Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03811535
Sponsor trial ID:	NN8640-4263
Official title of study:	A Trial Comparing the Effect and Safety of Once Weekly Dosing of Somapacitan With Daily Norditropin® in Children With Growth Hormone Deficiency
Document date:	22 February 2021

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of 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 personal identifiable information only.

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Protocol

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

Substance: somapacitan

Universal Trial Number: U1111-1207-9691

EUdraCT Number: 2018-000231-27

Trial phase: 3a

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 country(-ies) and/or site(s)
Protocol version 7.0	22 February 2021	All
Protocol version 6.0	31 March 2020	Spain
Protocol version 5.0	03 January 2020	Hungary
Protocol version 4.0	19 November 2019	Estonia
Protocol version 3.0	01 July 2019	All
Protocol version 2.0	16 November 2018	All
Original protocol, version 1.0	29 June 2018	All

Protocol version 7.0 (22 February 2021)

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 rationale for preparing protocol version 7.0:

Novo Nordisk would like to additionally test for superiority of somapacitan versus Norditropin® for height velocity (HV) from baseline (week 0) to visit 7 (week 52) (primary endpoint), in case non-inferiority of somapacitan versus Norditropin® for the primary endpoint has been confirmed. Furthermore, some secondary endpoints for effect has been removed, as they are not found relevant in the single-arm extension period of the trial.

Section # and name	Description of change	Rationale
Section 1 Synopsis, Key secondary endpoints, Effect	Alignment with adjustments in section 3.6.2.3	In alignment with rationale for change in section 3.6.2.3
Section 3.6.2.3 Effect	The time frames for secondary endpoints for effect has been adjusted. The following time frames are removed: From screening (visit 1) to visit 11 (week 104) From screening (visit 1) to visit 15 (week 156)	The secondary endpoints for effect are not found relevant in the single-arm extension period of the trial.

	From screening (visit 1) to visit 19 (week 208)	
Section 9.3 Statistical analysis	Additional test for superiority of somapacitan versus Norditropin®, in case non-inferiority for the primary endpoint has been confirmed, is described	Novo Nordisk would like to additionally test for superiority of somapacitan versus Norditropin®, in case non-inferiority of somapacitan versus Norditropin® for the primary endpoint has been confirmed. The superiority hypothesis is based on results from the phase 2 trial NN8640-4172 where observed mean HV was greater in the somapacitan 0.16 mg/kg/week group compared to the Norditropin group (11.5 cm versus 9.8 cm after 52 weeks). Observed mean annual HV was also greater for patients treated with somapacitan compared to Norditropin at year 2 and year 3 (preliminary results) which further supports the superiority hypothesis.
Appendix 5	Reference to Appendix 9 for Austria added to 'Pregnancy testing' section	In alignment with Appendix 9 and requirements from health authorities in Austria
Appendix 9	Year of birth collection requirement added to Appendix 9 for Hungary	Requirement from health authorities in Hungary

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1 Synopsis

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

Objectives and endpoints

Primary objective
To compare the effect of somapacitan vs Norditropin® on longitudinal growth in children with growth hormone deficiency.

Primary endpoint

Endpoint title	Time frame	Unit
Height velocity	From baseline (week 0) to visit 7 (week 52)	cm/year

Secondary objective
To compare the safety of somapacitan vs Norditropin® in children with growth hormone deficiency.

Key secondary endpoints
Effect:

Endpoint title	Time frame	Unit
Change in bone age	From screening (visit 1) to visit 7 (week 52)	Years
Change in Height Standard Deviation Score	From baseline (week 0) to visit 7 (week 52)	-10 to +10
Change in Height Velocity Standard Deviation Score	From baseline (week 0) to visit 7 (week 52)	-10 to +10

Safety:

Endpoint title	Time frame	Unit
Change in fasting plasma glucose	From screening (visit 1) to visit 7 (week 52) From screening (visit 1) to visit 11 (week 104) From screening (visit 1) to visit 15 (week 156) From screening (visit 1) to visit 19 (week 208)	mmol/L

Change in homeostatic model assessment	From screening (visit 1) to visit 7 (week 52) From screening (visit 1) to visit 11 (week 104) From screening (visit 1) to visit 15 (week 156) From screening (visit 1) to visit 19 (week 208)	%
Change in Glycated haemoglobin (HbA1c)	From screening (visit 1) to visit 7 (week 52) From screening (visit 1) to visit 11 (week 104) From screening (visit 1) to visit 15 (week 156) From screening (visit 1) to visit 19 (week 208)	% point

Pharmacodynamics:

Endpoint title	Time frame	Unit
Change in Insulin-like growth factor I (IGF-I) Standard Deviation Score	From baseline (week 0) to visit 7 (week 52) From baseline (week 0) to visit 11 (week 104) From baseline (week 0) to visit 15 (week 156) From baseline (week 0) to visit 19 (week 208)	-10 to +10
Change in Insulin-like growth factor binding protein 3 (IGFBP-3) Standard Deviation Score	From baseline (week 0) to visit 7 (week 52) From baseline (week 0) to visit 11 (week 104) From baseline (week 0) to visit 15 (week 156) From baseline (week 0) to visit 19 (week 208)	-10 to +10

Estimands

Differing feedback on the primary estimand from the Health Authorities at End of phase 2 has resulted in establishing distinct estimand strategies for FDA and EMA: one based on the treatment policy strategy (FDAs recommendation) and one based on the hypothetical strategy (EMAs recommendation).

Primary estimand (FDA and PMDA)

Treatment policy strategy: The treatment difference between somapacitan and Norditropin® in mean annualised height velocity at week 52 for all randomised subjects regardless of treatment adherence or initiation of ancillary therapy in children with growth hormone deficiency.

The estimand assesses the expected benefit a future paediatric population with Growth Hormone Deficiency can achieve if prescribed somapacitan as compared to Norditropin®. By not placing any restrictions on treatment adherence, this estimand aims to obtain a difference as close as possible to the one that can be expected in clinical practice, provided that the treatment adherence and use of ancillary therapy in trial reflects what would be seen in clinical practice.

Primary estimand (EMA)
Hypothetical strategy - ancillary therapy not available: The treatment difference between somapacitan and Norditropin® in mean annualised height velocity at week 52 if ancillary therapy had not been available prior to week 52 (i.e. assuming no initiation of ancillary therapy) in children with growth hormone deficiency.

The hypothetical strategy based estimand is expected to minimise potential confounding from use of ancillary therapy such as other Growth Hormone products when assessing the treatment effect on longitudinal growth. The use of ancillary therapy may lead to attenuation of the treatment effect of interest or even exaggerate the treatment effect and the estimand, thus aims to reflect the treatment difference attributable to the initially randomised treatments.

Overall design:
A randomised open-labelled two arm (somapacitan and Norditropin®) trial designed to compare the effect and safety of once weekly dosing of somapacitan with daily dosing of Norditropin® after 52 weeks in children with growth hormone deficiency followed by a 3 years single-arm extension period with once weekly dosing of somapacitan to evaluate safety.
The randomisation will be stratified by region (Japan versus rest-of-the-world) as well as age group (< 6 versus ≥ 6 years at randomisation), gender (boys versus girls) and growth hormone peak level (< 7.0 versus ≥ 7.0 ng/ml) to ensure equal distribution of these factor levels across treatments.

Key Inclusion criteria

- Prepubertal children:
  a) Boys:
     - Age ≥ 2 years and 26 weeks and < 11.0 years at screening
     - Testis 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)
- Confirmed diagnosis of growth hormone deficiency determined by two different growth hormone stimulation tests performed within 12 months prior to randomisation, defined as a peak growth hormone level of ≤ 10.0 ng/ml using the WHO International Somatropin 98/574 standard
- Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and gender at screening according to the standards of Center for Disease Control and Prevention
- Impaired height velocity, defined as annualised height velocity below the 25th 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
- Insulin-like Growth Factor-I < -1.0 Standard Deviation Score at screening, compared to age and gender normalized range measured at central laboratory

- 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
- 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
- Diagnosis of attention deficit hyperactivity disorder
- 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
- Prior history or presence of malignancy including intracranial tumours

Number of subjects:
Approximately 192 subjects will be randomly assigned to trial product.

Treatment groups and duration:
Duration of treatment will be 208 weeks (4 years).
The following trial products will be supplied by Novo Nordisk A/S:

- somapacitan 5 mg/1.5 ml in prefilled PDS290 pen-injector
- somapacitan 10 mg/1.5 ml in prefilled PDS290 pen-injector
- somapacitan 15 mg/1.5 ml in prefilled PDS290 pen-injector
- Norditropin® FlexPro® 10 mg/1.5 ml pen-injector

The trial products will be administered subcutaneously.

2 Flowchart

	Protocol section	Information	Screening	Randomisation	Main phase					Extension phase											End of treatment	Discontinuation of trial product	Follow-up
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 19A	Phone Visit 20[b]
Timing of Visit (weeks)			-2	0	4+1d	13	26 +1d	39	**52+5d**	65	78+1d	91	104	117	130+1d	143	156	169	182+1d	195	208		208 +30d
Visit Window (Days)		minimum 1 day prior to visit 1	±7		+3	±7	+3	±7	**±1**	±7	+3	±7	±7	±7	+3	±7	±7	±7	+3	±7	±7		+5
SUBJECT RELATED INFORMATION AND ASSESSMENTS																							
Informed consent	6 1	X																					
Child assent	6 1	X																					
Genetic consent	Appendix 8	X																					
Inclusion/Exclusion criteria	6 1 6 2		X	X																			
Discontinuation /Withdrawal criteria	8 1 8 2				X	X	X	X	**X**	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography[c]	2		X																				
Randomisation	7 3			X																			

	Protocol section	Information	Screening	Randomisation	Main phase					Extension phase										End of treatment	Discontinuation of trial product	Follow-up
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 19A	Phone Visit 20[b]
Timing of Visit (weeks)			-2	0	4+1d	13	26 +1d	39	**52+5d**	65	78+1d	91	104	117	130+1d	143	156	169	182+1d	195	208		208 +30d
Visit Window (Days)		minimum 1 day prior to visit 1	±7		+3	±7	+3	±7	**±1**	±7	+3	±7	±7	±7	+3	±7	±7	±7	+3	±7	±7		+5
Pregnancy test	Appendix 5 Appendix 2 Appendix 9Appendix 9				X	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		X	X	
Date of menarche	9 1 2				X	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 4		X						**X**				X				X				X	X[d]	
Body measurements	9 1 1		X	X	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height			X	X		X	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Weight			X	X	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body composition			X						X				X				X				X	X[d]	
Pharmacodynamics	9 6																						
IGFBP-3			X	X	X	X	X	X	**X**		X		X		X		X		X		X	X	
IGF-I			X	X	X	X	X	X	**X**		X		X		X		X		X		X	X	
PK	9 5 Table 7			X	X	X	X	X	**X**		X		X		X		X		X		X	X	
Patient reported outcome questionnaires	9 1 5			X			X		**X**														

	Protocol section	Information	Screening	Randomisation	Main phase					Extension phase										End of treatment	Discontinuation of trial product	Follow-up
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 19A	Phone Visit 20[b]
Timing of Visit (weeks)			-2	0	4+1d	13	26 +1d	39	**52+5d**	65	78+1d	91	104	117	130+1d	143	156	169	182+1d	195	208		208 +30d
Visit Window (Days)		minimum 1 day prior to visit 1	±7		+3	±7	+3	±7	**±1**	±7	+3	±7	±7	±7	+3	±7	±7	±7	+3	±7	±7		+5
SAFETY																							
Physical examination	9 4 1		X				X		**X**		X		X		X		X		X		X	X	
Vital signs	9 4 2		X				X		**X**		X		X		X		X		X		X	X	
ECG	9 4 3		X						**X**				X				X				X	X[d]	
Haematology	Appendix 2		X				X		**X**		X		X		X		X		X		X	X	
Biochemistry	Appendix 2			X			X		**X**		X		X		X		X		X		X	X	
Glucose metabolism	Appendix 2		X				X		**X**		X		X		X		X		X		X	X	
Lipids	Appendix 2			X			X		**X**				X				X				X	X	
Hormones	Appendix 2		X				X		**X**				X				X				X	X	
Antibodies	9 4 6 Table 7			X		X			**X**		X		X				X				X	X	
Adverse event	9 2 Appendix 4		X	X	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reaction	Appendix 4			X	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Protocol section	Information	Screening	Randomisation	Main phase					Extension phase										End of treatment	Discontinuation of trial product	Follow-up
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 19A	Phone Visit 20[b]
Timing of Visit (weeks)			-2	0	4+1d	13	26 +1d	39	**52+5d**	65	78+1d	91	104	117	130+1d	143	156	169	182+1d	195	208		208 +30d
Visit Window (Days)		minimum 1 day prior to visit 1	±7		+3	±7	+3	±7	**±1**	±7	+3	±7	±7	±7	+3	±7	±7	±7	+3	±7	±7		+5
Technical complaint	9 2 8			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication errors	9 2 1			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TRIAL MATERIAL																							
Drug accountability	7 5			X	X	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**[e]	X	X	X	X	X	X	X	X	X	X	X			
IWRS session			X	X	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																							
Genetic sampling	9 7 Appendix 8			X																			
Ensure that MRI/CT scan is available	9 4 4		X																		X[f]	X[f]	
Attend visit fasting	6 3 1		X				X		**X**		X		X		X		X		X		X	X	
Handout ID card	9		X																				
Training in trial product and pen handling	7 1 1			X			X		**X**[e]				X				X						
Hand out directions for use	7 1			X					**(X)**[e]														
Handout and instruct in e-diary	7 2 2			X																			
Diary review	7 6				X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	
Return e-diary																					X	(X)	

	Protocol section	Information	Screening	Randomisation	Main phase					Extension phase											End of treatment	Discontinuation of trial product	Follow-up
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 19A	Phone Visit 20[b]
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Visit Window (Days)		minimum 1 day prior to visit 1	±7		+3	±7	+3	±7	**±1**	±7	+3	±7	±7	±7	+3	±7	±7	±7	+3	±7	±7		+5
End of treatment	7 8 8																				X	(X)	
End of trial	5 2 8																						X

[a]Landmark visit (collection of primary endpoint data)
[b]The follow-up visit should also be performed after Visit 19A for subjects who discontinue treatment. The Follow-up visit can be performed as a phone visit.
[c] Demography consists of date of birth, sex, ethnicity and race (according to local regulation, for Spain, please refer to Appendix 9)
[d]Not to be done if performed within the last 6 months
[e]Subjects on Norditropin® will be switched to somapacitan
[f]Only applicable for subjects in France. Not to be done if performed within the last 6 months

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

The trial is a randomised, multinational, multi-centre, open labelled, and 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 GHD aims to induce growth, increase height velocity (HV) and improve final adult height.

3.2 Background

3.2.1 Growth hormone deficiency

GH is essential for normal longitudinal growth in children and acts partly by direct action on the growth plates and partly by stimulation of insulin-like growth factor-I (IGF-I) release [2]. 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[3].
Rapid proteolysis and ligand-receptor internalisation result in a short half-life for human growth hormone (hGH).
Consequently, hGH is given as daily injections. Children and adults with GHD currently require many years or lifelong treatment with a daily s.c injection regimen. Studies investigating treatment adherence have shown that approximately one-fourth of children on GH treatment misses more than two of the seven injections per week[4-6].

GHD may occur as an isolated hormonal deficiency or in combination with multiple pituitary hormone deficiencies. It may result from congenital, genetic, acquired (by tumours in the central nervous system, cranial irradiation, head trauma or other organic causes) or idiopathic causes. Idiopathic GHD is the most common form, accounting for approximately 75% of diagnosed patients[7].

GHD in children is characterised by a reduced HV and a markedly reduced final adult height compared to the predicted height based on mid-parental height. Normal growth can be restored with GH replacement therapy[7]. The treatment for GHD in children is the same whether the cause is congenital, genetic, acquired or idiopathic[7-9]. GHD may be present already at birth but is generally first discovered within the first years of childhood.

Experience gained during the last 15-20 years shows that GH treatment is also effective in restoring normal growth in children with other forms of growth retardation, including Turner and Noonan

syndromes, children with chronic renal failure and children born small for gestational age with insufficient catch up growth [9, 10].

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 [11]. 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 is evaluated as 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[12].

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 Investigator Brochure (IB)[12].

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[12].

3.2.5 Norditropin®

For information please refer to the IB[13].

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[12] 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.

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, body measurements and Tanner pubertal staging: No risks are expected to be associated with standard physical examination. Burden (embarrassment, discomfort, distress) associated with examinations that are related to sexual development (e.g., Tanner staging) can be expected. As this assessment is performed by paediatricians familiar with the population the burden is expected to be low.

Computerised tomography (CT) scan: Risks are related to the total dose of radiation received from the scan (possibly contributing to tissue damage, mutations and cancer) and to allergy / anaphylaxis with contrast agents. Burdens may include discomfort, fear, pain in case of contrast agent injection and need for specialised setting. The burden of this assessment is reduced by the possibility of using CT scans performed up to nine months prior to screening as part of local clinical practice. The investigator will decide if a CT scan or MRI will be performed.

Magnetic resonance imaging (MRI): Risks include those related to contrast agents, such as nausea, hypersensitivity reactions and accumulation and functional impact of contrast agents in several organs. Burdens may include discomfort, claustrophobia, fear, pain from venepuncture and heat sensation in case of contrast agent injection and need for specialised setting. The burden of this assessment is reduced by the possibility of using a MRI performed up to nine months prior to screening as part of local clinical practice. The investigator will decide if a CT scan or MRI will be performed.

X-Ray for bone age assessment: No risks are expected to be associated with the procedure. The risks are 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.

ECG: The procedure involves placing adhesive skin surface electrodes on the body. This procedure does not incur any risks. Burdens may include discomfort and fear. Electrocardiograms (ECGs) are collected at screening and every 12th 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.

GH stimulation tests: Risks are related to peripheral venepuncture, fasting prior to blood sampling and reactions to the stimulating agent. To reduce the burden the investigator should select the stimulation test most suitable for the subject's age. Results of stimulation tests performed as part of clinical practice can be used as screening data and do not need to be repeated.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of somapacitan may be found in the investigator's brochure for somapacitan[12].

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Norditropin® can be found in the investigator's brochure for Norditropin®[13].

4 Objectives and endpoints

4.1 Primary and secondary objectives

4.1.1 Primary objective

To compare the effect of somapacitan vs Norditropin® on longitudinal growth in children with growth hormone deficiency.

4.1.2 Secondary objective

To compare the safety of somapacitan vs Norditropin® in children with growth hormone deficiency.

4.2 Estimands

Differing feedback on the primary estimand from the Health Authorities at End of phase 2 has resulted in establishing distinct estimand strategies for FDA and EMA: one based on the treatment policy strategy (FDAs recommendation) and one based on the hypothetical strategy (EMAs recommendation).

4.2.1 Primary estimand (FDA and PMDA)

Treatment policy strategy: The treatment difference between somapacitan and Norditropin® in mean annualised HV at week 52 for all randomised subjects regardless of treatment adherence or initiation of ancillary therapy in children with GHD.

The estimand assesses the expected benefit a future paediatric population with GHD can achieve if prescribed somapacitan as compared to Norditropin®. By not placing any restrictions on treatment adherence, this estimand aims to obtain a difference as close as possible to the one that can be expected in clinical practice, provided that the treatment adherence and use of ancillary therapy in trial reflects what would be seen in clinical practice.

4.2.2 Primary estimand (EMA)

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

The hypothetical strategy based estimand is expected to minimise potential confounding from use of ancillary therapy such as other GH products when assessing the treatment effect on longitudinal growth. The use of ancillary therapy may lead to attenuation of the treatment effect of interest or even exaggerate the treatment effect and the estimand, thus aims to reflect the treatment difference attributable to the initially randomised treatments.

4.3 Primary, secondary and exploratory endpoints

4.3.1 Primary endpoint

Endpoint title	Time frame	Unit

Height velocity	From baseline (week 0) to visit 7 (week 52)	cm/year

4.3.2 Secondary endpoints

4.3.2.1 Confirmatory secondary endpoints

N/A

4.3.2.2 Supportive secondary endpoints

4.3.2.3 Effect

Endpoint title	Time frame	Unit
Change in bone age	From screening (visit 1) to visit 7 (week 52)	Years
Change in Height Standard Deviation Score	From baseline (week 0) to visit 7 (week 52)	-10 to +10
Change in Height Velocity SDS	From baseline (week 0) to visit 7 (week 52)	-10 to +10

4.3.2.4 Safety

Endpoint title	Time frame	Unit
Change in fasting plasma glucose	From screening (visit 1) to visit 7 (week 52) From screening (visit 1) to visit 11 (week 104) From screening (visit 1) to visit 15 (week 156) From screening (visit 1) to visit 19 (week 208)	mmol/L
Change in homeostatic model assessment (HOMA)	From screening (visit 1) to visit 7 (week 52) From screening (visit 1) to visit 11 (week 104) From screening (visit 1) to visit 15 (week 156) From screening (visit 1) to visit 19 (week 208)	%
Change in Glycated haemoglobin (HbA1c)	From screening (visit 1) to visit 7 (week 52) From screening (visit 1) to visit 11 (week 104)	% point

	From screening (visit 1) to visit 15 (week 156) From screening (visit 1) to visit 19 (week 208)	

4.3.2.5 Pharmacodynamics

Endpoint title	Time frame	Unit
Change in IGF-I SDS	From baseline (week 0) to visit 7 (week 52) From baseline (week 0) to visit 11 (week 104) From baseline (week 0) to visit 15 (week 156) From baseline (week 0) to visit 19 (week 208)	-10 to +10
Change in IGFBP-3 SDS	From baseline (week 0) to visit 7 (week 52) From baseline (week 0) to visit 11 (week 104) From baseline (week 0) to visit 15 (week 156) From baseline (week 0) to visit 19 (week 208)	-10 to +10

4.3.3 Exploratory endpoints

Score of patient reported outcome (PRO) questionnaires:

Endpoint title	Time frame	Unit
Treatment Burden Measure-Child GHD- Observer (TB-CGHD-O)	At visit 5 (week 26) At visit 7 (week 52)	0 to 100
Treatment Burden Measure-Child GHD- Parent (TB-CGHD-P)	At visit 5 (week 26) At visit 7 (week 52)	0 to 100
Growth Hormone Device Assessment Tool (G-DAT)	At visit 5 (week 26)	Count of answers
Change in Treatment Related Impact measure-Child-Growth Hormone Deficiency-Observer TRIM-CGHD-O (total and domain scores)	From baseline (week 0) to visit 5 (week 26) From baseline (week 0) to visit 7 (week 52)	-100 to 100

For subjects switching from Norditropin® to somapacitan

Endpoint title	*Time frame*	*Unit*
Growth Hormone Patient Preference Questionnaire (PPQ)	At week 56	Count of subjects choosing the individual response category.

5 Trial design

5.1 Overall design

A randomised open-labelled two arm (somapacitan and Norditropin®) trial designed to compare the effect and safety of once weekly dosing of somapacitan with daily dosing of Norditropin® after 52 weeks in children with growth hormone deficiency followed by a 3 year single-arm extension period with once weekly dosing of somapacitan to evaluate safety. The randomisation will be stratified by region (Japan versus rest-of-the-world) as well as age group (< 6 versus ≥ 6 years at randomisation), gender (boys versus girls) and growth hormone peak level (< 7.0 versus ≥ 7.0 ng/ml) to ensure equal distribution of these factor levels across treatments.

The total trial duration for a subject will be 4 years.

Eligible subjects will be randomised in a 2:1 manner to receive either somapacitan (2 out of 3 subjects) or Norditropin® (1 out of 3 subjects).

The follow-up period is a minimum of 30 days.

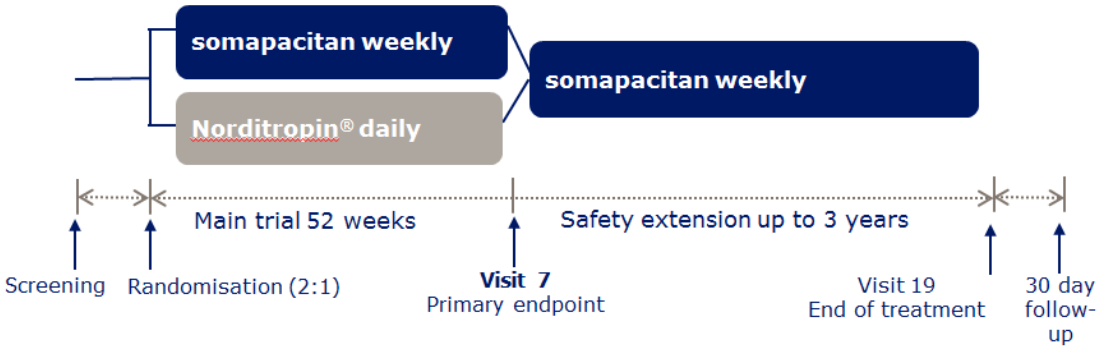

Figure 1 Trial design

5.2 Subject and trial completion

Approximately 192 subjects will be randomly assigned to trial product. For sample size determination see 10.1.

Trial period completion for a subject:
Trial period completion is defined as when the randomised subject has completed the final scheduled visit ('end of trial' according to the flowchart 2).
Date of trial completion is the date the subject completed the final scheduled visit.

Visit 7 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

Sensitivity to GH treatment is higher in GH deficient than non GH deficient conditions, therefore treatment-naïve children with GHD are considered a sensitive population and are also a well-known model for evaluating the primary endpoint; HV (cm/year) during first 52-weeks[14]. Only prepubertal children will be enrolled to minimize interference of the pubertal growth spurt with the treatment effect of GH. Some of the subjects may enter puberty during the trial however age and gender stratification will ensure that children who enter puberty during the main phase will be randomly distributed between the two 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.

No placebo-controlled GHD trial results are available to be used for supporting the choice of a non-inferiority margin for this GHD trial.
It has therefore been necessary to look for results in a related indication: paediatric patients with SGA.
In a Norditropin® trial in paediatric patients with SGA (GHLIQUID-1424)[15], the estimated treatment effect in delta height (change from baseline) for Norditropin® vs no treatment at 1 year was 3.3 cm [2.9; 3.7] for 0.033 mg/kg/day and 6.5 cm [6.0; 6.9] for 0.100 mg/kg/day of Norditropin®, respectively. This gives some indication that the expected effect of Norditropin® versus placebo would be well approximated by the 3.3 cm/year observed in trial GHLIQUID-1424 for SGA.
The observed mean values (SD) from the daily rhGH comparator in a pivotal phase 3 GHD trial[15] were 2.93 (1.09) cm/year at baseline and 11.97 (3.09) cm/year after 1 year. This large difference between baseline and 1 year HV data makes a hypothesized difference in HV after 1 year between a GH treatment arm and a no treatment arm of 4 cm/year in GHD not unreasonable in a pre-pubertal population as spontaneous HV as a function of age is expected to be approximately constant until the start of the pubertal growth spurt, while still allowing for a substantial trial effect impacting the change from baseline result. The 3.3 cm/year may therefore be viewed as a conservative approximation of the treatment effect vs no treatment in GHD. By using a non-inferiority margin of -1.8 cm/year, an improvement of at least 1.5 cm against no GH treatment would be expected to be preserved after the first year.

5.5 Justification for dose

The dose used for Norditropin® in the trial is 0.034 mg/kg/day, which is within label.

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

Norditropin®. The mean IGF-I SDS levels of the somapacitan 0.16 mg/kg/week dose were comparable to the mean IGF-I SDS level of Norditropin® (0.034 mg/kg/ day), and for the somapacitan 0.16 mg/kg/week dose the population mean for the IGF-I average was 0.5 SDS with a 90% range below 2.0 SDS.

Somapacitan will be administered once weekly and Norditropin® will be administered once daily. A fixed body weight based regimen is chosen as it is standard practise for GH treatment in most countries. Dosing of daily Norditropin® in this trial design is similar to the dosing used in the phase 2 dose finding trial in prepubertal, GH treatment naïve children with GHD.

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.

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. Prepubertal children:
   a) Boys:
      - Age ≥ 2 years and 26 weeks and < 11.0 years at screening
      - Testis volume < 4 ml[16].
   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)[16]

3. Confirmed diagnosis of growth hormone deficiency determined by two different growth hormone stimulation tests performed within 12 months prior to randomisation, defined as a peak growth hormone level of ≤ 10.0 ng/ml using the WHO International Somatropin 98/574 standard
   a) If only one growth hormone stimulation test is available before screening, then confirmation of growth hormone deficiency by second and different growth hormone stimulation test must be done
   b) For children with at least 2 additional pituitary hormone deficiencies (other than growth hormone deficiency) only one growth hormone stimulation test is needed

   For Japan: see Appendix 9

4. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and gender at screening according to the standards of Center for Disease Control and Prevention[17]

5. Impaired height velocity, defined as annualised height velocity below the 25th percentile for chronological age and gender according to the standards of Prader[18] 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. Bone age less than chronological age at screening

8. Body Mass Index >5th and <95th percentile according to Center for Disease Control and Prevention[17], Body Mass Index-for-age growth charts

9. IGF-I < -1.0 SDS at screening, compared to age and gender normalized range measured at central laboratory

10. Hormone replacement therapies for any other hormone deficiency should be adequate and stable for at least 90 days prior to randomisation

11. No intracranial tumour confirmed by magnetic resonance imaging or computer tomography scan. An image or scan taken within 9 months prior to screening can be used as screening data if the medical evaluation and conclusion is available

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

5. Children born small for gestational age (birth weight and/or birth length < -2 SDS for gestational age according to national standards)

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) $HbA_{1c} \geq 6.5$ %

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 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.

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 1 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	Daily
Packaging	PDS290 somapacitan pen-injector	Norditropin® FlexPro® pen-injector

The investigator must document that directions for use are given to the subject in writing at the first dispensing visit and when a subject change treatment from Norditropin® to somapacitan.

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 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-somapacitan antibodies 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 anti-hGH antibodies must occur at least 12 hours prior to planned blood sampling.
- If a subject randomised to Norditropin® forgets or is unable to inject the dose in the evening, the dose should be skipped. The subject should continue on the next evening with the next scheduled dose.

7.1.1 Medical devices

Information about the pre-filled PDS290 pen-injector can be found in the IB for somapacitan and any updates hereof[12].

Information about the use of the pre-filled PDS290 pen-injector for somapacitan can be found in the directions for use (DFU).

Information about the pre-filled Norditropin® FlexPro® can be found in the IB for Norditropin® and any updates hereof[13].

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

Training in the PDS290 somapacitan pen-injector and Norditropin® FlexPro®
The subjects must be trained according to the DFU in how to handle the PDS290 somapacitan pen-injector or Norditropin® FlexPro® when handed out the first time. Training must be repeated during the trial at regular intervals in order to ensure correct use of the PDS290 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 (thighs)
    - buttocks
    - upper arms
    - stomach area (abdomen)

7.2 Dose modification

The dose will be calculated 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.

For France: See Appendix 9

7.2.1 Dose reduction criteria

If adverse events with a probable relationship to the trial product are persistent but allow continuation in the trial, as judged by the investigator, dose reduction in consecutive steps of 25% of the current dose can be considered at the investigator's discretion. If after consecutive dose reduction steps AEs still persist, the subject's treatment may be discontinued according to treatment discontinuation (see Section 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.

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

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 stratification variables are:

- Region (Japan versus rest-of-the-world)
- Age (< 6 years versus ≥ 6 years at randomisation)
- Gender (boys versus girls)
- GH peak level (< 7.0 versus ≥ 7.0 ng/ml)

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 primary endpoint (visit 7).
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 investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- Drug accountability for somapacitan and Norditropin® is performed on a dispensing unit number (DUN) level using the IWRS drug accountability module to account for the status of each pen for each DUN.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- 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 patient, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use

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

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
- 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 trial phase (up to week 52) 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 product, either at the scheduled end of treatment visit or if trial product is discontinued, the subject should be transferred to a suitable marketed product at the discretion of the investigator.

If a subject discontinue 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 7 to collect the required data for the analysis of the primary endpoint. 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 IEC/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:

1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
4. 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 adverse events. For convenience of the subject the follow up visit can be performed as a telephone contact. The follow up visit should be performed as a site visit for subjects with an ongoing injection site reaction at visit 19. 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.

Trial product discontinuation prior to visit 7

If a subject discontinues treatment prior to visit 7, visit 19A 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 visit should be performed a minimum of 30 days after the last dose of trial product.

At visit 19A the following assessments are not applicable if performed within the last 6 months.

- X-ray for bone age assessment

- ECG
- Body composition

For France: See Appendix 9

Although the treatment has been discontinued, the subject should continue to follow the planned visit schedule until the landmark visit 7 (52 weeks) in order to collect data for the primary endpoint and should then be withdrawn.

If subject or family refuses to attend the planned visit schedule, then visit 7 is of utmost importance to attend. Visit 7 should be performed on planned visit date compared to baseline.

After visit 19A the following assessments are not applicable for subjects that discontinue trial product:

- Trial drug administration
- Drug accountability (when completed for the subject)
- PK sampling
- Collection of technical complaints
- Injection site reactions
- Medication errors
- PROs

Trial product discontinuation after visit 7

If a subject discontinues treatment after visit 7 the treatment discontinuation visit (Visit 19A) 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 visit should be performed a minimum 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 19A 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, PRO instruments, ECG, laboratory reports etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary or PRO instrument 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[19] 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 electronic CRF (eCRF).

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[16].

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 GH stimulation test

Subjects with two additional pituitary deficiencies other than GHD need one GH stimulation test to confirm GHD. All other subjects need two different GH stimulation tests to confirm GHD. As a minimum the first test should have been performed as part of clinical practice and the result must be available prior to screening and fulfil inclusion criterion 3 (see Section 6.1). The second stimulation test can be performed according to local practice between screening and randomisation. The result(s) must be available prior to randomisation in order to evaluate eligibility. The WHO International Somatropin 98/574 standard should be used to evaluate inclusion criterion 3 (see Section 6.1). If other standards similar to WHO International Somatropin 98/574 standard are used locally, this is acceptable.

9.1.4 X-ray for bone age assessment

X-rays of left hand and wrist for bone age assessment according to the Greulich and Pyle atlas[20] 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 screening data if the image is acquired according to the required standards defined by the central imaging laboratory and available to be sent to the central

imaging laboratory.
For Germany See Appendix 9

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

9.1.5 Patient reported outcome questionnaires

PRO questionnaires will be completed by the parent/LAR. The PROs should preferable be completed by the same parent/LAR.

- G-DAT
- TB-CGHD-O
- TB-CGHD-P
- TRIM-CGHD-O (only in countries were available)

For subjects who have changed treatment from Norditropin® to somapacitan at week 52.

- Growth hormone PPQ will be completed in the ediary at week 56.

For Estonia, Hungary, Ireland, Latvia, Norway, Poland, Serbia, Spain: See Appendix 9

9.1.6 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 medication errors observed during the trial. The relevant specific events are listed in Table 2 and the reporting timelines in Figure 2.

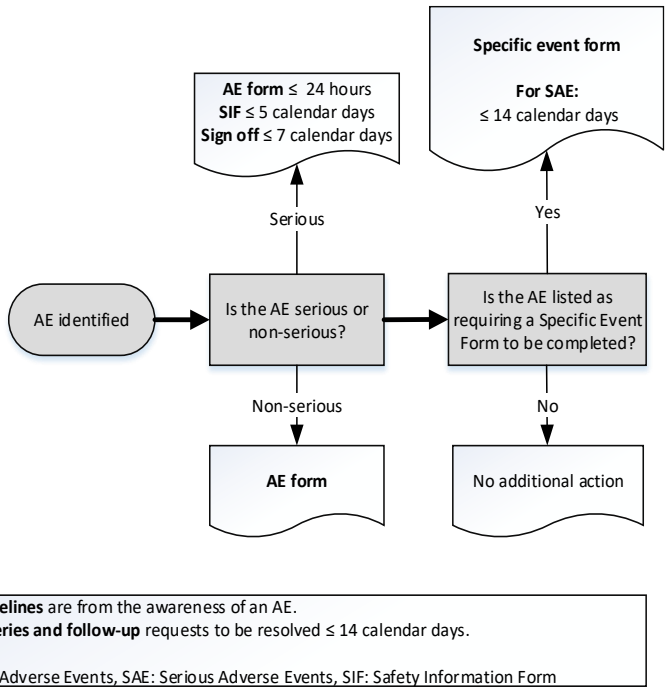

Figure 2 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 2 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 investigators discretion.

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 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 in 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.

9.2.7 Medical device incidents (including malfunctions)

Not applicable for this trial. Refer to technical complaints in section 9.2.8.

9.2.8 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.

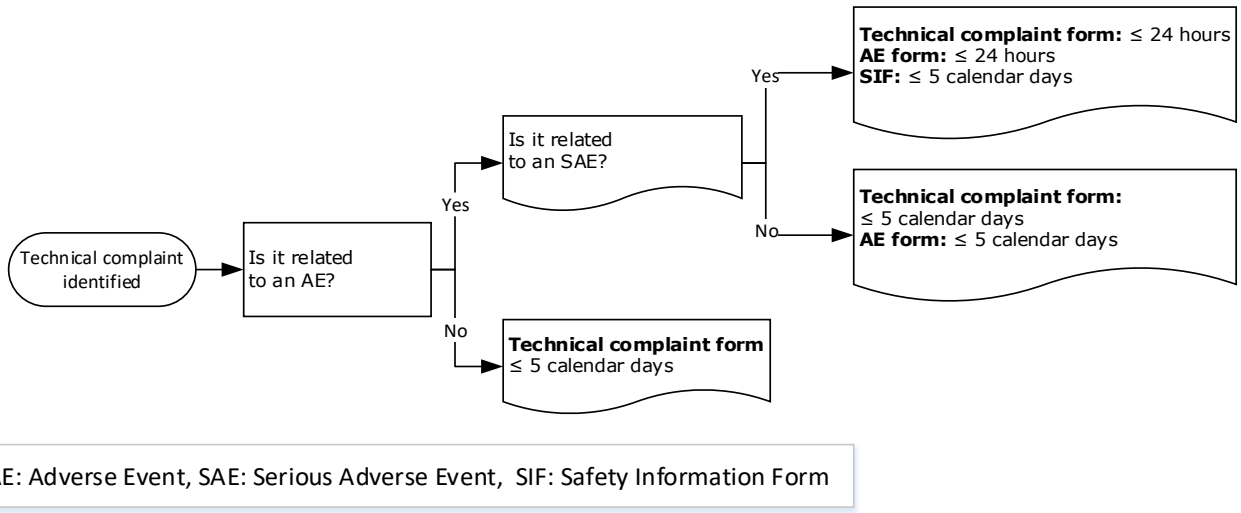

Figure 3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

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.

Accidential overdose 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[13].

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).

GHD history

- Type of GH stimulation tests and result of peak GH values

- Standing height measured minimum 6 and maximum 18 months prior to screening. 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 criterion 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.

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.

9.4.2 Vital signs

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 Electrocardiograms

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 of the trial, the finding will be recorded as a concomitant illness.
The ECG results must be dated and signed by the investigator to verify that the data have been reviewed.

9.4.4 MRI and CT scans

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

For France: See Appendix 9.

9.4.5 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.

9.4.6 Immunogenicity assessments

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

A tiered approach including screening of samples, confirmation of anti-drug antibodies 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.

In a case of two consecutive positive antibody tests the Novo Nordisk safety committee see Appendix 3 will assess if the antibodies have an impact on the efficacy and/or safety. The investigator will be informed, after a Novo Nordisk safety committee assessment if any clinically relevant impact on efficacy and/or safety.

All subjects who have had two consecutive positive antibody test results (high titer and/or persistent in vitro neutralising antibody response) 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. During the trial this will be covered by regular anti-drug antibody sampling, and after last patient last visit, the subjects may be requested to have additional blood samples collected for follow-up analyses.

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

9.4.6.1 Anti somapacitan antibodies

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

9.4.6.2 Anti hGH antibodies

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

9.4.6.3 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 pharmacokinetics of somapacitan and Norditropin®.

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

9.6 Pharmacodynamics

IGF-I and IGFBP-3 will be used to evaluate the PD of somapacitan and Norditropin®.
Bioactive IGF-I is an exploratory analysis and will be measured at selected visits.

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

9.7 Genetics

A blood sample for RNA (ribonucleic acid) analysis will be collected from subjects who have consented to participate in the genetic analysis component of the trial. Participation in the genetic research is optional. Subjects who do not wish to participate in the genetic research may still participate in the trial.

Genetic analyses will be used for exploratory purpose. The genetic data will be used, to evaluate a prediction model for growth response, for future purpose.

Results from genetic testing will not be reported to the sites since it will not be of clinical relevance. Only in the event that the findings show any results that may seriously affect the subject the site will be informed.

In the event of sample handling failure, a replacement genetic blood sample may be requested from the subject.

See Appendix 8 for further information regarding the genetic research. Details on processes for collection, shipment and destruction of these samples can be found in the laboratory manual.

For country specific requirements see Appendix 9.

9.8 Biomarkers

Not applicable for this trial.

10 Statistical considerations

10.1 Sample size determination

The sample size calculation is based on the primary estimand described in Section 4.2.

It is expected based on phase 2 trial data (NN8640-4172) that the proportion of subjects with no landmark visit data or who discontinued randomised treatment before landmark visit is 10% with similar withdrawal reasons in the two treatment arms (5% discontinuing randomised treatment but have landmark visit data and 5% withdrawn /lost to follow up with no landmark visit data). It is expected that subjects discontinuing their randomised treatment will start on ancillary treatment, if no medical reasons prohibits this. The term "retrieved subjects" will be used in this section as a short form for "subjects discontinuing randomised treatment but have landmark visit data". Assuming the same proportions of subjects with no landmark visit and retrieved subjects in the two arms leads to the following sample size calculation.

Primary estimand (FDA and PMDA)
The sample size is determined using a non-inferiority margin of 1.8 cm/year and a one sided two-group t-test with a significance level of 2.5% for a 2:1 randomisation ratio between somapacitan and Norditropin®.

As trial results from trials allowing ancillary therapy or having retrieved landmark data included in the analysis are limited, a conservative standard deviation for HV at week 52 was chosen (SD=3.5cm/year) and the different scenarios giving 90% power for the primary analysis are presented in the table below under the assumption of a true difference in annualized HV of 0 cm/year between the two treatment arms and no true difference in annualized HV between retrieved subjects and subjects staying on randomised treatment at landmark visit.

Table 3 Sample size for various standard deviations

SD	3.0 cm/year	3.25 cm/year	3.5 cm/year	3.75 cm/year
Primary estimand (Treatment policy strategy)	144	171	192	219

The SD candidates are based on reported SD values from clinical trials [21-23]. For sensitivity analysis a tipping point analysis is planned and based on a penalty for imputed values in the somapacitan arm of 1.8 cm/year this gives a power of 87% (adjusted treatment effect: 0.9*0 - 0.05*1.8= -0.09), under the assumption of 5% of subjects not having landmark visit data (corresponding to an analysis that performs an imputation under the non-inferiority null method).[24]

Primary estimand (EMA)
With the same assumptions as for the other primary estimand presented and Ns from Table 3 above, the different scenarios leads to a conservative power evaluation of 88%-89%for the primary analysis under the hypothetical estimand. For total N=192 the power is calculated to be 88%.

If the per protocol analysis set (PP) is assumed to consist of ~85% of the trial subjects (same proportion across treatment groups), giving 108 subjects in the somapacitan arm and 54 subjects in the Norditropin® arm, then repeating the primary analysis based on the primary estimand (hypothetical strategy) on the PP should result in a power of 86% for confirming non-inferiority of somapacitan compared to Norditropin®, under the assumption of no true treatment difference between the two treatments.

10.2 Definition of analysis sets

The full analysis set (FAS): all randomised subjects. Subjects will be analysed "as randomised".

The safety analysis set (SAS): all randomised subjects exposed to at least one dose of randomised treatment. Subjects will be analysed "as treated".

The per protocol analysis set (PP): subjects from the FAS who have not violated any inclusion/exclusion criteria and have used the randomised treatment for at least 47 weeks (for subjects receiving somapacitan) or 329 days (for subjects receiving Norditropin®) corresponding to 90% of the planned exposure, during the main trial period. Subjects will be analysed "as treated".

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 interim database lock for the main trial (52 weeks of treatment). The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CTR. Three observation periods are defined,

- on-treatment: from first administration and up until last trial contact, visit 7 or 14 days after last administration, whichever comes first
- in-trial without use of ancillary therapy: from first administration and up until last trial contact, visit 7 or first use of ancillary therapy, whichever comes first
- in-trial: from first administration and up until visit 7 or last trial contact, whichever comes first

10.3 Statistical analyses

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

The one-sided test used for the primary endpoint is based on an alpha level of 2.5%. All other statistical tests conducted will be two-sided on the 5% significance level. Age group is defined as a factor with 2 levels: < 6 years, >= 6 years. Region and GH peak group, respectively, used as factors in the analysis models are defined identically to the stratification variables region and growth hormone peak level, respectively. All effect endpoints will be analysed using FAS and all safety endpoints will be analysed using SAS. The primary endpoint will additionally be analysed using PP as a support to the results achieved using FAS under the hypothetical strategy.

10.3.1 Primary endpoint

The primary endpoint:

- Height velocity (cm/year) during the first 52 weeks will be derived from height measurements taken at baseline and the week 52 visit (landmark visit) in the following way: HV = (height at 52 weeks visit - height at baseline)/(time from baseline to 52 weeks visit in years).

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

Primary estimand (FDA and PMDA)
The primary objective is to compare the effect of somapacitan vs Norditropin® on longitudinal growth in children with GHD and the primary analysis of the primary endpoint will be used for confirming non-inferiority of somapacitan compared to Norditropin® based on the primary estimand Section 4.2.1

The primary analysis of the primary endpoint is based on the FAS. Subjects with no landmark visit data will have landmark visit data imputed based on available landmark visit data from retrieved subjects from the same treatment arm using Multiple Imputations (MI). If number of retrieved subjects per arm is less than 20 for at least one of the treatment arms (based on the assumptions: ~6 from the largest treatment arm), MI will be done in a model using all landmark visit data from the same treatment arm but with different mean parameters for the two status subgroups: (stayed on randomised treatment at the landmark visit; combined group of withdrawals and retrieved subjects), but same variance.

The analysis will be implemented as follows:
In the first step, missing week 52 values are imputed using a Markov Chain Monte Carlo method. This imputation is done for each treatment group separately and 100 copies of the dataset will be generated (seed=5297). The number of copies can be increased if the estimation process does not result in robust estimates.

For each of the complete data sets, HV at week 52 is analysed using an analysis of covariance model with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, and baseline height as covariate.

The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula:

$$m_{MI} = \frac{1}{100}\sum_{i=1}^{100} m_i, \quad SD_{MI} = \sqrt{\frac{1}{100}\sum_{i=1}^{100} SD_i^2 + \left(1+\frac{1}{100}\right)\left(\frac{1}{100-1}\right)\sum_{i=1}^{100}(m_i - m_{MI})^2},$$

where m_i and SD_i are the estimated means and standard deviations for the 100 copies of the dataset, and m_{MI} and SD_{MI} are the pooled estimates.

From these pooled estimates the confidence interval for the treatment difference and the associated p-value will be calculated.

Non-inferiority of somapacitan will be considered confirmed if the lower boundary of the two-sided 95% confidence interval is above -1.8 cm/year or equivalent if the p-value for the one-sided test of

H_0: D ≤-1.8 cm/year vs H_A: D >-1.8 cm/year is less than 2.5 %, where D is the mean treatment difference (somapacitan – Norditropin®). If non-inferiority is confirmed, superiority will be considered confirmed if the lower boundary of the two-sided 95% confidence interval is above 0 cm/year. If superiority is confirmed, the p-value from the two-sided superiority test will also be reported.

If the actual number of retrieved subjects turns out to be 20 or more from each treatment arm (so more retrieved subjects than expected from the assumptions), it will be possible to model the mean with more parameters using height baseline value and time to last dose as covariates and then do MI within each treatment arm for the status subgroup consisting of withdrawals and retrieved subjects. The rest of the analysis procedure will be identical to the procedure stated above.

A tipping point analysis will be conducted as a sensitivity analysis for the primary analysis of the primary endpoint for the primary estimand where imputed landmark visit values will be penalized by a value c>0 in the somapacitan treated arm (by subtracting c multiplied by the fraction of subjects with imputed landmark visit values in the somapacitan treated arm from the treatment difference estimate and the corresponding 95% CI). The analysis is used to investigate the robustness of the results, targeting the chosen imputation method of missing landmark data. It will be conducted by increasing c until the resulting 95% CI no longer is completely above -1.8cm/year.

Additionally, a value b≥0 will be added to the imputed landmark visit value for Norditropin® treated subjects prior to analysis, so that the tipping point analysis also can address scenarios where withdrawals from the active comparator arm achieve greater HV than the value estimated from retrieved subjects (two-dimensional tipping point analysis).

Primary estimand (EMA)
The primary analysis of the primary endpoint addressing the alternative primary estimand Section 4.2.2 is based on FAS but data assessed after discontinuation of randomised treatment will be disregarded in the analysis.

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

From this analysis an estimate of the treatment difference at week 52 with corresponding 95% CI and p-value will be presented.

Non-inferiority of somapacitan will be considered confirmed if the lower boundary of the two-sided 95% confidence interval is above -1.8 cm/year or equivalent if the p-value for the one-sided test of

H_0: D≤-1.8 cm/year vs H_A: D>-1.8 cm/year is less than 2.5 %, where D is the mean treatment difference (somapacitan – Norditropin®). If non-inferiority is confirmed, superiority will be considered confirmed if the lower boundary of the two-sided 95% confidence interval is above 0 cm/year. If superiority is confirmed, the p-value from the two-sided superiority test will also be reported.

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

Let δ be defined as the difference between the mean of the observed data and the mean of the unobserved data μ_{obs}-μ_{unobs}, adjusted for other observed data. Under an MAR analysis, δ is assumed to be 0. Positive values of δ indicate that subjects with missing endpoint values have smaller HV than subjects with observed endpoint values. If subjects primarily withdraw or discontinue randomised treatment due to a perceived lack of efficacy then this could be the most likely direction of departure from MAR. Let f_1 and f_0 be the fractions of subjects with unobserved endpoint data in the somapacitan and Norditropin® arms, respectively. The sensitivity analysis is done by subtracting a quantity Δ from the treatment effect estimate under the MAR assumption, where $\Delta = f_1\delta$ if data depart from MAR in the somapacitan arm only, $\Delta = -f_0\delta$ if data depart from MAR in the Norditropin® arm only, and $\Delta = (f_1-f_0)\delta$ if data depart from MAR in the same way in both arms. The calculations for the 3 scenarios will use a range of δ values increasing from 0 until the resulting 95% CI no longer is completely above -1.8cm/year for the most conservative evaluation (data depart from MAR in the somapacitan arm only) and the approximation that the standard error of the treatment difference is unaffected by the sensitivity analysis[25]. All subjects from the FAS can be viewed as included in this analysis as subjects with missing endpoint data will be contributing to one of the fraction values f_1 and f_0.

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

10.3.2 Secondary endpoints

Confirmatory secondary endpoints

N/A

Supportive secondary endpoints

Effect

Change from screening (visit 1) to visit 7 (week 52):

- Bone age (years)

Change from baseline (week 0) to visit 7 (week 52):

- Height SDS (-10 to +10)
- Height Velocity Standard Deviation Score (HV SDS) (-10 to +10)

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

Height SDS will be derived using Centre for Disease Control and Prevention (CDC)[17] standards and HV SDS will be derived using Prader standards as reference data.

The time interval used for the derivation of baseline HV is defined as: from date of pre-trial height assessment (a minimum of 6 months and maximum of 18 months prior to screening) to date of randomisation visit.

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

Change in bone age will be analysed using an ANCOVA model on change in bone age/ chronological age assessed at week 52 and the model will include treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors and bone age/chronological age at screening 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.

Safety

Change from screening (visit 1) to visit 7 (week 52):

- Fasting plasma glucose (mmol/L)
- HOMA (%)
- HbA_{1c} levels (% points)

HOMA will be reported as steady state beta cell function (HOMA-B) and insulin resistance (HOMA-IR). The safety endpoints will be analysed using descriptive statistics based on the 'on – treatment' observation period and the 'in-trial' observation period.

Pharmacodynamics

Change from baseline (week 0) to visit 7 (week 52):

- IGF-I SDS (-10 to +10)
- IGFBP-3 SDS (-10 to +10)

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

Change in IGF-I SDS and IGFBP-3 SDS will be analysed using a MMRM with an unstructured covariance matrix on all relevant post-baseline change from baseline values as dependant variables. The model will include treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors and baseline value as a covariate, all nested within week as a factor. From the MMRM, the treatment difference at Week 52 will be estimated and the corresponding 95% CI and p-value will be reported for each endpoint. Subjects without post-randomisation data for the analysed endpoint will not be included in the analysis.

10.3.3 Exploratory endpoints

The exploratory endpoints will be analysed based on the 'on-treatment' observation period. TB-CGHD-O and TB-CGHD-P scores will be analysed using a MMRM with an unstructured covariance matrix on all relevant post-baseline values as dependant variables. The model will include treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, all nested within week as a factor. From the MMRM, the treatment differences will be estimated and the corresponding 95% CI and p-values will be reported for week 26 and week 52, respectively. Changes from baseline to week 26 and week 52 in TRIM-CGHD-O scores will be analysed using a MMRM with an unstructured covariance matrix. The model will include treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors and baseline value as a covariate, all nested within week as a factor. From the MMRM, the treatment differences will be estimated and the corresponding 95% CI and p-values will be reported for week 26 and week 52, respectively. G-DAT and 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 7 will be included in an interim database lock. At this interim DBL the sponsor will become unblinded regarding the somapacitan vs Norditropin® allocation during the main trial period. The results from the main part of the trial is planned to be used as basis for regulatory filings.

10.3.5 Other analyses

Adverse events will be analysed using descriptive statistics based on the 'on –treatment' observation period (primary evaluation) and 'in-trial' observation period (secondary evaluation) within the main trial period (52 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. Adverse events 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. Adverse events with onset before first dosing will be reported in a separate listing.

Similar tables will be made for adverse events in the extension trial period.

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 prospective modelling analysis plan.

11 References

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Appendices

Appendix 1 Abbreviations and Trademarks

ADA	anti drug antibodies
ADHD	Attention deficit hyperactivity disorder
AE	adverse event
BIA	bioelectrical impedance analysis
CRF	case report form
CT	computerised tomography
CTR	clinical trial report
DFU	directions for use
DMC	data monitoring committee
DUN	dispensing unit number
eCRF	electronic case report form
ECG	Electrocardiogram
EMA	Euoropean Medicins Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
G-DAT	growth hormone device assessment tool
GH	growth hormone
GCP	Good Clinical Practice
GHD	growth hormone deficiency
HbA_{1c}	glycated haemoglobin
hGH	human growth hormone
HOMA	homeostatic model assessment
HV	height velocity
IB	investigator brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
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
MI	multiple imputations
MMRM	mixed model for repeated measurements
MRI	magnetic resonance imaging
PCD	primary completion date
PD	pharmacodynamics
PK	pharmackinetics
PP	per protocol
PPQ	patient preference questionniare
PRO	patient reported outcome
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
s.c	subcutaneous
SDS	standard deviation score
SGA	Small for gestational age
SUSAR	suspected unexpected serious adverse reaction
TB-CGHD-O	treatment burden-child growth hormone deficiency-observer
TB-CGHD-P	treatment burden-child growth hormone deficiency-parent
TMM	trial materials manual
TRIM-CGHD-O	Treatment Related Impact measure-Child-Growth Hormone Deficiency-Observer

Appendix 2 Clinical laboratory tests

The tests detailed in Table 5 and Table 6 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 study drug administration should always be followed.

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

Table 4 Approximate blood volumes collected during the trial

Visit	mL
Visit 1	9
Visit 2	7+2.5 mL for genetic testing, separate consent needed
Visit 3	2.5
Visit 4	6
Visit 5	11
Visit 6	2.5
Visit 7	13.5
Visit 8	0
Visit 9	11
Visit 10	0
Visit 11	13.5
Visit 12	0
Visit 13	9
Visit 14	0
Visit 15	13.5
Visit 16	0
Visit 17	9
Visit 18	0
Visit 19	13.5
Follow up	0
Total volume collected during the trial	**121.0**

2.5 Genetic testing

- 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.

For subjects with a lower body weight

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

Table 5 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
PD	IGF-I IGFBP-3 Bioactive IGF-I
PK	somapacitan Norditropin®
Notes: IGF-I and IGFBP-3 will be blinded to site staff during the trial. At visit 1 IGF-I SDS will be reported to sites in order to evaluate eligibility. Novo Nordisk will monitor IGF-I throughout the trial. The results of Bioactive IGF-I will be reported in the CTR or in a separate trial report. Bioactive IGF-I and PK will not be reported to the sites.	

Table 6 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 9.4.6

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 7. 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 7 Timing of visits and blood sampling

Visit	Timing of visit
3	1 to 4 days after dosing
4	On a planned dosing day
5	1 to 4 days after dosing
6	On a planned dosing day
7	4 to 6 days after dosing
8	No blood sampling
9	1 to 4 days after dosing
10	No blood sampling
11	On a planned dosing day
12	No blood sampling
13	1 to 4 days after dosing
14	No blood sampling
15	On a planned dosing day
16	No blood sampling
17	1 to 4 days after dosing
18	No blood sampling
19	At least 7 days after last dose of trial product
19A	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 Good Clinical Practice (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 clinical trial report 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 clinical trial report (CTR) synopsis to the IRB/IEC.

2) Financial disclosure

Investigators and subinvestigators 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.
- A separate written consent form for genetic testing should be signed by the LAR if they consent to participate in the genetic testing part of the trial. The subject can abstain from genetic testing while still participate in the non-genetic part of the trial.

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 will constitute 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.

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 clinical trial report for this trial. One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (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) + 52 weeks corresponding to visit 7. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 7. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

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 ediaries , 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 GHD 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 subinvestigator 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 administration of wrong drug. Wrong route of administration, such as intramuscular instead of subcutaneous. Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

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.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 and safety information 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 8 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 9 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
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.

For Estonia, Ireland, Latvia, Norway, Spain, and UK: See Appendix 9

Pregnancy testing

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

For Spain and Austria: See Appendix 9

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.

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 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 Genetics

Transcriptomics

Use/Analysis of RNA

To date there has been limited progress in the development of a test to predict an individual's response to treatment with recombinant human growth hormone. An individual's response to GH therapy may be influenced by developmental stage, environment, genetic variants (which may impact drug absorption, distribution, metabolism and excretion), mechanism of action of the drug, disease aetiology, and/or molecular subtype of the disease being treated. While many previous studies[35-37] have examined Deoxyribonucleic acid (DNA) variants, these have so far proven to be of limited clinical utility. Recent studies[38] have suggested that analysis of RNA (gene expression levels) may be useful in predicting GH response and superior to DNA analysis.

DNA variants are only one of many factors influencing gene expression and no DNA extraction or sequence analysis are part of this study. The methods used are different to whole exome or whole genome sequencing as RNA not DNA are being used and no analysis of the genetic sequence is being undertaken. The technique focuses of measuring number of copies of each transcript.

Where local regulations and IRB/IEC allow, a blood sample will be collected for RNA analysis from separate consenting subjects.

RNA samples will be used for research related to trial product or indication and related diseases. RNA samples will be analysed for gene expression. Data will be associated with peak GH concentrations and other relevant data as predictor for growth response. Additional analyses may be conducted if it is hypothesised that this may help further understand the clinical data.

The results of genetic analyses will be reported in the CTR or in a separate trial report.

The RNA samples will be stored in a secure storage space with adequate measures to protect confidentiality, as described in Appendix 7 , at a Novo Nordisk designated laboratory.

The samples will be retained while research on trial product(s) of this class or indication continues, but no longer than 15 years.

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

Appendix 9 Country-specific requirements

Only applicable for Algeria:
No subjects from Algeria will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in Section 9.7, Appendix 7 and Appendix 8.

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 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

The risk category for somapacitan and Norditropin® are identified as category 2.2.3 “Contraception and pregnancy testing recommendation for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy”. Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 8. In addition to Table 8, 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 9 are not considered acceptable and Table 9 is not applicable for Estonia.

No subjects from Estonia will participate in the PRO part of the trial.

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®.

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.

If a subject on trial product begins oral oestrogen therapy, the trial product dose may be increased to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a subject on trial product discontinues oral oestrogen therapy, the trial product dose may need to be reduced to avoid excess of growth hormone and/or side effects.

Female subjects will be asked about the date of last menstruation at visit 1 and visit 2.

An MRI or CT scan of the brain should be performed at visit 19 or visit 19A. It should not be performed at visit 19A if an MRI or CT scan has been performed within the last 6 months.

Only applicable for Germany:
Only X-Rays taken as normal routine will be used. No additional X-Rays will be performed for the trial.
Date of Birth will be recorded only as year of birth.

Only applicable for Hungary:
No subjects from Hungary will participate in the PRO part of the trial.
Date of Birth will be recorded only as year of birth.

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

The risk category for somapacitan and Norditropin® are identified as category 2.2.3 "Contraception and pregnancy testing recommendation for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy". Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 8. In addition to Table 8, 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 9 are not considered acceptable and Table 9 is not applicable for Ireland.

No subjects from Ireland will participate in the PRO part of the trial.

Only applicable for Israel:
No subjects from Israel will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in Section 9.7, Appendix 7 and Appendix 8.

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

The risk category for somapacitan and Norditropin® are identified as category 2.2.3 "Contraception and pregnancy testing recommendation for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy". Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 8. In addition to Table 8, 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 9 are not considered acceptable and Table 9 is not applicable for Latvia.

No subjects from Latvia will participate in the PRO part of the trial.

Only applicable for Japan:
Inclusion criterion 3: Confirmed diagnosis of growth hormone deficiency within 12 months prior to screening as determined by one growth hormone stimulation test for patients with intracranial organic disease or symptomatic hypoglycaemia and two different growth hormone stimulation tests for other subjects defined as peak growth hormone level of ≤ 6 ng/ml by assay using recombinant growth hormone standard.

a) If only one growth hormone stimulation test is available before screening, then confirmation of growth hormone deficiency by second and different growth hormone stimulation test must be done.
b) For children with at least 2 additional pituitary hormone deficiencies only one growth hormone stimulation test is needed.

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 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

The risk category for somapacitan and Norditropin® are identified as category 2.2.3 "Contraception and pregnancy testing recommendation for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy". Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5 Table 8. In addition to Table 8, 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 9are not considered acceptable and Table 9 is not applicable for Norway.

No subjects from Norway will participate in the PRO part of the trial.

Only applicable for Poland:
No subjects from Poland will participate in the PRO part of the trial.

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 Serbia:
No subjects from Serbia will participate in the PRO part of the trial.

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
The risk category for somapacitan and Norditropin® are identified as category 2.2.3 "Contraception and pregnancy testing recommendation for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy". Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5 ,.Table 8 In addition to Table 8, 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 9 are not considered acceptable and Table 9 is not applicable for Spain.
A pregnancy test at all trial visits is mandatory for female subjects becoming of childbearing potential during the trial.
No subjects from Spain will participate in the PRO part of the trial.
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 the UK:
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
The risk category for somapacitan and Norditropin® are identified as category 2.2.3 “Contraception and pregnancy testing recommendation for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy”. Only highly effective contraceptive methods are considered acceptable and these are listed in Appendix 5, Table 8. In addition to Table 8, 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 9 are not considered acceptable and Table 9 is not applicable for UK.

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 version 6.0 (31 March 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 rationale for preparing protocol version 6.0:
The overall rationale for this updated protocol is to add requirements from Spanish Health Authority.

Section # and name	Description of change	Rationale
2 Flowchart	Reference to Appendix 9 for country-specific requirements for Spain.	Requirement from Spanish Health Authority.
6.2 Exclusion criteria	Reference to Appendix 9 for country-specific requirements for Spain.	Requirement from Spanish Health Authority.
Appendix 5	Reference to Appendix 9 for country-specific requirements for Spain.	Requirement from Spanish Health Authority.
Appendix 9	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®. Addition of pregnancy tests at all trial visits is mandatory for female subjects becoming of childbearing potential during the trial. Date of birth will be collected as year of birth. Race and ethnicity will not be collected.	Requirement from Spanish Health Authority.

Protocol version 5.0 (03 January 2020)

The overall rationale for this local protocol amendment is to remove the requirement to participate in the Patient reported outcome (PRO) evaluation, by parent/LAR completion of questionnaires, as described in section 9.1.5 for Hungary.

Section # and name	Description of change	Rationale
9.1.5 Patient reported outcome questionnaires	Additional information for Hungary about PRO questionnaires.	Translated and validated PRO questionnaires are not available for Hungary before First Patient First Visit. They are only used for exploratory endpoints, and therefore, it is considered acceptable for the evaluation of these endpoints to exclude the questionnaires without jeopardising the exploratory conclusions.
Appendix 9	Additional information about PRO questionnaires added in the Country-specific requirements appendix 9.	Rationale as described in the section above.

Protocol version 4.0 (18 November 2019)

The overall rationale for this local protocol amendment is to remove the requirement to participate in the Patient reported outcome (PRO) evaluation, by parent/LAR completion of questionnaires, as described in section 9.1.5 for Estonia.

Section # and name	Description of change	Rationale
9.1.5 Patient reported outcome questionnaires	Additional information for Estonia about PRO questionnaires.	Translated and validated PRO questionnaires are not available for Estonia before First Patient First Visit. They are only used for exploratory endpoints, and therefore, it is considered acceptable for the evaluation of these endpoints to exclude the questionnaires without jeopardising the exploratory conclusions.
Appendix 5	Additional contraceptive guidance for Estonia	According to local requirements.
Appendix 9	Additional information about PRO questionnaires and	Rationale as described in the two sections above.

	contraceptive guidance added in the Country-specific requirements appendix 9.	

Protocol amendment 3, applicable for Ireland, Latvia, Norway, Poland, Serbia, and Spain (01 November 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 rationale for preparing protocol amendment 3:
The overall rationale for this local protocol amendment is to remove the requirement to participate in the Patient reported outcome (PRO) evaluation, by parent/LAR completion of questionnaires, as described in section 9.1.5 for the following countries: Ireland, Latvia, Norway, Poland, Serbia, and Spain.

Section # and name	Description of change	Rationale
9.1.5 Patient reported outcome questionnaires Appendix 9	Additional information for Ireland, Latvia, Norway, Poland, Serbia, Spain about PRO questionnaires in Appendix 9.	Translated and validated PRO questionnaires are not available for these countries before First Patient First Visit. They are only used for exploratory endpoints, and therefore, it is considered acceptable for the evaluation of these endpoints to exclude the questionnaires in these countries without jeopardising the exploratory conclusions.
Appendix 5 Appendix 9	Additional contraceptive guidance for Ireland, Latvia, Norway, and Spain added in Appendix 9.	According to local requirements.

Protocol version 3.0 (01 July 2019), including version 1.0 and 2.0, global
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 rationale for protocol version 3.0
The overall rationale for amending the protocol is to add a Data Monitoring Committee (DMC) for the trial. The DMC has been a request from the French Health authorities, ANSM

Section # and name	Description of change	Rationale
Appendix 1 Abbreviations and Trademarks	Addition of Data Monitoring Committee	Request from French Health authorities.

Appendix 3 Trial governance considerations		
1 Synopsis 4.3.2.3 Effect 4.3.3 Exploratory endpoints 10.3.3 Exploratory endpoints	Alignment between section 1, 4.3.2.3, 4.3.3 and 10.3.3	Clarification of exploratory endpoints and statistical analyses hereof.
2 Flowchart 8.1 Discontinuation of trial treatment 9.4.4 MRI and CT scans Appendix 9	Additional information for France added about MRI/CT scan added in Appendix 9.	Request from French Health authorities.
5.4 Scientific rational for trial design	Few words added.	Typo.
5.5 Justification of dose	The dose used for Norditropin® in the trial has been added.	Clarification of Norditropin® dose according to label.
6.2 Exclusion criteria Appendix 9	Exclusion criteria for UK added in Appendix 9	According to Amendment 1
7.1 Treatments administered 7.2 Dose modification 7.2.1 Dose reduction criteria 7.7 Concomitant medication Appendix 9	Somapacitan can be dosed the day ahead of dosing day. Dose considerations for France added in Appendix 9. Rule for dose reduction added. Additional information for France added about concomitant medication in Appendix 9.	Clarification of dosing requirements and implementation of country-specific requirements
7.6 Treatment compliance	Details added about treatment compliance	Clarification of Investigator responsibilities with regards to treatment compliance

9.1.2 Pubertal status Appendix 9	Additional information for France added about evaluation of pubertal status in Appendix 9.	Additional information about evaluation of pubertal status for France.
9.1.3 GH stimulation test	If other standards similar to WHO International Somatropin 98/574 standard are used locally, this is acceptable	To allow participation of countries using growth standards similar to WHO.
10.3.1 Primary endpoint	A more detailed description of the tipping point analysis	Providing necessary statistical description
11 References Appendix 8 Genetics	Additional text on how RNA analysis can be used for predicting growth response.	Clarification of why exploratory RNA sampling is done.
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.
Appendix 5 Contraceptive guidance and collection of pregnancy information	Deletion of documented sexual abstinence from the definition of women not considered women of child bearing potential.	Typo; updated to be in alignment with EMA requirements. Sexual abstinence is considered a highly effective method of contraception as already listed.
Appendix 5 Contraceptive guidance and collection of pregnancy information	Additional information for UK added in Appendix 9	According to MHRA requirements.
Appendix 5 Contraceptive guidance and collection of pregnancy information	Clarification of which terminations of pregnancies will be reported as AE or SAE	Clarification

16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.