial period completion for a subject:

Trial period completion is defined as when the last randomised subject has completed the final scheduled visit ('end of trial' according to the flowchart 2), but will be CCI [redacted], where an 'end of trial' visit should be conducted irrespective of how far in the extension II period the subject is.

Date of trial completion' is the date the subject completed the final scheduled visit.

Visit 6 is defined as the landmark visit as this is the last visit in the main phase where the primary endpoint is assessed.

Treatment period completion for a subject:
Treatment period completion is defined as when the randomised subject has received the required treatment, and attended the 'end of treatment' visit according to the flowchart 2.

5.3 End of trial definition

The end of the trial is defined as the date of the last visit of the last subject in the trial.

5.4 Scientific rationale for trial design

Treatment-naïve children with short stature born SGA with no catch-up growth by 2 years of age or older are the target population. The children must be treatment naive to ensure that no pharmacological catch-up growth have occurred. Most children born SGA have sufficient GH secretion and IGF-I levels and show spontaneous catch-up growth to a normal weight and height above 2 SDS by 2 years of age. However ten percent of children born SGA do not catch-up despite

sufficient GH and IGF-I levels and do therefore have a markedly reduced final adult height compared to the predicted height[8, 9].

In clinical practice, both children with short stature born SGA with no catch-up growth by 2 years of age or older and children with GHD are treated with GH for insufficient growth. Therefore, evaluation of HV in a population treated with non-replacement therapy will remain within established clinical practise. CCI [redacted] CCI [redacted] CCI [redacted].

The primary endpoint (HV) assessed after 26 weeks of treatment will serve as predictor for growth response in relation to dose [15]. CCI [redacted] CCI [redacted] CCI [redacted]. Additional data obtained in the extension I period will support the main period data and data from the extension II period will provide long term safety data for the selected somapacitan dose. Only pre-pubertal children will be enrolled to minimise interference of the pubertal growth spurt with the treatment effect. Age and gender stratification as well as region (Japan versus non-Japan) will ensure that subjects will be equally distributed between the five arms.

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

5.5 Justification for dose

CCI [redacted]

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 dose in the extension II period will be based on totality of evidence from the main period.

For UK: see Appendix 9

6 Trial population

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

6.1 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 the Child Assent Form or provide oral assent (if required according to local requirements).

2. Pre-pubertal children:
   a) Boys:
      - Age ≥ 2 years and 26 weeks and < 11.0 years at screening.
      - Testes volume < 4 ml.

   b) Girls:
      - Age ≥ 2 years and 26 weeks and < 10.0 years at screening.
      - Tanner stage 1 for breast development (no palpable glandular breast tissue).

3. Born small for gestational age (birth length and/or weight < -2 SDS) (according to national standards).
   - **For Israel and Japan:** see Appendix 9

4. Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and gender at screening according to the standards of Centers for Disease Control and Prevention.
   For India: see Appendix 9

5. Impaired height velocity defined as annualised height velocity below the 50th percentile for chronological age and gender according to the standards of Prader calculated over a time span of minimum 6 months and maximum 18 months prior to screening.

6. No prior exposure to growth hormone therapy or IGF-I treatment.

7. Gestational age at birth ≥ 32 weeks.

8. Body Mass Index <95th percentile according to Centers for Disease Control and Prevention, Body Mass Index-for-age growth charts.
   For India: see Appendix 9

6.2 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 at time of randomisation.

4. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements:

   a) Turner Syndrome (including mosaicisms)

   b) Chromosomal aneuploidy and significant gene mutations causing medical "syndromes" with short stature, including but not limited to Laron syndrome, Noonan syndrome, Prader-Willi Syndrome, abnormal SHOX-1 gene analysis or absence of GH receptors

   c) Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants

   d) Congenital abnormalities (causing skeletal abnormalities), including but not limited to Russell-Silver Syndrome or skeletal dysplasias

   e) Family history of skeletal dysplasia

   For India: see Appendix 9

5. Children with hormonal deficiencies including suspected or confirmed growth hormone deficiency according to local practise.

6. Children diagnosed with diabetes mellitus or screening values from central laboratory of

   a) Fasting plasma glucose ≥126 mg/dl (7.0 mmol/L) or

   b) HbA1c ≥ 6.5 %

7. Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.

8. Children requiring inhaled glucocorticoid therapy at a dose of greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks within the last 12 months prior to screening.

9. Concomitant administration of other treatments that may have an effect on growth, e.g. but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).

10. Diagnosis of attention deficit hyperactivity disorder.

11. Prior history or known presence of malignancy including intracranial tumours.

12. Prior history or known presence of active Hepatitis B or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B).

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

    For France, Spain, and UK: see Appendix 9

14. The subject or the parent/legally acceptable representative is likely to be non-compliant in respect to trial conduct, as judged by the investigator.

15. Children who are small due to malnutrition defined as -2 SD according to standards: 0-5 years: weight for height on World Health Organisation Multicentre Growth Reference Study 2006 and >5 years: World Health Organisation 2007 Body Mass Index.
    For India: see Appendix 9

6.3 Lifestyle restrictions

6.3.1 Meals and dietary restrictions

- Subjects should be fasting (only water is allowed) for 6 hours prior to blood sampling for fasting plasma glucose.

6.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/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 demography screen failure

details, eligibility criteria, and any serious adverse event (SAE). 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. Re-sampling is not allowed if the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

7 Treatments

7.1 Treatments administered

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.

Trial product somapacitan must only be used, if it appears clear and almost colourless.

Trial product Norditropin® must only be used, if it appears clear and colourless.

Table 3 Trial products provided by Novo Nordisk A/S

Trial product name:	somapacitan 5 mg/1.5 ml somapacitan 10 mg/1.5 ml somapacitan 15 mg/1.5 ml	Norditropin® FlexPro® 10 mg/1.5 ml
Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneous	Subcutaneous
Dosing instructions:	Once weekly	Once daily
Packaging	CCI somapacitan pen-injector	Norditropin® FlexPro® pen-injector

The investigator must document that directions for use are given to subject in writing at the first dispensing visit as specified in the flowchart 2. When subjects randomised to Norditropin® are switched to somapacitan, the investigator must document that the directions for use for somapacitan is given to the subject.

Only needles provided or approved by Novo Nordisk must be used for administration of trial product. Maximum needle length should be 6 mm.

Three different strengths of somapacitan will be used somapacitan 5 mg/1.5 ml, somapacitan 10 mg/1.5 ml and somapacitan 15 mg/1.5 ml. The strength to be used is dependent on the subject´s current weight.

Time of injections somapacitan

- Somapacitan can be injected any time during the dosing day
- Injection with somapacitan the day before blood sampling for anti-drug- antibodies (ADA) must occur at least 12 hours prior to planned blood sampling
- 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 2 days after the planned dosing day, the dose should be skipped. The next dose afterwards should be taken on the originally planned weekday compared to baseline (randomisation).
- 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 Norditropin®

- Subjects randomised to Norditropin® should inject s.c. daily in the evening (to reflect standard treatment practice) throughout the trial.
- Injections with Norditropin® the night before blood sampling for ADA 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 continue on the next evening with the next scheduled dose.

7.1.1 Medical devices

Information about the pre-filled CCI pen-injector can be found in the IB for somapacitan[13] and any updates hereof.

Information about the use of the pre-filled CCI pen-injector for somapacitan can be found in the directions for use.

Information about the pre-filled Norditropin® FlexPro® can be found in the IB for Norditropin®[14] and any updates hereof.

Information about the use of the pre-filled Norditropin® FlexPro® for Norditropin® can be found in the directions for use.

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

The subjects must be trained according to the direction for use in how to handle the CCI somapacitan pen-injector or Norditropin® FlexPro® and injection technique when handed out the first time. Training must be repeated during the trial at regular intervals in order to ensure correct use of the CCI somapacitan pen-injector or Norditropin® FlexPro®. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and ensure correct dose.
- The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection. If the needle is removed too early, then the full dose may not have been delivered.
- In-use conditions of the pen-injector including in-use time and storage.
- Injection site should be rotated each time.

- Injections can be given s.c. in
  - upper legs
  - buttocks
  - upper arms
  - stomach area (abdomen)

7.2 Dose modification

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

The Investigator will communicate the dose to the subjects at each visit.

Modifications to the calculated dose should only be performed as described in Section 7.2.1. Dose titration is not allowed.

For France: see Appendix 9

7.2.1 Dose reduction criteria

If AEs with a probable relationship to the trial product are persistent but allow continuation in the trial, as judged by the investigator, dose reduction in CCI [redacted] can be considered at the investigator's discretion. If after CCI [redacted] dose reduction steps AEs still persist, the subject's treatment may be discontinued according to treatment discontinuation (see Section 8.1) or withdrawal criteria (see Section 8.2).

When the AE is resolved the dose can be resumed to the original planned dose at the investigator's discretion.

7.2.2 e-Diary

At visit 2, the subjects will be provided with an e-Diary device for electronic recording of data. Information about the injection of trial product will be recorded in the e-Diary device.

The overall process for handling e-Diaries is described in a manual.

7.3 Method of treatment assignment

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

All subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart 2.

Stratification will be performed in the IWRS at randomisation.

- The randomisation will be stratified by region (Japan versus rest-of-the-world). The randomisation within the rest-of-the -world will additionally be stratified according to:
  - Age (< 6 years versus ≥ 6 years at randomisation)
  - Gender (boys versus girls)

7.4 Blinding

This is an open-label trial.

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

For blinding of site staff performing the height measurements please refer to Section 9.1.1.

7.5 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the trial may receive trial product and only authorised 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).

For country specific requirements see Appendix 9.

- Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation.
- The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and 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 authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.
- Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator
- The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).

- 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.
- Destruction of trial products must be documented in the IWRS.
- All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) 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 trial site.

7.6 Treatment compliance

Throughout the trial, the investigator will remind the subjects in a non-judgemental manner to follow the trial procedures and requirements to ensure subject compliance.
When subjects self-administer trial product at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit. If any suspicion of non-compliance arises the site must enter into a dialogue with the subject, 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

7.7 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 9.2.

- During the main period initiation of treatment that may affect growth (primary endpoint) e.g. but not limited to methylphenidate for treatment of ADHD is not recommended. However medical judgment should always be according to investigator’s discretion.

- **For France:** see Appendix 9

7.7.1 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 7.8.
Any ancillary therapy must be recorded along with:

- Trade name or generic name
- Start and stop dates

7.8 Treatment after the end of the trial

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued, the subject should be transferred to a suitable marketed product according to local treatment guidance at the discretion of the investigator.

If a subject discontinues trial product during the trial and is transferred to a marketed product this should be recorded as ancillary therapy according to Section 7.7.1.

8 Discontinuation/Withdrawal criteria

The subject may be discontinued at any time during the trial at the discretion of the investigator.

Efforts must be made to have the subjects, who discontinue trial product, attend the planned visit schedule until visit 8. 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.

8.1 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 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 subject must be discontinued from trial product, if the following applies:

- Pregnancy
- Intention of becoming pregnant
- Simultaneous participation in another clinical trial of an approved or non-approved IMP
- Tumour development
-

See the flowchart 2 for data to be collected at the time of treatment discontinuation 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 AEs.
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 24. If pregnancy is suspected the subject must come to the site for the follow up visit where a pregnancy test is performed.

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

Treatment discontinuation prior to visit 8
If a subject discontinues treatment prior to visit 8, visit 24A should be performed at least 7 days after the last dose of trial product and prior to starting treatment with a marketed product. The follow up should be performed a minimum of 30 days after the last dose of trial product. Although the treatment has been discontinued, the subject should continue to follow the planned visit 5, 6, 7 and 8. If subject or family refuses to attend the planned visit schedule, then the first coming visit 6 or 8 is of most importance to attend.

After treatment discontinuation (visit 24A) only the following assessments are required:

- Height
- IGF-1
- AEs
- Concomitant medication

- **Treatment discontinuation at or after visit 8**
- If a subject discontinues treatment at or after visit 8, visit 24A should be performed at least 7 days after the last dose of trial product and prior to starting treatment with a marketed product. The follow up should be performed a minimum of 30 days after the last dose of trial product and the subject should then be withdrawn from the trial.

8.2 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 or the 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 24A and the follow up visit. See the flowchart 2 for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS.

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.

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

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 CRF.

8.2.1 Replacement of subjects

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

8.3 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 trial site.

The following actions must be taken if a subject fails to return to the trial 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 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'.

9 Trial assessments and procedures

Trial procedures and their timing are summarised in the flowchart 2.

Informed consent and child assent if applicable must be obtained before any trial related activity, see Appendix 3.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility 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, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.

Adherence to the trial design requirements, including those specified in the flowchart 2, is essential and required for trial conduct.

Review of completed diaries, 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 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.

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.

9.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart 2.

9.1.1 Body measurements

Body measurements will be assessed according to the flowchart 2.

Height
For height measurements, European Medicines Agency (EMA) guideline[20] 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 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 or in inches with one decimal
-

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

Body weight
Body weight will be measured in kilos (kg) or pounds (lb) 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.

Body Mass Index
Body Mass Index will be calculated at the screening visit (Visit 1) using the CRF.

Body composition
Body composition will be measured using bioelectrical impedance analysis (BIA) including assessments such as muscle, fat and bone parameters.
Instructions will be provided to the sites describing procedures for body composition measurement.

9.1.2 Pubertal status

Pubertal status according to Tanner staging will be assessed[21].

The date of menarche will be collected for girls, when applicable.

Female subjects becoming of childbearing potential and male subjects becoming of reproductive age during the trial should be given age appropriate sexual counselling and instructed to use adequate contraceptive methods (see Appendix 5) according to local regulations throughout the trial, if applicable.

For France: see Appendix 9

9.1.3 X-ray for bone age assessment

X-Rays of left hand and wrist for bone age assessment according to the Greulich and Pyle atlas[22] 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 can be used as baseline 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.

9.1.4 Patient reported outcome questionnaire

A paper PRO questionnaire (GH-PPQ) will be handed out to the parents/LARs of subjects who change treatment from Norditropin® to somapacitan in the extension II period. The GH-PPQ will be handed out at the visit where the subject is switched to somapacitan and should be completed at 4 weeks after the switch.

9.1.5 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the flowchart 2 and the laboratory manual.

9.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until the follow up visit/end of trial visit, at the time points specified in the flowchart 2.

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk 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 investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

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 4.

Timelines for reporting of AEs are listed in Figure 2.

Some AEs require additional data collection via a specific event form. This includes injection site reactions and medication errors observed during the trial. The relevant specific events are listed in Table 4 and the reporting timelines in Figure 2.

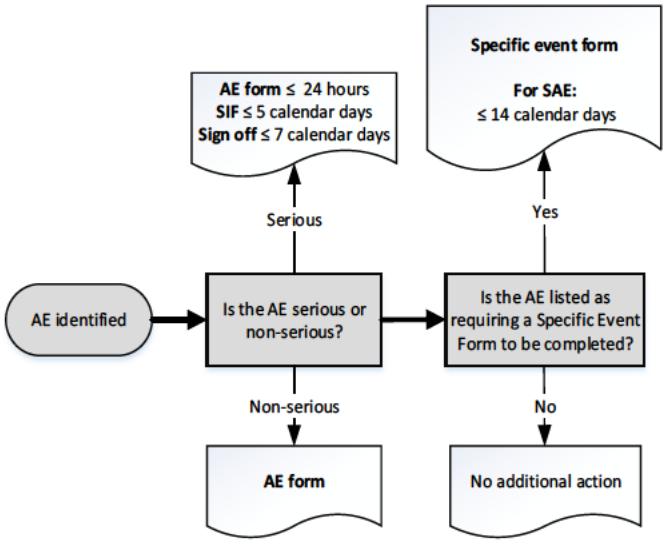

Figure 2 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 4 AEs requiring additional data collection (via specific event form)

Event type	AE requiring additional event form
Injection site reaction	X
Medication error	X

In subjects with severe headache, a fundoscopy should be performed at the investigator's discretion to rule out intracranial hypertension.

9.2.2 Method of detecting AEs and SAEs

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.

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, or if the event

is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of a 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.

Investigator safety reports must be prepared for suspected unexpected serious adverse reaction (SUSARs) according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a 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.

9.2.5 Cardiovascular and death events

Not applicable for this trial

9.2.6 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

Not applicable for this trial

9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects and female partners of male subjects (paternal) will be collected after the first trial related activity after obtaining informed consent and until end of trial visit.

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined Appendix 5.

Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

9.2.8 Medical device incidents (including malfunctions)

Not applicable for this trial. Refer to technical complaints in section 9.2.9

9.2.9 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.

The definitions and reporting process for technical complaints can be found in Appendix 6.

Timelines for reporting technical complaints are listed in Figure 3.

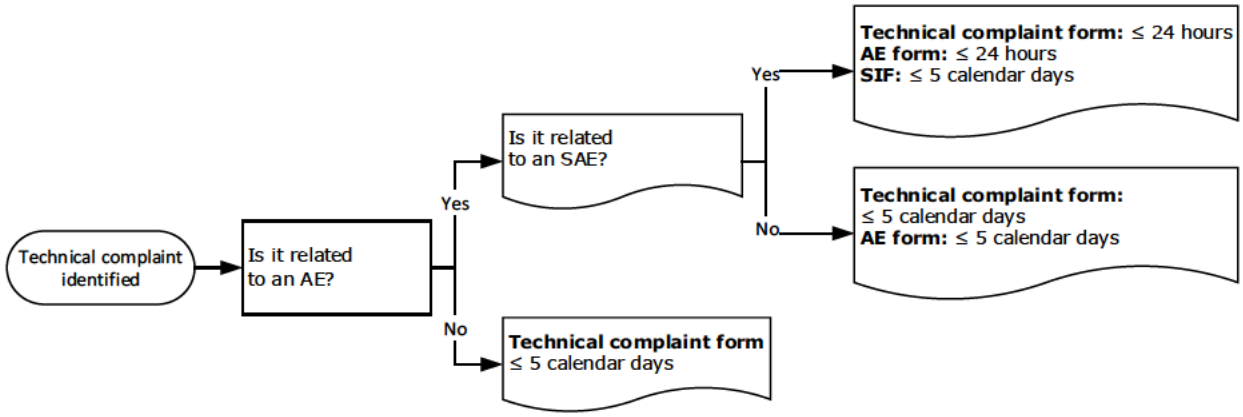

Figure 3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.3 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.

The overdose if accidental must be reported as a medication error. Refer to Section 9.2.1 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.

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

9.4 Safety assessments

Planned time points for all safety assessments are provided in the flowchart Section 2.

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) 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 has experienced in the past.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (Visit 2) must be reported as an AE (see Section 9.2).

Information related to children with short stature born SGA with insufficient catch-up growth

- Birth related information
- Height data
  - Standing height measured minimum 6 and maximum 18 months prior to screening in order to assess inclusion criterion 5. Standing height should be reported in centimetres with one decimal to the nearest 1 mm or in inches with one decimal. The pre-trial height assessment is collected to be used when evaluating inclusion criteria 5 and for baseline HV derivation.
  - Parental height: Standing height for both biological parents in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- GH status, if available
  - Type of GH stimulation test and result of peak GH values.

9.4.1 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.
- For US: See Appendix 9

9.4.2 Vital signs

- Pulse rate, diastolic and systolic blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.3 ECG

- 12-lead ECG will be obtained as outlined in the flowchart 2

- 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 from 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.

9.4.4 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the flowchart in Section 2.

9.4.5 Immunogenicity assessments

All ADA samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day.

A tiered approach including screening of samples, confirmation of ADA as well as characterisation of cross-reactivity towards endogenous hGH and in vitro neutralising activity against the trial product will be used. To evaluate the impact of antibody formation, results of antibody analyses will be compared to PK and pharmacodynamics (PD) markers.

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.

ADA samples will be analysed at end of trial or if presence of neutralising ADA are suspected by investigator or sponsor. Subjects who have had a positive *in vitro* neutralising antibody test result at the last visit will be offered an appropriate follow-up period until the antibody response remains unchanged, is decreasing or until the investigator or the sponsor decides that no further follow-up is warranted. The subjects may be requested to have additional blood samples collected for follow-up analyses. If deemed relevant, i.e. due to an antibody relevant AE, unexpected low PK, or per request from the safety committee, specific samples may be analysed at other time-points during the trial.

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

9.4.5.1 Anti-somapacitan antibodies

Determination of antibodies against somapacitan in subjects randomised to somapacitan will be performed by a special laboratory using a validated antibody assay. Confirmed anti-somapacitan

antibody positive samples will be further tested for cross-reactivity to hGH and for in vitro neutralising effect in a validated neutralising antibody assay and by correlation to PK/PD.

9.4.5.2 Anti-hGH antibodies

Anti-hGH antibodies in subjects randomised to Norditropin® will be analysed by a special laboratory using a validated antibody assay. Confirmed anti-hGH antibodies will be further assessed for in vitro neutralising effect of anti-hGH antibodies in a validated neutralising antibody assay and by correlating to PK/PD.

9.4.5.3 Assessment in case of suspicion of severe systemic hypersensitivity

In the event of a severe local and/or systemic hypersensitivity reaction possible or probably related to trial product, blood sampling for assessment of anti-somapacitan or anti-Norditropin® IgE antibodies as well as binding antibodies should be performed in relation to the reaction and no later than 1-2 weeks after the event.

In the event of a severe systemic hypersensitivity reaction to trial product it is recommended also to analyse a sample collected within 3 hours of the reaction for tryptase (total and/or mature tryptase) at the local laboratory. Moreover, a baseline tryptase measurement is necessary 1-2 weeks after the immediate severe hypersensitivity reaction due to individual variation in tryptase baseline concentration.

A follow up visit should be conducted 3-4 weeks after the allergic reaction with repeated blood sampling for assessment of anti-somapacitan or anti-Norditropin® IgE antibodies as well as binding antibodies and, if possible, also at a visit 3 months post the hypersensitivity reaction for assessing the persistence of the IgE response. Tryptase measurements are not required at the follow up visits.

9.5 Pharmacokinetics

Samples will be used to evaluate the PK 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.

9.6 Pharmacodynamics

IGF-I and IGFBP-3 will be used to evaluate the PD of somapacitan and Norditropin®. CCI [redacted].

9.7 CCI [redacted]

CCI [redacted]

CCI

9.8 Biomarkers

Not applicable for this trial

10 Statistical considerations

10.1 Sample size determination

The trial will have 5 treatment arms with a total of 60 subjects randomised using a 1:1:1:1:1 randomisation ratio. The primary endpoint is assessed 26 weeks after randomisation. At this time point few or no trial participants are expected to be withdrawn based on data from NN8640-4172, a phase 2 trial (somapacitan) in children with GHD. Assuming 55 subjects are available in total (11 subjects per treatment arm) and a SD of 2.6 cm/year for annualised HV after 26 weeks of treatment (SD value based on data from hgh-1424, a phase 3 trial[23] (daily hGH) in children born SGA), the trial should have a probability of 80% to detect a difference between two specific treatment arms if the true difference between the two treatments is at least 3.25 cm/year. The power of the trial for 3 SD scenarios is:

True difference	SD		
	2.4 cm/year	2.6 cm/year	2.8 cm/year
3.0 cm/year	80%	73%	67%
3.25 cm/year	85%	80%	74%
3.5 cm/year	90%	85%	80%

10.2 Definition of analysis sets

The Full analysis set (FAS) is defined as all randomised subjects exposed to the trial product. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented before database lock (DBL). The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CTR. Subjects will be analysed "as treated".

The Safety analysis set (SAS) is defined as all randomised subjects exposed to trial product. Subjects will be analysed "as treated".

The Per Protocol (PP) analysis set is defined as subjects from FAS who have not violated any inclusion/exclusion criteria and have used the randomised treatment for at least 22 weeks (for subjects receiving somapacitan) or 154 days (for subjects receiving Norditropin®). Subjects will be analysed "as treated".

All efficacy endpoints will be analysed using FAS and all safety endpoints will be analysed using SAS.

Two observation periods are defined,

- on-treatment: from first administration and up until last trial contact, visit 6 or 14 days after last administration, whichever comes first
- in-trial: from first administration and up until visit 6 or last trial contact, whichever comes first

The observation periods for the extension I part of the trial are defined analogously by exchanging "visit 6" in the definitions above with "Follow-up visit 25" for subjects who do not continue in extension II or "visit 8" for subjects continuing in extension II.
For the on-treatment observation period of the extension II part of the trial,"visit 6" in the on-treatment observation period definition above is exchanged with visit 24 or visit 24A for subjects who do not attend visit 24. The in-trial observation period for the extension II part of the trial is defined analogously by exchanging "visit 6" in the definition above with "Follow-up visit 25".

10.3 Statistical analyses

Biostatistics, Novo Nordisk, will be responsible for the statistical analyses.

All statistical tests will be conducted as two sided tests on the 5% significance level, unless stated otherwise. Age group is defined as a factor with 2 levels: < 6 years, ≥ 6 years and region as a factor with 2 levels: Japan, rest of the world. No adjustment for multiple testing will be applied for this exploratory phase 2 trial.

10.3.1 Primary endpoint

Endpoint title	Time frame	Unit
HV	From baseline (week 0) to visit 6 (week 26)	cm/year

Height is measured at baseline and 26 weeks and the primary endpoint is derived as:

HV= (height at 26 weeks visit – height at baseline)/(time from baseline to 26 weeks visit in years).

Annualised HV at 13 weeks, 39 weeks and 52 weeks will be derived analogously to the primary endpoint : (height at d weeks visit – height at baseline)/(time from baseline to d weeks visit in years), where d=13,39,52.

The primary objective is to evaluate the effect of somapacitan vs Norditropin® on longitudinal growth in children with short stature born SGA with no catch-up growth by 2 years of age or older and the primary analysis of the primary endpoint is the main tool for achieving this. Conclusions from the primary analysis will be based on CIs for the specified treatment differences and not on hypothesis testing.

The primary analysis of the primary endpoint is based on FAS and the 'in-trial' observation period.

Annualised HV at 13 and 26 weeks will be analysed using a mixed model for repeated measurements (MMRM) with treatment, age group, sex, region and sex by age group interaction term as factors and height at baseline as a covariate, all nested within week as a factor. An unstructured covariance matrix will be used to describe variability for the repeated measurements for a subject. From the model the treatment differences at week 26: somapacitan 0.24 mg/kg/week vs Norditropin® CCI mg/kg/day, somapacitan 0.20 mg/kg/week vs Norditropin® CCI mg/kg/day, somapacitan 0.20 mg/kg/week vs Norditropin® CCI mg/kg/day, and somapacitan 0.16 mg/kg/week vs Norditropin® CCI mg/kg/day will be estimated with the corresponding 95% CI. Subjects without post-randomisation HV data will not be included in the primary analysis. Data from subjects who have discontinued randomised treatment before week 26 will be used in the primary analysis.

The analysis will be repeated on the PP analysis set as a sensitivity analysis.

10.3.2 Secondary endpoints

Confirmatory secondary endpoints
NA

Supportive secondary endpoints

Main period:
Effect

Endpoint title	Time frame	Unit
Change in height SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10
Change in HV SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10

Pharmacodynamics

Endpoint title	Time frame	Unit
Change in IGF-I SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10
Change in IGFBP-3 SDS	From baseline (week 0) to visit 6 (week 26)	-10 to +10

The analysis of change in HVSDS, change in height SDS and change in bone age is based on FAS and the 'in-trial' observation period. The analysis of change in IGF-I SDS and change in IGFBP-3 SDS is based on FAS and the 'on-treatment' observation period.

Height SDS will be derived using Centres for Disease Control and Prevention (CDC) standards[24] and HV SDS will be derived using Prader standards[25] as reference data.

The secondary endpoints: change in height SDS, HV SDS, IGF-I SDS and IGFBP-3 SDS from baseline will be analysed using MMRM on available assessments from planned visits with baseline assessment as covariate and treatment, age group, sex, region and sex by age group interaction term as factors, all nested within week as a factor. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.

Extension I period:

Endpoint title	Time frame	Unit
Change in bone age	From baseline (week 0) to visit 8 (week 52)	Years

Bone age will be analysed using an ANCOVA model on change from baseline in bone age/chronological age assessed at week 52 and the model will include treatment, age group, sex, region 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. Subjects without post-randomisation data for the analysed endpoint will not be included in the analysis.

Supportive secondary safety endpoints

Endpoint title	Time frame	Unit
Change in fasting plasma glucose	From screening (visit 1) to visit 6 (week 26)	mmol/l
Change in HOMA	From screening (visit 1) to visit 6 (week 26)	%
Change in HbA1c	From screening (visit 1) to visit 6 (week 26)	% point

The safety endpoints will be analysed using descriptive statistics based on the corresponding 'on – treatment' observation period.

10.3.3 Exploratory endpoints

- For subjects switching from Norditropin® to somapacitan:
  -

• Endpoint title	• Time frame	• Unit

• Growth Hormone Patient Preference Questionnaire (GH-PPQ)	• At 4 weeks after switching from Norditropin® to somapacitan	• Count of subjects choosing the individual response category.

GH-PPQ data will be analysed using descriptive statistics.

10.3.4 Reporting of the main part of the trial

Data for all subjects up to and including visit 6 who have completed or discontinued the main trial will be included in a final database lock of the main trial. After the DBL of the main trial the sponsor will become unblinded for this open-label trial. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]. Data from the extension period will support the primary and secondary objective of evaluating the effect and safety of somapacitan vs Norditropin® on longitudinal growth in children with short stature born SGA with no catch-up growth by the age of 2 years or older.

10.3.5 Other analyses

Annualized HV at 13 weeks, 26 weeks, 39 weeks and 52 weeks will be analysed using a MMRM with treatment, age group, sex, region and sex by age group interaction term as factors and height at baseline as a covariate, all nested within week as a factor. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From the MMRM the treatment differences at week 52 weeks will be estimated for the same treatment contrasts as for the primary analysis of the primary endpoint.

Height profiles will be presented by subject with time point for treatment switch in the extension II period (if applicable) and start of puberty (if applicable) indicated in the graphs. Annualised HV for the second year in trial will be derived as: (height at 104 weeks visit – height at 52 weeks visit) /(time from 52 weeks visit to 104 weeks visit in years). Annualised HV for the second year in trial will be analysed using descriptive statistics by treatment arm (treatment arm from main trial period), as well as by extension II period treatment arm. Annualised HV for third, fourth and fifth year in trial will be derived analogously and analysed using descriptive statistics.

Change in height SDS, HV SDS, IGF-I SDS and IGFBP-3 SDS from baseline to week 52 will be analysed using an MMRM on available assessments from planned visits similar to the MMRM used for the analysis of week 26 data, with baseline assessment as covariate and treatment, age group, sex, region and sex by age group interaction term as factors, all nested within week as a factor.

IGF-I SDS and IGFBP-3 SDS data from extension II will be analysed using descriptive statistics.

Adverse events will be analysed using descriptive statistics based on the 'on –treatment' observation period within the main trial period (26 weeks of treatment). The adverse events will be summarised by treatment, MedDRA (Medical Dictionary for Regulatory Activities) system organ class and MedDRA preferred term. The descriptive statistics will include the number and percentage of subjects who experienced adverse events, the number of events and rate. AEs will be listed by treatment and subject with information on severity, relationship to trial product and demographics based on the 'on –treatment' observation period. Adverse events with onset 14 days or more after last trial drug administration will be reported in a separate listing. AEs with onset before first dosing will be reported in a separate listing.

Similar tables will be made for AEs in the extension trial periods (I and II).

Muscle, fat and bone parameters measured using bioelectrical impedance analysis will be analysed using descriptive statistics based on the 'on –treatment' observation period within the main trial period.

Analogous analysis will be made for the muscle, fat and bone parameters assessed in the extension trial periods (I and II).

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Somapacitan and IGF-I serum concentration data will 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. A more technical and detailed elaboration of the population PK, population PK/PD and exposure-response analyses will be given in a modelling analysis plan.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ADA	anti drug antibodies
ADHD	attention deficit hyperactivity disorder
AE	adverse event
CCI	[redacted]
CRF	case report form
CTR	clinical trial report
DBL	database lock
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DUN	dispensing unit number
ECG	electrocardiogram
FAS	full analysis set
FDAAA	FDA Amendments Act
GH	growth hormone
GCP	Good Clinical Practice
GHD	growth hormone deficiency
$HbA1_c$	glycated haemoglobin
hGH	human growth hormone
HOMA	homeostatic model assessment
HV	height velocity
IB	investigators brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IGF-I	insulin-like growth factor I
IGFBP-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

MMRM	mixed model for repeated measurements
PCD	primary completion date
PD	pharmacodynamics
PPQ	patient preference questionnaire
PRO	patient reported outcome
PK	pharmacokinetics
PP	per protocol
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
SUSAR	suspected unexpected serious adverse reaction
TMM	trial materials manual

Appendix 2 Clinical laboratory tests

The tests detailed in Table 6 and Table 7 will be performed by the central and special laboratories. All samples should be shipped to central lab for analysis or further distribution.

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 trial drug administration should always be followed.

Blood sampling volume

The investigator should follow local guidelines such as the European guideline [26] for blood sampling and volume of blood at each visit, in relation to the subject's body weight and age.

Table 5 Approximate blood volumes collected during the trial

Visit	mL	
Visit 1	9	
Visit 2	6	CCI [redacted]
Visit 3	9	
Visit 4	3.5	CCI [redacted]
Visit 5	9	
Visit 6	9	
Visit 7	7.5	
Visit 8	9	
Visit 9	0	
Visit 10	9	
Visit 11	0	
Visit 12	13.5	
Visit 13	0	
Visit 14	9	
Visit 15	0	
Visit 16	13.5	
Visit 17	0	
Visit 18	9	

Visit	mL
Visit 19	0
Visit 20	13.5
Visit 21	0
Visit 22	9
Visit 23	0
Visit 24	13.5
Follow up	0
Total volume collected during the trial	152[a] CCI [redacted]

[a]For subjects switching from Norditropin® to somapacitan during the trial CCI [redacted]
CCI [redacted]

For subjects with a low body weight

- At visits where blood sampling require higher blood volumes 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 trial drug administration should always be followed.
- Blood sampling can be prioritised as described in the laboratory manual
- 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 laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.
- 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. Human biosamples for retention will be stored as described in Appendix 7.

Table 6 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
PD	• IGF-I • IGFBP-3 • CCI [redacted]
PK	• somapacitan • Norditropin®
Notes: IGF-I and IGFBP-3 will be blinded to site staff during the trial. CCI [redacted] CCI [redacted]	

Table 7 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Haematocrit • Haemoglobin • Leucocytes • Thrombocytes
Biochemistry	• Alanine Aminotransferase (ALT) • Alkaline phosphatase (AP) • Bilirubin (total) • Aspartate Aminotransferase (AST) • Creatine Kinase • Creatinine • Potassium • Sodium
Glucose metabolism	• Fasting Insulin • Fasting plasma glucose • HbA_{1c} • 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)
Pregnancy testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women becoming of childbearing potential during the trial)[1]
Antibodies	• Anti somapacitan antibodies • Anti hGH-antibodies • Results will not be reported to the sites other than described in section 9.4.5
• Notes: [1]Local urine testing will be standard unless serum testing performed at local laboratory is required by local regulation or IRB/IEC.	

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 2 and Table 8. Blood sampling should always be collected prior to trial product administration if the visit is planned on a dosing day.

For subjects randomised to somapacitan:

Table 8 Timing of visits and blood sampling

Visit	Timing of visit
3	On a planned dosing day
4	1 to 4 days after dosing
5	On a planned dosing day
6	4 to 6 days after dosing
7	1 to 4 days after dosing
8	4 to 6 days after last dosing
9	No Blood sampling
10	1 to 4 days after dosing
11	No Blood sampling
12	On a planned dosing day
13	No Blood sampling
14	1 to 4 days after dosing
15	No Blood sampling
16	On a planned dosing day
17	No Blood sampling
18	1 to 4 days after dosing
19	No Blood sampling
20	On a planned dosing day
21	No Blood sampling
22	1 to 4 days after dosing
23	No Blood sampling
24	At least 7 days after last dose of trial product
24A	Preferably at least 7 days after last dose of trial product

Appendix 3 Trial governance considerations

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[27] and applicable ICH /GCP Guideline[28]
  - 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 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 trial 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 ICH guidelines, the IRB/IEC, and all other applicable local regulations
  - ensuring submission of the CTR synopsis to the IRB/IEC.

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.
For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

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 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 or their LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[28], Declaration of Helsinki[27] and the IRB/IEC or trial site.
- Whenever possible informed assent must also be obtained from the child. '
- In addition the information given to the subject's LAR, the child must be given information according to his/her capacity to understand, always taking into consideration the child's presumed willingness to participate in a clinical trial.
- 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 of informing to a medically qualified person, in accordance with local requirements.
- Subjects and/or their 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 LAR.
- If the minor reaches legal age while participating in the trial and has only signed an age specific informed consent/assent form, the subject has to re-consent to the informed consent form signed by the subject's LAR.

CCI [redacted]

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 "welcome to the trial letter" and 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.

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; subject names or any information which would make the subject identifiable will not be transferred.
- 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 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.

6) Committee structure

Novo Nordisk safety committee
Novo Nordisk has constituted an internal somapacitan safety committee to perform ongoing safety surveillance. The somapacitan safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

Data monitoring committee
The data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad hoc. This is done in order to protect the safety of the subjects and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on trial continuation, modification or termination. Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

Trial safety group
Novo Nordisk will constitute an internal trial safety group to review and evaluate the partially blinded preliminary safety, PK and PD data obtained for each subject during the first 13 weeks. The trial safety group will report their evaluations to the safety committee as appropriate. The TSG may

continue its activities beyond the 13 weeks period if requested by the somapacitan safety committee.

Information regarding composition, responsibilities and procedures to be used by the trial safety group are specified in a separate charter.

For UK: see Appendix 9

7) 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.
One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators.

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 clinical trial report 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.

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[29].

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 trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

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.

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.
Individual investigators will have their own research subjects' data.

8) Dissemination of clinical trial data

Information of the trial will be disclosed at 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)[30], the Food and Drug Administration Amendment Act (FDAAA)[31], European Commission Requirements[32-34] 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) + 26 weeks corresponding to visit 6. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 6. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- 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 CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory and diary 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:
    - Pregnancy forms

- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)

- 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.

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 trial 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 trial sites.

- Monitors will review the subject's medical records and other source data e.g. the diaries, to ensure consistency and/or identify omissions compared to the CRF.

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor 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) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the electronic CRF 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 related to diagnosis of SGA 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 trial site. There will only be one source document defined at any time for any data element.

11) 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 and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices 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 trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. 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

12) Trial and site closure

Novo Nordisk reserves the right to close the trial 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.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed. The investigator may initiate trial 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 trial 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.

13) 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 trial 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).

14) 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.

Novo Nordisk accepts liability in accordance with: Please refer to Appendix 9 Country-specific requirements.

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or • disease (new or exacerbated) temporally associated with the use of a medicinal product.
Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Abuse: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful, • physical or physiological effects (e.g. overdose with the intention to cause harm) • Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the • protocol or the terms of marketing authorization • A CLAE: a clinical abnormal laboratory finding which is clinically significant, i.e. an abnormality that suggests a • disease and/or organ toxicity and is of a severity that requires active management. Active management includes • active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to • the abnormality. • Exacerbation of a chronic or intermittent pre-existing 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 trial product 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
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. • Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **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.
• **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 serious 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 of a pre-existing condition that did not worsen from baseline is not considered an
- AE.
- Note:
  - Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.
  - Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

- **Results in persistent 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, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere
  - with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **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 hospitalisation, but may jeopardise 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 trial product.
    - 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).

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

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).

In addition digital photos should be taken of the injection site reaction at the time of identification and hereafter as frequent as judged by the investigator. The photos will be evaluated by an external dermatologist and subsequently transferred to Novo Nordisk.

The overall process for photo acquisition, central analysis, transfer of photos reporting of results and archiving will be described in a manual prepared by the vendor performing the dermatology review.

Medication error:

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

- Administration of wrong drug or use of wrong device.

- Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
-
- Accidental administration of a 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.

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.
- 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 “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 intensity 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: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as ‘serious’ when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE. Causality assessment must be performed by investigator or sub-investigator with a medical background.
Relationship between an AE/SAE and the relevant trial product(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 trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the Investigators brochures 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 send a follow-up report with the updated causality assessment. 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 at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **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 sequelae 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.
- **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.

SAE reporting via electronic CRF

- Relevant forms (AE form, safety information form and event specific form (injection site reaction form and medication error form)) must be completed in the CRF.
- For reporting and sign-off timelines, see box 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, see section 9.2.1
- After the trial is completed at a given site, 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.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or
- courier.
- 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 time frames (as illustrated in Figure 2):
- AE form within 24 hours.
- Safety information form within 5 calendar days.
- Both forms must be signed within 7 calendar days.

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

Appendix 5 Contraceptive guidance and collection of pregnancy information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP
Premenarcheal
Premenopausal female with one of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of subject's medical records, medical examination or medical history interview.

Contraception guidance:

Male subjects

- Male subjects becoming of reproductive age during the trial should, if applicable, receive age appropriate sexual counselling and be instructed to use adequate contraceptive methods according to local regulations until end of trial.

Female subjects

- Female subjects becoming of childbearing potential during the trial (defined as having menarche) should, if applicable, receive age appropriate sexual counselling and be instructed to use adequate contraceptive methods according to local regulations until end of trial.

Table 9 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and c] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [b] oral intravaginal transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation oral injectable
Highly effective methods that are user independent [a and c]

Implantable progestogen only hormonal contraception associated with inhibition of ovulation [b] Intrauterine Device (IUD) Intrauterine hormone-releasing System (IUS) Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [b]Hormonal contraception may be susceptible to interaction with the trial product, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilised during the treatment period and for at least 30 days after the last dose of trial product. [c]Contraception should be utilised during the treatment period and for at least 30 days after the last dose of trial product.

Table 10 Acceptable effective contraceptive methods

Acceptable effective contraceptive methods[a]
Failure rate of >1% per year when used consistently and correctly • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. • Male or female condom with or without spermicide • Cervical cap, diaphragm or sponge with spermicide
Note: [a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials.

Pregnancy testing

Pregnancy testing should be performed for women of childbearing potential whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.

- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the trial will discontinue trial product.

For **Denmark, Estonia, France, Ireland, Italy, Latvia, Norway, Spain and UK:** see Appendix 9

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

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 medical 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 trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form.

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: 1. One technical complaint form must be completed for each affected DUN 2. 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 the timelines specified in Figure 3. If the CRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier 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 trial 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.

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.

Appendix 7 Retention of human biosamples

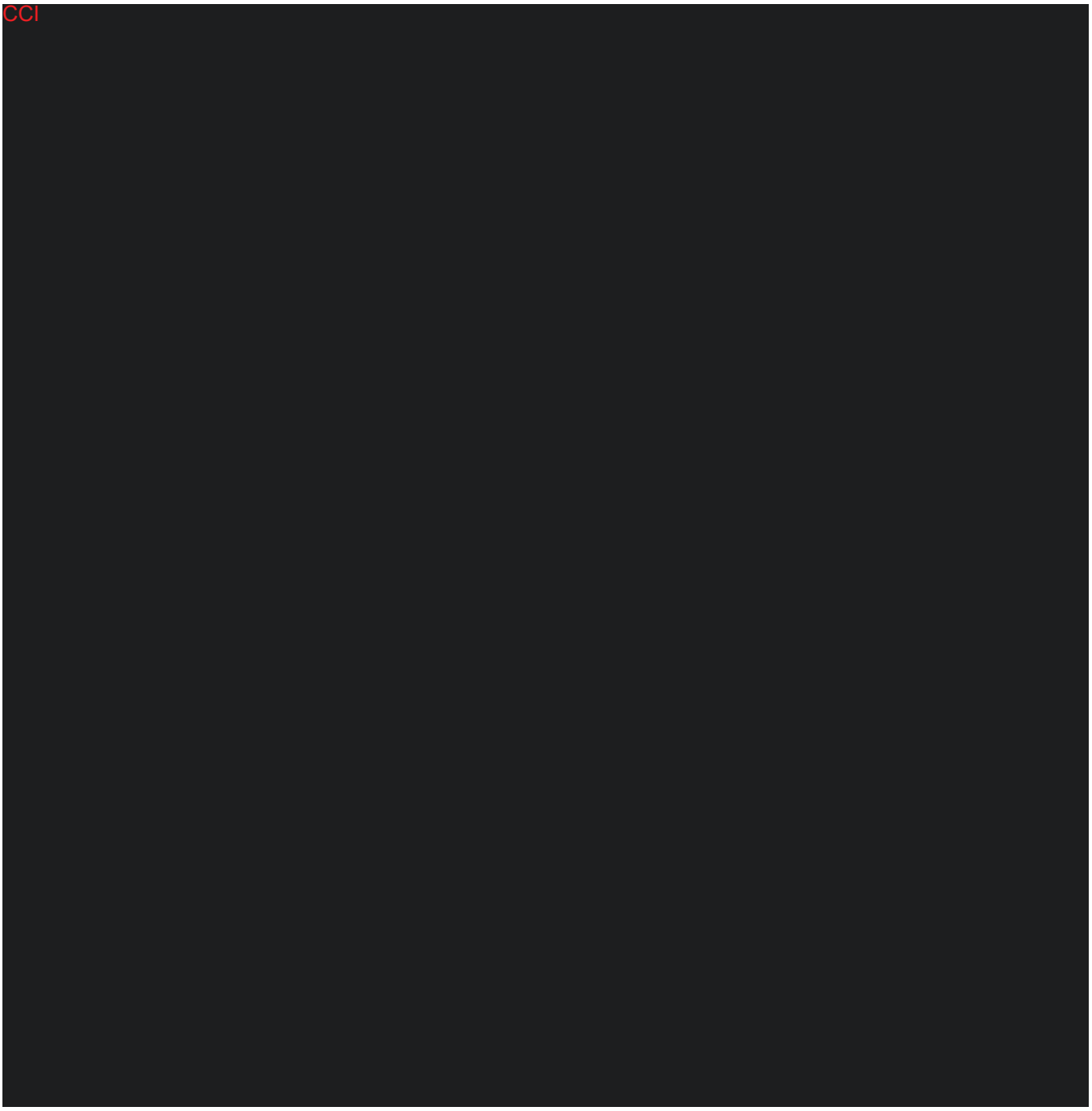
Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons.

The samples will be stored at a Novo Nordisk designated laboratory after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

For Algeria: see Appendix 9
For Israel: see Appendix 9

Appendix 8 CCI

CCI



Appendix 9 Country-specific requirements

Only applicable for Algeria:

CCI [redacted]

CCI [redacted]

For subjects with child bearing potential who expressly declare that they are free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.

Only applicable for Austria

A specific indemnity statement is required: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. I Nr. 59/2018

A monthly pregnancy test is mandatory for female subjects becoming of childbearing potential during the trial.

Only applicable for Canada:

Race and ethnicity will not be collected

Only applicable for Denmark:

Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01
About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

CCI [redacted]

CCI [redacted]

CCI [redacted]. Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the CTFG guideline above. Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for Denmark.

Only applicable for Estonia:

Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01-
About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

[redacted]

CCI [redacted]

CCI [redacted] Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the

CTFG guideline above. Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for Estonia.

Only applicable for Ireland:
Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

[redacted] Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the CTFG guideline above. Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for Ireland.

Only applicable for Israel:
Inclusion criteria 3: The first length measured and recorded [redacted] can be used as birth length to assess inclusion criteria 3. "Guidelines for approval of reimbursement of Growth hormone treatment in children as part of the national health basket". The Israeli Medical Association, the institute of quality in medicine-Jan 2016.

[redacted]

Only applicable for Italy:
Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

[redacted] Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the CTFG guideline above. Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for Italy.

Only applicable for Japan:

Inclusion criteria 3: Children in whom both the birth weight and birth length were <10th percentile of the level corresponding to the gestational age, and either the birth weight or birth length was < -2 SDS (according to Japanese standards).

Head of trial site is responsible for drug accountability. The head of trial site should assign some or all of the responsibilities to a trial product storage manager.

The trial will be registered in JapicCTI. (http://www.clinicaltrials.jp)

Only applicable for Latvia:
Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01
About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

CCI [redacted] CCI [redacted]
CCI [redacted]
CCI [redacted] Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the CTFG guideline above. Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for Latvia.

Only applicable for Norway:
Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01
About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

CCI [redacted]
CCI [redacted]
CCI [redacted] Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the CTFG guideline above. Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for Norway.

Only applicable for Russia:
The trial will be conducted in compliance with the protocol and Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016 "Approval of rules of good clinical practice" and legal requirements of the Russian Federation regulating circulation of medicines.

Only applicable for Spain:

Exclusion criterion 13: Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol and patients having contraindication to start treatment with Norditropin®.

Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01
About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

CCI CCI CCI CCI Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the CTFG guideline above. Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for Spain.

Date of Birth will be recorded only as year of birth. Race and ethnicity will not be collected.

Only applicable for Switzerland:
The trial will be conducted in compliance with Therapeutic Products Act of 15 December 2000 (Status as of 1 January 2018) (TPA/HMG) and Ordinance on clinical trials in Human Research (HRO/KlinV) of 20 September 2013 Status as of 1 January 2018.
Date of birth will be collected as year of birth.

Only applicable for US:
Clarification of physical examination: A fundoscopic exam should be performed at baseline and according to local practice.

CCI CCI mg/kg/day CCI CCI CCI mg/kg/day.
The US subjects who are randomised to Norditropin® CCI mg/kg/day and enter puberty during the main phase will be switched to Norditropin® CCI mg/kg/day after the assessment of primary endpoint data has been completed.

Only applicable for France:
A specific indemnity statement is required: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research.

Race and ethnicity will not be collected.

Exclusion criterion 13. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol and patients having contraindication to start treatment with Norditropin®.

Dose modification. Data from an interaction study performed in GH deficient adults suggests that GH administration may increase the clearance of compounds known to be metabolized by cytochrome P450 isoenzymes. The clearance of compounds metabolized by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

In insulin treated subjects adjustment of insulin dose may be needed after initiation of GH treatment.

Pubertal status. Female subjects will be asked about the date of last menstruation at visit 1 and visit 2. The date of menarche will be collected for girls, when applicable.

Only applicable for United Kingdom:
Exclusion criterion 13. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol and patients having contraindication to start treatment with Norditropin®.

References:
Bang P, et al. Horm Res Paediatr 2011; 75:335–45
Cabrol S, et al. Horm Res Paedriatr 2011, 76:419-427
Jensen RB, et al. Horm Res Paediatr 2013, 80:38-46
Jensen RB, et al. Eur J Endocrinol 2014; 171:509–518
Ranke et al. Horm Res 2005, 64(2): 68-76

CCI [redacted]

Contraception requirements as per: CTFG guideline
http://www.hma.eu/fileamin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_contraception.pdf

CCI [redacted] CCI [redacted]
CCI [redacted]
CCI [redacted] Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 9. In addition to Table 9, implantable progestogen-only hormonal contraception associated with inhibition of ovulation is also considered acceptable according to the CTFG guideline above.

Contraceptive methods listed in Appendix 5, Table 10 are not considered acceptable and Table 10 is not applicable for UK.

Only applicable for India
Inclusion criterion 4: Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and gender at screening according to standards: 0-5 years: World Health Organisation Multicentre Growth Reference Study 2006 and >5 years: Revised Indian Academy of Pediatrics 2015 Growth charts.

Inclusion criterion 8: Body Mass Index <95th percentile according to standards: 0-5 years: weight for height on World Health Organisation Multicentre Growth Reference Study 2006 and >5 years: Revised Indian Academy of Pediatrics 2015 Body Mass Index.

Exclusion criterion 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) confirmed by karyotyping

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

Information regarding some abnormalities likely to affect growth or the ability to evaluate growth with standing height measurements is included in a separate guidance document.

Exclusion criterion 15: Children who are small due to malnutrition defined as -2 SD according to standards: 0-5 years: weight for height on World Health Organisation Multicentre Growth Reference Study 2006 and >5 years: Revised Indian Academy of Pediatrics 2015 Body Mass Index.

Appendix 10 Protocol amendment history

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

Protocol amendment 1, applicable for UK (05 April 2019):

The purpose of this local UK amendment is to address comments raised in the non-acceptance letter dated 15th March 2019 from the Medicines and Healthcare products Regulatory Agency.

Overall rationale for preparing protocol amendment 1:

- update eligibility criteria to exclude patients with any contraindication to Norditropin®.
- add the justification for the proposed doses; and give the rationale for not implementing dose adjustments based on IGF-I.

Protocol version 3.0, including versions 1.0 and 2.0: (17 July 2019), global (protocol amendment no.2)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rational for preparing protocol version 3.0:

CCI [redacted]

Section # and name	Description of change	Brief rationale
Appendix 1 Abbreviations and Trademarks Appendix 3 Trial governance considerations	CCI [redacted] CCI [redacted]	CCI [redacted] CCI [redacted].
Section 1 Synopsis Section 2 Flowchart 4.3.1 CCI [redacted]	CCI [redacted]	CCI [redacted]

4.3.2.2 Supportive secondary endpoints 5.1 Overall design 5.4 Scientific rationale for trial 10.1 Sample size determination 10.3.1 Primary endpoint 10.3.2 Secondary endpoints 10.3.5 Other analyses Appendix 2 Clinical laboratory tests, Table 5 and 8. Appendix 3 Trial Governance considerations. 6) Committee structure. 8) Dissemination of clinical trial data	Assessments added at visit 6 (26 weeks).	
Flowchart	Footnote "e" added to flowchart	To specify that HbA_{1c} will not be collected at visit 3.
Flowchart 10.2 Definition of analysis sets	Visit 9 is not applicable if subjects continue in a new Novo Nordisk clinical trial receiving Norditropin® or somapacitan.	To clarify that follow-up visit (visit 9) is not applicable for subjects continuing in a new Novo Nordisk trial receiving Norditropin® or somapacitan.
Section 5.4 Scientific rationale for the trial	Deletion of duplicate text in section 5.4.	Editorial change to delete duplicate text.
7.1 Treatments administered 7.7 Concomitant medication Appendix 9 Country-specific requirements	Somapacitan can be dosed the day ahead of dosing day. Additional information for France added about concomitant medication.	Clarification of dosing requirements and implementation of country-specific requirements.

7.6 Treatment compliance	Additional details for treatment compliance.	Clarification of Investigator responsibilities with regards to treatment compliance.
9.4.1 Physical Examination Appendix 9 Country-specific requirements	Additional details for US: Fundoscopic exam being part of physical examination.	Clarification of physical eye examination.
Appendix 2 Clinical laboratory tests	Correction of blood draw volumes at certain visits.	Done to reflect up to date actual blood draws.
Appendix 3 Trial governance considerations	Deletion of the section about long term storage of human samples.	Samples for long-term storage are not collected in this trial.
Section 9.1.2 CCI [redacted] Appendix 9 Country-specific requirements	CCI [redacted]	CCI [redacted]
1. Synopsis 4.3.2.3 Effect 10.3.2 Main period 10.3.5 Other analyses	Alignment between section 1, 4.3.2.3, 10.3.2 and 10.3.5.	Clarification of secondary endpoints and statistical analyses hereof.
Appendix 9 Country-specific requirements	Editorial changes in order of presentation.	To clarify which country specific requirements are for France only.

Protocol amendment 3, applicable for US (16 September 2019)

CCI [redacted],
CCI [redacted].

CCI

[redacted]

Protocol version 4.0 (12-Dec-2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rational for preparing protocol, version 4.0:

The overall rationale for amending the protocol is to add a 4 year safety extension period to the original 1 year trial in order to evaluate the long-term safety of somapacitan in children with short stature born small for gestational age (SGA) with no catch-up growth by 2 years of age or older.

Section # and name	Description of change	Brief rationale
1 Synopsis	Addition of extension II period to overall trial design.	To evaluate long term safety.
2 Flowchart	Update to flowchart to reflect that visit 8 is no longer the end of treatment visit. Addition of the following: • Visits for extension II period • Assessments for date of menarche and pregnancy test, if applicable • PRO questionnaire • Footnotes added. Footnote “e” editorial change. Minor editorial changes made.	To reflect the updated trial design. Correction of typo.
3.3 Benefit-risk assessment	Addition of description that all subjects will receive somapacitan during the trial.	To reflect the updated trial design.

	Inclusion of frequency of ECGs.	
4.3.3 Exploratory endpoints	Addition of exploratory endpoint: GH-PPQ.	To assess patient preferences for subjects that change treatment from Norditropin® to somapacitan.
5.1. Overall design	Addition of extension II period to overall trial design.	To evaluate long term safety.
5.2 CCI [redacted] CCI [redacted]	CCI [redacted]	CCI [redacted]
5.4 Scientific rationale for trial design	Addition of rationale for extension II trial design.	To justify the updated trial design.
5.5 CCI [redacted]	Addition of description of the dose in the extension II period.	To reflect the updated trial design.
7.1. Treatments administered	Addition of description that investigators must document that directions for use are provided to subjects that switch from Norditropin® to somapacitan treatment.	To reflect the updated trial design.
7.2 Dose modification	Addition of description that dose modification is not allowed.	To clarify that no modification is allowed.
8.1 Discontinuation of trial treatment	Addition of discontinuation criteria. Update to description of follow-up visit and treatment discontinuation.	Due to the possibility that enrolled subjects could become of childbearing/reproductive potential during the trial. To reflect the updated trial design.
8.2 Withdrawal from the trial	Update to discontinuation visit number according to updated trial design.	To reflect the updated trial design

8.3 Lost to follow-up	Minor editorial changes made.	To improve readability.
9.1.2 Pubertal status	Inclusion of additional information about pubertal status and contraceptive guidance.	Due to the possibility that enrolled subjects could become of childbearing/reproductive potential during the trial.
9.1.4 Patient reported outcome questionnaire	Inclusion of patient reported outcome questionnaire.	To assess patient preferences for subjects that change treatment from Norditropin® to somapacitan.
9.2.7 Pregnancies and associated adverse events	Inclusion of information on pregnancies and associated adverse events.	Due to the possibility that enrolled subjects could become of childbearing/reproductive potential during the trial.
10.2 Definition of analysis set	Update to section to align with updated trial design.	To reflect the updated trial design.
10.3.3 Exploratory endpoints	Addition of exploratory endpoint: GH-PPQ	To assess patient preferences for subjects that change treatment from Norditropin® to somapacitan.
10.3.4 Reporting of the main part of the trial	Update to section to align with updated trial design.	To reflect the updated trial design.
10.3.5 Other analysis	Update to section to describe other analysis of data from extension II period.	To clarify the other analysis of data from extension II period.
Appendix I Abbreviations and Trademarks	Addition of Patient Reported Outcome Questionnaire.	To include all abbreviations
Appendix 2 Clinical laboratory tests	Update to Table 5 to include approximate blood volumes during extension II period. Update to Table 7 to include pregnancy testing, if applicable. Update to Table 8 to include timing of visits and blood	To reflect the updated trial design. Due to the possibility that enrolled subjects could become pregnant during the trial. To reflect the updated trial design.

	sampling during extension II period.	
Appendix 3 Trial governance consideration	Addition of pregnancy forms as CRFs.	Due to the possibility that enrolled subjects could become pregnant during the trial.
Appendix 5 Contraceptive guidance and collection of pregnancy information	Addition of contraceptive guidance and collection of pregnancy information.	Due to the possibility that enrolled subjects could become of childbearing/reproductive potential during the trial.
Appendix 9 Country specific requirements	Addition of country specific requirements about contraception and pregnancy for Algeria, Austria, Estonia, Ireland, Latvia, Norway and Spain. Relocation of country specific section for France on Contraceptive guidance and collection of pregnancy information to appendix 5.	To comply with country specific requirements. Due to applicability for all countries.

Protocol version 5.0 (09-Mar-2020)

CCI [redacted]

Sections # and name	Description of change	Brief rationale
6.1 Inclusion criteria	CCI [redacted]	CCI [redacted]
6.2 Exclusion criteria	CCI [redacted]	CCI [redacted]

Appendix 9	CCI [redacted]	CCI [redacted]

Protocol version 6.0 (06-Apr-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rational for preparing protocol, version 6.0:

CCI [redacted]

Section # and name	Description of change	Brief rationale
2 Flowchart	Reference to Appendix 9 for country-specific requirements for Spain.	CCI [redacted]
6.1 Inclusion criteria	Reference to Appendix 9 for country-specific requirements for Israel.	CCI [redacted]

6.2 Exclusion criteria	Reference to Appendix 9 for country-specific requirements for Spain.	CCI [redacted]
Appendix 5	Reference to Appendix 9 for country-specific requirements for Italy.	CCI [redacted]
Appendix 9	Inclusion criteria 3: The first length measured and recorded within 65 days after birth can be used as birth length to assess inclusion criteria 3.	In Israel length is rarely being measured at birth: The length is measured when children are 1 or 2 months of age in accordance with: “Guidelines for approval of reimbursement of Growth hormone treatment in children as part of the national health basket”. The Israeli Medical Association, the institute of quality in medicine-Jan 2016. These guidelines are used when the child starts the endocrine assessment regarding growth delay.
Appendix 9	CCI [redacted]	CCI [redacted]
Appendix 9	CCI [redacted]	CCI [redacted]

16.1.01 Statement Attachment I and II

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff.