Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03075644
Sponsor trial ID:	NN8640-4244
Official title of study:	A multicentre, randomised, open-labelled, parallel-group, active-controlled trial to evaluate the safety of once-weekly dosing of somapacitan (NNC0195-0092) and daily Norditropin® FlexPro® for 52 weeks in previously human growth hormone treated Japanese adults with growth hormone deficiency (AGHD)
Document date:	22 March 2019

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID: NN8640-4244

A multicentre, randomised, open-labelled, parallel-group, active-controlled trial to evaluate the safety of once weekly dosing of somapacitan (NNC0195-0092) and daily Norditropin® FlexPro® for 52 weeks in previously human growth hormone treated Japanese adults with growth hormone deficiency

Trial phase: 3a

Protocol originator

[redacted]

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List of abbreviations

AE	adverse event
AGHD	adult growth hormone deficiency
ALT	alanine aminotransferase
AUC	area under the curve
BMD	bone mineral density
CCDS	company core data sheet
CRF	case report form
CRO	Contract Research Organisation
CT	computed tomography
CTR	clinical trial report
DBL	data base lock
DFU	direction for use
DUN	dispensing unit number
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FSFV	first subject first visit
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
HbA1c	glycated haemoglobin
hCG	human chorionic gonadotropin
hGH	human growth hormone
HOMA	Homeostasis Model Assessment

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF-I	insulin-like growth factor – I
IGFBP-3	insulin-like growth factor binding protein – 3
IMP	investigational medicinal product
IR	insulin resistance
IRB	Institutional Review Board
IWRS	interactive web response system
LBM	lean body mass
LSFV	last subject first visit
LSLV	last subject last visit
MD	mean deviation
MMRM	mixed model for repeated measurements
MRI	magnetic resonance imaging
MVSS	mean value during steady state
NNC0195-0092	once weekly growth hormone derivative
NOAEL	no observed adverse event level
PD	pharmacodynamics
PK	pharmacokinetic
PRO	patient reported outcome
RA	regulatory authority
SAE	serious adverse event
SAP	statistical analysis plan
SAT	subcutaneous adipose tissue
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score

SGA	short for gestational age
SIF	safety information form
SmPC	summary of product characteristics
TAT	total adipose tissue
TSH	thyroid stimulating hormone
TSQM-9	treatment satisfaction questionnaire for medication-9 items
UTN	universal trial number
VAT	visceral adipose tissue

1 Summary

The aim of this trial is to investigate safety, tolerability and efficacy of once weekly subcutaneous administration of somapacitan in Japanese adults with growth hormone deficiency (GHD). The trial will add to the overall safety data generated, supporting regulatory submission in Japan.

Objective(s) and endpoint(s):

Primary objective

- To evaluate the safety of once weekly dosing of somapacitan during 52 weeks of treatment in Japanese GHD subjects previously treated with daily human growth hormone (hGH)

Secondary objective

- To evaluate the efficacy of once weekly dosing of somapacitan by measuring the effect on abdominal adipose tissue during 52 weeks of treatment in Japanese GHD subjects previously treated with hGH
- To evaluate the degree of treatment satisfaction of once weekly dosing of somapacitan during 52 weeks of treatment in Japanese GHD subjects previously treated with daily hGH

Primary endpoint

- Incidence of adverse events, including injection site reactions, from first administration of trial product to end of the trial period (53 weeks including follow-up)

Key secondary endpoints

Efficacy

- Change from baseline (randomisation) to end of treatment period (52 weeks) in:
    - cross-sectional total adipose tissue compartments (TAT),
    - subcutaneous adipose tissue compartments (SAT), and
    - intra-abdominal or visceral adipose tissue compartments (VAT)

determined by quantitative computed tomography (CT) scans

- Change from baseline (randomisation) to end of treatment period (52 weeks) in Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores for:
    - effectiveness
    - convenience
    - global satisfaction

Safety

- Occurrence of anti-somapacitan antibodies for subjects randomised to somapacitan from randomisation to end of the trial period (53 weeks including follow-up)

Trial design:
This is a multicentre, randomised, open-labelled, parallel-group, active-controlled trial to compare the safety of once weekly dosing of somapacitan with daily Norditropin® FlexPro® in previously hGH treated Japanese GHD subjects for 52 weeks (20 weeks dose titration and 32 weeks fixed dose treatment) followed by one week washout.

Trial population:
Sixty (60) subjects will be randomised in a 3:1 ratio to receive somapacitan or Norditropin® FlexPro® during a 52 weeks period.

Key inclusion criteria

- Male or female of at least 18 years of age and not more than 79 years of age at the time of signing informed consent
- GHD diagnosed ≥ 6 months (defined as 180 days) prior to screening.
- Treatment with hGH for at least 6 consecutive months (defined as 180 days) at screening.
- If applicable, hormone replacement therapies for any other hormone deficiencies, adequate and stable for at least 90 days prior to randomisation as judged by the investigator

Key exclusion criteria

- Active malignant disease or history of malignancy. Exceptions to this exclusion criterion:
    - Resected in situ carcinoma of the cervix and squamous cell or basal cell carcinoma of the skin with complete local excision
    - Subjects with GHD attributed to treatment of intracranial malignant tumours or leukaemia, provided that a recurrence-free survival period of at least 5 years is documented in the subject's medical records
- For subjects with surgical removal or debulking of pituitary adenoma or other benign intracranial tumour within the last 5 years:

- Evidence of growth of pituitary adenoma or other benign intracranial tumour within the last 12 months (defined as ≤ 365 days) before randomisation. Absence of growth must be documented by two post-surgery magnetic resonance imaging (MRI) scans or CT scans. The most recent MRI or CT scan must be performed ≤ 9 months (defined as ≤ 270 days) prior to randomisation

Assessments:

- Assessments for safety: adverse events including injection site reactions, ECG, vital signs, assessments of drug antibodies, biochemistry, haematology, hormones, glucose markers and physical examination
- Assessments of efficacy: abdominal adipose deposition and treatment satisfaction

Trial product(s):

Investigational medicinal products:

- Test product: Somapacitan PDS290 10mg/1.5ml
- Reference therapy: Norditropin® FlexPro® 10mg/1.5ml

All trial products will be administered as subcutaneous injections.

2 Flow chart

Trial Periods	Protocol section	Information	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Follow-up
Type of visit		site	site	site	site	phone	site	phone	site	phone	site	phone	site	site	site	site	site	site
Visit number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Timing of visit **Weeks**		V1 minus minimum 1D	V2 minus 3 - 2W	0W	3W+ 3D	4W	7W+ 3D	8W	11W +3D	12W	15W +3D	16W	19W +3D	20W	32W+ 4D	42W	51W+ 4D	53W
Visit window **Days**					+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	±7D[a]	±7D	+2D	
SUBJECT RELATED INFO/ASSESSMENTS																		
Informed consent	8.1, 18.2	x																
Attend visit fasting	8.5.2		x		x		x		x		x		x		x		x	
Randomisation	11			x														
In/exclusion criteria	6.2, 6.3		x	x														

Trial Periods	Protocol section	Information	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Follow-up
Type of visit		site	site	site	site	phone	site	phone	site	phone	site	phone	site	site	site	site	site	site
Visit number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Timing of visit **Weeks**		V1 minus minimum 1D	V2 minus 3 - 2W	0W	3W+ 3D	4W	7W+ 3D	8W	11W +3D	12W	15W +3D	16W	19W +3D	20W	32W+ 4D	42W	51W+ 4D	53W
Visit window **Days**					+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	±7D[a]	±7D	+2D	
Concomitant illness	8.2.2		x															
Concomitant medication	8.2.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Body measurements	8.2.5		x		x		x		x		x		x	x	x	x	x	
Demography	8.2.1		x															
Medical history	8.2.2		x															
Pregnancy test	8.5.2.7		x	x	x		x		x		x		x	x	x	x	x	x
Discontinuation/ withdrawal criteria	6.4, 6.5			x	x		x		x		x		x	x	x	x	x	

Trial Periods	Protocol section	Information	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Follow-up
Type of visit		site	site	site	site	phone	site	phone	site	phone	site	phone	site	site	site	site	site	site
Visit number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Timing of visit **Weeks**		V1 minus minimum 1D	V2 minus 3 - 2W	0W	3W+ 3D	4W	7W+ 3D	8W	11W +3D	12W	15W +3D	16W	19W +3D	20W	32W+ 4D	42W	51W+ 4D	53W
Visit window **Days**					+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	±7D[a]	±7D	+2D	
EFFICACY																		
CT scan (abdominal tissue area, efficacy assessment)	8.3.1			x													x	
CT scan (excl. criterion # 8)	6.3, 8.2.2.1		x															
MRI scan (excl. criterion # 8)	6.3, 8.2.2.1		x															
PRO questionnaires	8.3.2			x											x		x	

Trial Periods	Protocol section	Information	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Follow-up
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Visit number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
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Visit window **Days**					+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	±7D[a]	±7D	+2D	
SAFETY																		
Adverse events	12			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Injection site reactions	8.4.1.2			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints	12.1.6			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	8.4.2		x						x					x	x		x	
Vital signs	8.4.4		x	x			x						x	x	x	x	x	
Antibodies	8.5.2.2			x														x
Biochemistry	8.5.2.5		x				x						x		x		x	
Haematology	8.5.2.4		x				x						x		x		x	

Trial Periods	Protocol section	Information	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Follow-up
Type of visit		site	site	site	site	phone	site	phone	site	phone	site	phone	site	site	site	site	site	site
Visit number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
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Visit window **Days**					+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	±7D[a]	±7D	+2D	
Hormones	8.5.2.6		x				x						x		x		x	
PK Sampling	8.5.2.3			x	x		x		x		x		x		x		x	
Biomarkers	8.5.2		x		x		x		x		x		x		x		x	
Glucose metabolism	8.5.2.1		x				x						x		x		x	
Physical examination	8.4.3		x	x			x						x	x	x		x	

Trial Periods	Protocol section	Information	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Follow-up
Type of visit		site	site	site	site	phone	site	phone	site	phone	site	phone	site	site	site	site	site	site
Visit number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Timing of visit **Weeks**		V1 minus minimum 1D	V2 minus 3 - 2W	0W	3W+ 3D	4W	7W+ 3D	8W	11W +3D	12W	15W +3D	16W	19W +3D	20W	32W+ 4D	42W	51W+ 4D	53W
Visit window **Days**					+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	±7D[a]	±7D	+2D	
TRIAL MATERIAL																		
New dose of trial product	5.3.1			x		x		x		x		x		x				
Dispensing visit				x	x		x		x		x		x		x	x		
Dosing (observed trial drug administration)	8.6.1			x	x		x											
Drug accountability	9.4			x	x		x		x		x		x		x	x		x
IWRS session	10		x	x	x		x		x		x		x		x	x		x
Hand out Directions for Use	9.2			x														

Trial Periods	Protocol section	Information	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Follow-up
Type of visit		site	site	site	site	phone	site	phone	site	phone	site	phone	site	site	site	site	site	site
Visit number		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Timing of visit **Weeks**		V1 minus minimum 1D	V2 minus 3 - 2W	0W	3W+ 3D	4W	7W+ 3D	8W	11W +3D	12W	15W +3D	16W	19W +3D	20W	32W+ 4D	42W	51W+ 4D	53W
Visit window **Days**					+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	+1D	±7D[a]	±7D	+2D	
REMINDERS																		
Training in trial product and pen handling	8.6.1			x	x													
Handout ID card	8.1		x															
Handout and instruct in diary	8.6.2			x	x		x		x		x		x		x	x	x	
Collection of diary	8.6.2				x		x		x		x		x		x	x	x	x
End of trial																		x

Footer	Description
[a]	Time window +/- 7 days only allows a full week deviation - so either one week before or one week after (to secure optimal timing for antibody sampling)

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

For an assessment of benefits and risks of the trial, see Section 18.1.

3.1.1 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[3]. Besides GH and IGF-I being important in facilitating growth in children, both GH and IGF-I are also involved in various metabolic processes in children as well as in adults[4]. IGF-I bioactivity is regulated through complex mechanisms involving GH, IGFBP-3, acid labile subunit (ALS), and other IGF binding proteins[5-7]. GH replacement therapy has proved beneficial in adult growth hormone deficiency (AGHD) due to its metabolic actions[4, 8-10]. AGHD usually results from pituitary or peripituitary tumours and the associated treatments and has been recognized as a syndrome with distinct features, such as increased body fat mass, decreased lean body mass (LBM), reduced exercise capacity, reduced bone mineral density (BMD), disturbed lipoprotein metabolism and decreased psychological well-being [5, 11]. The aim of GH replacement is to correct GHD related metabolic disturbances and to optimise the therapeutic response with minimal incidence of adverse reactions. Although the incidence of adult onset GHD has not been fully established, indirect estimates based on the incidence of pituitary tumours suggest an incidence of 10 people/million annually[5].
Although hGH treatment has proved both efficacious and safe, one major drawback of the treatment has been the need for daily subcutaneous (s.c.) injections — for several years, or lifelong. It is anticipated that a long-acting GH therapy that could be dosed once weekly, thereby requiring fewer injections, would improve convenience, subject compliance and quality of life. Studies conducted with various long-acting GH products have shown efficacy both in children and adults with GHD[12-16].

3.1.2 Somapacitan

Somapacitan is human growth hormone with a single amino acid substitution to which a non-covalent albumin binding moiety has been attached. Somapacitan will be provided in a liquid formulation in a pen system[17].

The primary pursued therapeutic indications considered for somapacitan are GHD in children and adults.

3.1.3 Non-clinical data

The pharmacodynamic (PD) profile of somapacitan has been investigated in the standard GHD animal model – the hypophysectomised rat, where once weekly s.c. injection of somapacitan performed on-par with, or better than, daily s.c. injection of hGH. Further results from minipigs and Cynomolgus monkeys indicate that single s.c. doses of somapacitan can induce increased and sustained levels of IGF-1 for 4−10 days, thus supporting a once weekly dosing schedule.

Somapacitan has been tested in toxicity studies of up to 26 weeks duration in Han Wistar rats and Cynomolgus monkeys (safety pharmacology endpoints included in the studies in monkeys), *in vitro* and *in vivo* genotoxicity studies, fertility studies in Han Wistar rats and embryo-foetal development studies in pregnant Han Wistar rats and New Zealand White rabbits.

In safety pharmacology studies, somapacitan did not cause any overt adverse effects on the function of the central nervous, respiratory or cardiovascular systems after testing of s.c. doses up to 9 mg/kg/twice weekly in Cynomolgus monkeys and up to 3 μM in *in vitro* studies investigating possible interaction with ion channels in the heart.

No genotoxic potential was identified in the *in vitro* and *in vivo* studies conducted with somapacitan.

In the 13-week toxicity study in rats, animals were dosed with 0.4, 2 and 9 mg/kg/day. The study findings were attributed to the pharmacological action of GH and most findings have been reported in previous studies with hGH. The compound was well tolerated until week 9-10 where males dosed with 9 mg/kg/day showed signs of diabetes (increased water consumption, increased urine production and decreased body weight gain). The diabetic symptoms were confirmed by marked increase of glucose levels in the blood and urine of these animals. Histopathological findings were observed in a number of tissues (mammary tissue, liver, pancreas, kidneys, heart, spleen, thymus, parathyroids, adrenals, pituitary, parotid salivary gland, oesophagus, stomach, intestinal tract, urinary bladder, skin, lachrymal glands, sternum and femoro-tibial joint, brain, reproductive organs (testes, prostate, epididymis, seminal vesicles, preputial glands, ovaries, vagina, clitoral glands), s.c. injection sites, periaortic and interscapular brown adipose tissue, mandibular axillary and inguinal lymph nodes and eyes). All findings were considered related to either the pharmacological effect of growth hormone or secondary to the development of diabetes.

In the 26-week study, animals were dosed less frequently (twice weekly) with doses up to 4 mg/kg. In this study, all findings were related to the pharmacological effects of growth hormone and no signs of diabetes were observed.

In the toxicity studies in Cynomolgus monkeys, animals were dosed twice weekly with 0.4, 2 and 9 mg/kg. The only findings observed were related to the expected pharmacological effect of growth hormone (i.e. swelling of the mammary area, acinar development and glandular dilation). Fertility studies in rats did not show any effects related to treatment.

No post-implantation loss was observed in the embryo-foetal development study in rats. No findings considered of relevance to humans were observed in the study and the no observed adverse event level (NOAEL) for maternal toxicity was 18 mg/kg/day, whilst the NOAEL for embryo-foetal development was 6 mg/kg/day, when administered during organogenesis.

In the embryo-foetal study in rabbits, the only treatment related effect was a reduction in foetal weight at all dose levels, when compared with controls. The reductions in foetal weight at 3 or 9 mg/kg/occasion exceeded 10% and were considered potentially adverse. The NOAEL for maternal toxicity and embryo-foetal survival and morphological development was 9 mg/kg/day, and the NOAEL for foetal growth was 1 mg/kg/occasion.

Additional details on non-clinical data are described in the Investigator's Brochure (IB)[17].

3.1.4 Clinical studies

A first human dose trial (NN8640-3915) in healthy male adults (Japanese and non-Asian subjects) investigated safety, tolerability (i.e. injection site reactions), PK and PD of s.c. doses of somapacitan (single and multiple dose) compared to placebo. Single doses were administered to non-Asian subjects only; multiple doses were administered to both Japanese and non-Asian subjects. Somapacitan administered to healthy male subjects was well tolerated at all doses (single dose up to 0.32 mg/kg and multiple dose up to 0.24 mg/kg), with no serious safety issues or significant injection site reactions identified. No differences in AUC (0-tau) and Cmax were observed between Japanese and non-Asian subjects. A significant dose-dependent IGF-I response was induced at all dose levels, with significantly increased IGF-I levels at all doses of somapacitan.

Trial NN8640-3947 was a multiple dose, dose-escalating trial investigating safety, tolerability, PK and PD of somapacitan compared to Norditropin® in AGHD subjects. Subjects received multiple s.c. doses of somapacitan or Norditropin®. Somapacitan was well tolerated at all doses investigated (0.02, 0.04, 0.08 and 0.12 mg/kg), with no serious safety issues or clinically significant injection site reactions identified. There was a dose dependent increase in the frequency and severity of AEs. The AEs were most frequently observed at the highest dose levels (somapacitan 0.08 and 0.12 mg/kg) and some were similar to well-known GH AEs (i.e., peripheral oedema, weight increase). The percentage of subjects with AEs following somapacitan 0.02−0.08 mg/kg was similar to that reported for Norditropin® treated subjects. No anti-somapacitan antibodies or anti-hGH antibodies were detected. The IGF-I response after once weekly somapacitan (0.02 and 0.04 mg/kg) and once-

daily Norditropin® appear similar. The IGF-I profiles indicate that somapacitan may be suitable for once weekly dosing.
Trial NN8640-4043 was a multicentre, multinational, randomised, open-labelled, parallel-group, active-controlled trial comparing the safety of once-weekly dosing of somapacitan (NNC0195-0092) with daily Norditropin® FlexPro® for 26 weeks in previously human growth hormone treated adults with growth hormone deficiency. Somapacitan was well tolerated with no clinically significant safety and local tolerability issues identified, and no positive test results for anti-somapacitan antibodies or anti-hGH antibodies were reported in this trial. The IGF-I profile was maintained throughout the trial in both treatment groups, supporting a once-weekly dosing of somapacitan. Once-weekly dosing of somapacitan was more convenient than daily dosing of Norditropin® FlexPro® in AGHD patients previously treated with daily hGH.

3.1.5 Risks and benefits

The non-clinical safety programme of somapacitan reveals no hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity. Non-clinical data is summarised in section 3.1.3.

Currently available data on clinical safety and efficacy of somapacitan is summarised in section 3.1.4. The safety profile of somapacitan has been evaluated in healthy adult subjects receiving single or multiple doses of the drug (NN8640-3915), in subjects with AGHD receiving multiple doses of the drug (NN8640-3947) and in non-naïve subjects with AGHD receiving IGF-I titrated dosing (NN8640-4043). Overall, the drug was well tolerated, and the safety profile of somapacitan observed so far is similar to that of the existing growth hormone products for daily administration, e.g. Norditropin® FlexPro®.

Additional details on the trial product are described in the IB[17].

3.1.6 Norditropin® FlexPro®

Norditropin® is the registered trademark for Novo Nordisk's recombinant hGH product, somatropin. Norditropin® FlexPro® is the prefilled pen with liquid hGH to be used as comparator.

Norditropin® FlexPro® is currently approved in the EU countries for GHD, Turner syndrome, Short for Gestational Age (SGA), AGHD and growth retardation in prepubertal children due to chronic renal disease. In the US, Norditropin® FlexPro® is approved for GHD, Noonan syndrome, Turner syndrome, AGHD and SGA. In other parts of the world, the main therapeutic indications are GHD, Turner syndrome, growth retardation in pre-pubertal children due to chronic renal disease, SGA and AGHD. Norditropin® FlexPro® has in these subject populations proven to be a safe and efficacious treatment.

For further information please refer to the Summary of Product Characteristics (SmPC)[18].

3.2 Rationale for the trial

The aim of the project is to develop a long-acting once weekly GH product which is as safe and efficacious, but has greater convenience and thus potentially better compliance compared to standard once daily hGH treatment.

The aim of the trial is to investigate safety, tolerability, efficacy and treatment satisfaction of multiple once weekly s.c. dosing of somapacitan in Japanese adults with growth hormone deficiency (GHD).

Pharmaceuticals and Medical Devices Agency (PMDA) has requested 52 weeks safety data for Japanese GHD subjects previously treated with hGH, to further substantiate the data from the 26 weeks global safety trial NN8640-4043. It has been agreed with PMDA that 60 subjects will be enrolled into this study.

PMDA has further requested that this 52 weeks trial should include evaluation of efficacy after switching to somapacitan from existing hGH treatment.

Novo Nordisk has decided that this 52 weeks trial should evaluate the degree of treatment satisfaction of once weekly dosing of somapacitan versus once daily hGH treatment.

4 Objective(s) and endpoint(s)

4.1 Objectives

Primary objective

- To evaluate the safety of once weekly dosing of somapacitan during 52 weeks of treatment in Japanese GHD subjects previously treated with hGH

Secondary objective

- To evaluate the efficacy of once weekly dosing of somapacitan by measuring the effect on abdominal adipose tissue during 52 weeks of treatment in Japanese GHD subjects previously treated with hGH
- To evaluate the degree of treatment satisfaction of once weekly dosing of somapacitan during 52 weeks of treatment in Japanese GHD subjects previously treated with daily hGH

4.2 Endpoints

4.2.1 Primary endpoint

- Incidence of adverse events, including injection site reactions from first administration of trial product to end of the trial period (53 weeks including follow-up)

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT) are marked with an asterisk (*).

- Supportive secondary efficacy endpoints
    - Change from baseline (randomisation) to end of treatment period (52 weeks) in:
        - cross-sectional total adipose tissue compartments (TAT)*,
        - subcutaneous adipose tissue compartments (SAT)*, and
        - intra-abdominal or visceral adipose tissue compartments (VAT)*

determined by quantitative computed tomography (CT) scans

    - Change from baseline (randomisation) to end of treatment period (52 weeks) in Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores for:
        - effectiveness*
        - convenience*
        - global satisfaction*

- Supportive secondary safety endpoints
    - Change from baseline to the end of treatment period (52 weeks) in:
        - Physical examination
        - Body weight
        - Vital signs
        - Electrocardiogram (ECG)
        - Clinical laboratory test results including haematology, biochemistry, fasting glucose, fasting insulin, steady state beta cell function (%B) and insulin resistance (IR) (HOMA estimates), and HbA1c levels
    - Occurrence of anti-somapacitan antibodies for subjects randomised to somapacitan from randomisation to end of the trial period (53 weeks including follow-up)*
    - Occurrence of anti-hGH antibodies for subjects randomised to Norditropin® FlexPro® from randomisation to end of the trial period (53 weeks including follow-up)
    - Incidence of clinical technical complaints

5 Trial design

5.1 Type of trial

This is a multicentre, national, randomised, open labelled, parallel-group, active controlled trial to compare safety of once weekly somapacitan with daily Norditropin® FlexPro® in previously hGH treated Japanese GHD subjects for 52 weeks. (20 weeks dose titration, 32 weeks fixed dose treatment) followed by 1 week washout.

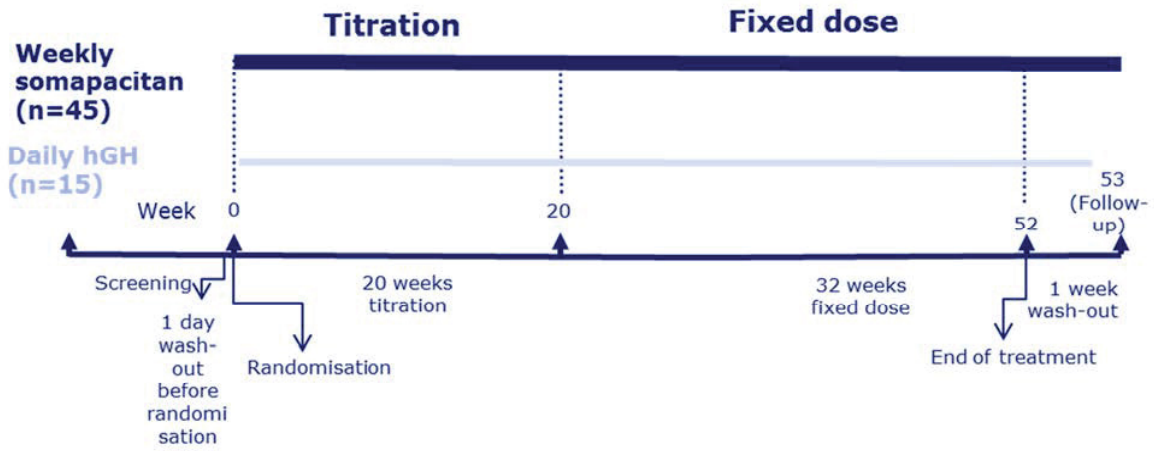


Figure 5–1 Trial design

Sixty (60) subjects will be randomised in a 3:1 (somapacitan : Norditropin® FlexPro®) ratio to receive somapacitan (approximately 45 subjects) or Norditropin® FlexPro® (approximately 15 subjects) during a 52 weeks period (20 weeks dose titration followed by 32 weeks fixed dose treatment). The randomisation will be stratified according to sex (male and female). Discontinued subjects will not be replaced.

5.2 Rationale for trial design

The inclusion of the active controlled arm in the open-labelled design is to compare safety including local tolerability (i.e. injection site reactions) of somapacitan to daily Norditropin® FlexPro® treatment. The open-labelled design is chosen because a blinded design would not be technically feasible due to the difference in injection frequency, and in order to be able to compare the degree of subject satisfaction related to daily vs. weekly injections, which would not be possible if a double-dummy design was applied.

Trial NN8640-4043 showed that at baseline and during the titration period, the number of patients with IGF-I standard deviation score (SDS) below -2 was different in the somapacitan group than in the Norditropin® FlexPro® group. Based on these data, the following will be implemented:

1. Addition of an inclusion criteria ensuring that only patients with IGF-I levels between –2 SDS and +2 SDS will be included.
2. Addition of one titration visit, allowing up to five opportunities for dose adjustments.

No positive test results for anti-somapacitan antibodies or anti-hGH antibodies were reported in trial NN8640-4043. Therefore, antibody samplings will be performed only at randomisation and at the final follow-up visit.
The somapacitan PK modelling results from trial NN8640-4043 showed steady state from 2 weeks and forward following initial dose as well as following each dose adjustment, allowing a titration schedule in alignment with normal clinical practise and facilitating patient recruitment.

The treatment period is 52 weeks, consisting of a 20 week titration period and a 32 week fixed dose period. Two washout periods are included for measurement of antibodies; before treatment start and following last treatment, as hGH or somapacitan in serum may cause false negative results in antibody assays. First washout is at randomisation where sampling for antibodies must take place minimum 12 hours after last dose of daily hGH. Second washout period is at end of trial, where samplings for antibodies are taken at the follow-up visit (week 53). Because IGF-I is a biomarker of hGH mediated effect, IGF-I has been chosen as a titration marker. An individualised dose titration regime rather than a fixed body weight based regime will be used. Clinical studies have shown that adverse effects were less frequent in subjects receiving dose-titration compared to weight based dosing, and current clinical practice for hGH treatment in AGHD is individual dose titration[19, 20].
The suggested titration period allows for five opportunities to adjust the dose of somapacitan or Norditropin® FlexPro® to achieve an optimal targeted serum IGF-I concentration.

5.3 Treatment of subjects

Time of injections:

- Somapacitan subjects will inject themselves once a week s.c. in the morning no later than 10 AM to ensure consistency of PK/PD with previous trials. On site visit days this can be extended until 12 PM (noon). Trial drug may not be administered in the morning before relevant visit procedures have been performed (see section 2).
- Norditropin® FlexPro® subjects will inject themselves daily s.c. in the evening (to reflect standard treatment practice) throughout the trial and only in the morning (no later than 12 PM (noon) and at least 12 hours after injection the evening before) during observed trial drug administration. Injections with Norditropin® FlexPro® the night before blood sampling for anti-hGH antibodies must occur at least 12 hours prior to sampling.

The first dose will be administered by the subject on Day 0 (at randomisation).The first dose will be fixed, and will be provided by the electronic case report form (eCRF). The last dose will be

administered by the subject at home, for subjects in the somapacitan treatment arm prior to the visit at week 51+4 days and for subjects in the Norditropin® FlexPro® arm 3 times after that visit (so that Norditropin® FlexPro® will be administered 7 times in week 51). No trial drug will be administered in Week 52 prior to the follow-up visit. The maximal treatment duration for a single subject is 52 weeks.
Subjects in both arms will be trained in the use of the pen-injector and inject themselves with trial drug under the supervision of the site staff at the visits where administration is observed, and will inject themselves at home.

5.3.1 Dose titration

During the first 20 weeks the dose will be titrated every fourth week starting from week 4. The last dose adjustment will be done at week 20. This allows five opportunities for dose adjustment (weeks 4, 8, 12, 16 and 20). Dose titration is based on insulin-like growth factor-I standard deviation score (IGF-I SDS) values used for calculation of the next dose. The dose adjustment calculations will provide the new doses for the subjects in the eCRF. IGF-I, insulin-like growth factor binding protein – 3 (IGFBP-3) and IGF-I SDS results will not be made available to the investigator during the trial.
The dose administered to the subject must be entered in the IWRS.

Subjects will come to the clinic 3 weeks and 3 days after the previous dose adjustment visit for an IGF-I, IGFBP-3 and PK blood sample draw. Handling deviations from this schedule is described in section 5.3.5. The dose adjustments are performed at weeks 4, 8, 12, 16 and 20, i.e. four days after the IGF-I titration samples have been collected. Dose adjustments will be provided over the phone, except for the last dose adjustment (week 20) which will happen at site. After last dose adjustment visit (week 20), the individual dose level is fixed.

Besides the IGF-I based dose adjustment during the titration period, dose reduction can be considered during the entire trial period (including the titration period) at the investigator's discretion for safety concerns. If adverse events with a probable relationship to the trial drug are persistent but continuation in the trial is acceptable, as judged by the investigator and subject, dose reduction in steps of 25% can be considered. If, after consecutive dose reduction steps, AEs still persist, the subject's treatment may be discontinued or the subject may withdraw as described in section 6.4 and 6.5.

If a subject reports symptoms of GH related AEs at a dose adjustment visit, the dose titration in the eCRF should be performed prior to potentially reducing the dose by 25% (performing the dose reduction in the eCRF), as the IGF-I based titration might reduce the dose.

5.3.2 Dose titration algorithm

The titration algorithm depends on the obtained IGF-I SDS. The baseline IGF-I value (i.e. when not on hGH treatment) for each subject is unknown, as the 1-day washout period before randomisation will not allow IGF-I SDS to fall to baseline value.
The algorithm for the dose adjustments in Table 5–2 is based on PK/PD analysis of data from previous trials with somapacitan. The dose titration of Norditropin® FlexPro® Table 5–4 is designed based on clinical experience, and results from NN8640-3947 which contained a comparator arm with daily Norditropin NordiFlex® doses and also in alignment with a titration algorithm from literature[12].

5.3.3 Titration for subjects treated with somapacitan

The fixed starting dose of somapacitan at randomisation visit (Day 0) are described in Table 5–1, dose titration in Table 5–2.The starting doses were tested to be safe in NN8640-3947 and are expected to be below the ideal maintenance dose for IGF-I SDS target for most subjects.

Table 5–1 Starting doses for somapacitan subjects

Group	Starting dose of somapacitan*	Starting dose converted to daily exposure
Subjects between 18 and 60 years of age	1.5 mg/week	0.214 mg/day
Females on oral oestrogen irrespective of age	2.0 mg/week	0.286 mg/day
Subjects older than 60 years	1.0 mg/week	0.143 mg/day

*The starting doses are expected to be below the ideal maintenance dose for IGF-I SDS target for most subjects. Individual adjustment of dose based on individual IGF-I response will be performed during the first 20 weeks.

Table 5–2 Dose Titration Algorithm for somapacitan subjects

IGF-I SDS Interval (3 weeks and 3 days after last dose adjustment)	**Increment/reduction of weekly dose**
IGF-I SDS > 3	-1 mg
2 < IGF-I SDS ≤ 3	-0.5 mg
0 < IGF-I SDS ≤ 2	-
-2 < IGF-I SDS ≤ 0	+0.7 mg
IGF-I SDS ≤ -2	+1.5 mg

If the algorithm returns a dose of less than 0.1 mg, the weekly dose of somapacitan must be 0.1 mg. Hence, the minimum weekly dose of somapacitan is 0.1 mg. The maximum weekly dose of somapacitan is 8 mg. If the dose is larger than 4 mg, the dose should be split into two injections of equal size.
If somapacitan subjects forget or are unable to inject the dose in the morning, they have to take the drug as soon as possible during the same day. If the subjects have failed to inject the trial product on the planned dosing day in the titration period, they should contact the trial site since the following IGF-I visit will have to be rescheduled, i.e. postponed two weeks (see section 5.3.5). Injections should remain in the body areas of thighs and/or abdomen with rotation within these body areas for every injection.

5.3.4 Titration for subjects treated with daily Norditropin® FlexPro®

The fixed starting dose of Norditropin® FlexPro® given daily from randomisation visit (Day 0) is described in Table 5–3, dose titration in Table 5–4.

Table 5–3 Starting doses for Norditropin® FlexPro® subjects

Group	**Starting dose of Norditropin® FlexPro®***
Subjects between 18 and 60 years of age	0.2 mg/day
Females on oral oestrogen irrespective of age	0.3 mg/day
Subjects older than 60 years	0.1 mg/day

*The starting doses are expected to be below the ideal maintenance dose for IGF-I SDS target for most subjects. Individual adjustment of dose based on individual IGF-I response will be performed during the first 20 weeks.

Table 5–4 Dose Titration Algorithm for Norditropin® FlexPro® subjects

IGF-I SDS Interval (3 weeks and 3 days after last dose adjustment)	**Increment/reduction of daily dose**
IGF-I SDS > 3	-0.1 mg/day
2 < IGF-I SDS ≤ 3	-0.05 mg/day
0 < IGF-I SDS ≤ 2	-
-2 < IGF-I SDS ≤ 0	+0.1 mg/day
IGF-I SDS ≤ -2	+0.2 mg/day

If the algorithm returns a dose of less than 0.05 mg, the daily dose of Norditropin® FlexPro® must be 0.05 mg. Hence, the minimum daily dose of Norditropin® FlexPro® is 0.05 mg. The maximum daily dose of Norditropin® FlexPro® is 1.0 mg.
If Norditropin® FlexPro® subjects forget or are unable to inject the dose in the evening they should skip the dose and continue on the next evening with the next scheduled dose. If a subject failed to inject the trial product the evening before a planned IGF-I visit in the titration period, the subject should contact the trial site since the IGF-I visit will have to be rescheduled, i.e. postponed two weeks. Injections should only be performed in the thighs and/or abdomen with rotation within these body areas for every injection.

5.3.5 Deviations from titration schedule

The dose titration schedule in the protocol should be followed in order to allow titration to an optimal therapeutic dose for all subjects. Five dose adjustment evaluations are required for optimal dose titration.
If for any reason a subject cannot be dose titrated on a scheduled dose adjustment day (e.g.: IGF-I value not available, subject comes for IGF-I sampling in a non-fasting state, or subject has not taken the dose as prescribed),

- the **previous IGF-I sampling** will be repeated or rescheduled to two weeks later
- the **affected dose adjustment** will be rescheduled to two weeks later

Consecutive postponements are not allowed, i.e. no visit may be rescheduled more than once.

Changes to the dose titration like those described above and dose reduction in steps of 25% will not be considered protocol deviations. Reasons for dose reduction should be entered in the eCRF. Based on this information it may be decided to ask for additional information regarding the deviation (see section 14). If the answer explains the deviation no further action will be taken.

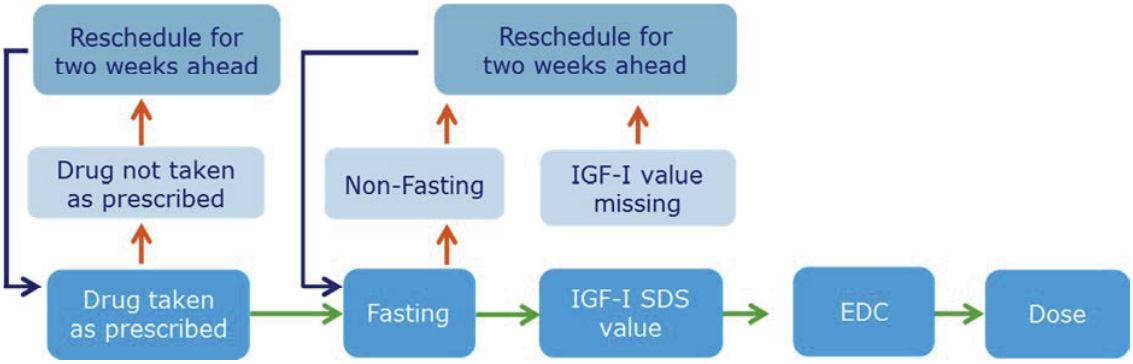


Figure 5–2 Flow of rescheduling visits in the titration period

If a subject has not completed at least 3 dose adjustment evaluations, this will be considered a protocol deviation because fewer than three completed dose adjustment evaluations are not expected to be sufficient to achieve therapeutic doses in a majority of subjects. Trial visits after week 20 will not be postponed.

5.4 Treatment after discontinuation of trial product

No treatment will be offered after end of trial. When discontinuing trial products, either after the follow-up visit (week 53) or if trial product is discontinued prematurely, the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

All doses will be administered subcutaneously as this is the intended route of administration of somapacitan when marketed.
The dosing regimen is once weekly for somapacitan as the compound is developed as a once weekly therapy for adults with GHD to provide greater convenience, and thus potentially better compliance, compared to standard hGH treatment which must be dosed daily. A healthy subject trial (NN8640-3915) and a trial in adults with GHD (NN8640-3947) showed that increased IGF-I levels from baseline were maintained for at least one week after dosing. A 26 weeks trial in subjects with AGHD (NN8640-4043) showed that IGF-I titrated dosing resulted in an IGF-I profile that was maintained throughout the trial, supporting a once weekly dosing with somapacitan. Trial product in these three trials was given in the morning, therefore morning injection for somapacitan has been

chosen also for this trial to ensure the consistency of PK/PD with previous trials. Norditropin® FlexPro® will be administered in the evening following standard treatment practice[18].
As IGF-I is a biomarker of GH mediated effects[4], IGF-I has been chosen as a titration marker. The dose titration is described in detail in section 5.3.1.

The dose titration algorithm has been selected to reach a mean IGF-I SDS value during steady state (MVSS) of -0.5 SDS to + 1.75 SDS and is based on PK/PD analysis of data from previous trials with somapacitan. Dose reduction in steps of 25% has been selected as lowest anticipated reduction with significant change in GH related AEs.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 90

Number of subjects planned to be randomised: 60

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.

2. Male or female, aged 18-79 years (both inclusive) at the time of signing informed consent.

3. GHD fulfilling either one of the following criteria:
    a. Adult onset: subjects diagnosed with GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or traumatic brain injury (TBI)
    b. Childhood Onset: Subjects who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

4. GHD diagnosed ≥ 6 months (defined as 180 days) prior to screening.

5. Treatment with hGH for at least 6 consecutive months (defined as 180 days) at screening.

6. IGF-I level between -2SDS and +2SDS, both inclusive (-2SDS ≤ IGF-I level ≤ +2SDS).

7. If applicable, hormone replacement therapies for any other hormone deficiencies, adequate and stable for at least 90 days prior to randomisation as judged by the investigator.

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products.

2. Previous participation in this trial. Participation is defined as randomisation.

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method. Adequate contraceptive measures are abstinence, diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

4. Male of reproductive age who or whose partner(s) is not using adequate contraceptive methods.

5. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 180 days before screening or participation in any other trial within 90 days before randomisation.

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

7. Active malignant disease or history of malignancy. Exceptions to this exclusion criterion:
    a. Resected in situ carcinoma of the cervix and squamous cell or basal cell carcinoma of the skin with complete local excision.
    b. Subjects with GHD attributed to treatment of intracranial malignant tumours or leukaemia, provided that a recurrence-free survival period of at least 5 years is documented in the subject's medical records.

8. For subjects with surgical removal or debulking of pituitary adenoma or other benign intracranial tumour within the last 5 years:

    a. Evidence of growth of pituitary adenoma or other benign intracranial tumour within the last 12 months (defined as ≤ 365 days) before randomisation. Absence of growth must be documented by two post-surgery MRI or CT scans. The most recent MRI or CT scan must be performed ≤ 9 months (defined as ≤ 270 days) prior to randomisation.

9. Clinically significant hepatic disease defined as alanine aminotransferase (ALT) level greater than 3 times upper normal limit according to the central laboratory measurements.

10. Clinically significant chronic renal impairment defined as creatinine level greater than 1.5 times upper normal limit according to the central laboratory measurements.

11. History of positive results of tests for hepatitis B and/or C or suspicion of hepatitis.

12. History of positive result of test for human immunodeficiency virus (HIV) antibodies.

13. Mental incapacity or language barriers which preclude adequate understanding or cooperation, who are unwilling to participate in the trial or who in the opinion of their general practitioner or the investigator should not participate in the trial.

14. Female subject who plans to change oestrogen therapy during the trial.

15. Diabetes mellitus.

6.4 Criteria for premature discontinuation of trial product

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see section 6.5).

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures.

The subject must be prematurely discontinued from trial product if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria

2. Pregnancy

3. Intention of becoming pregnant

4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

5. AE: If a subject reports symptoms which are considered unacceptable by the subject or the investigator, regardless of relationship to trial product, treatment must be discontinued

6. If physicians definitely diagnose diabetes mellitus in accordance with diagnostic criteria established by the Japan Diabetes Society[21] during the course of the trial the subject should be discontinued from treatment

See Section 8.1 for procedures to be performed for subjects discontinuing trial product prematurely.

6.5 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected.
See Section 8.1 for procedures to be performed for subjects withdrawing consent.

6.6 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

Somapacitan is being developed for treatment of adults with GHD. Therefore adults with GHD have been chosen as trial population to support marketing authorization for somapacitan. This is a safety trial recruiting subjects with GHD who have been treated with hGH for at least 6 months (defined as 180 days) at screening. The requirement for 6 months (defined as 180 days) of treatment with hGH is necessary in order for efficacy measures to have stabilised before entering NN8640-4244.
Both male and female adults with GHD are chosen to be enrolled in this trial, to obtain information on the safety of the drug product in both sexes.

7 Milestones

Planned duration of recruitment period (FSFV - LSFV): 28 weeks.

End of trial is defined as last subject last visit (week 53).

Recruitment:
The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart (see section 2).

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[22], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[23], the Food and Drug Administration Amendment Act (FDAAA)[24], European Commission Requirements[25, 26] 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 trial data will also be registered at Japan Pharmaceutical Information Centre Clinical Trials Information (JapicCTI).

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. Timing of the assessments at specific visits and visit windows are defined in the flow chart (see section 2).

Informed consent must be obtained at least one day before any trial related activity, see section 18.2.

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

At the first visit the subjects will be provided with information regarding the trial and asked to sign the informed consent form. At the screening visit, subjects will be provided with a subject ID card stating that they are participating in a trial and giving contact addresses and telephone numbers of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. A screening session must be performed in the IWRS.

Screening failures: For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section 12.

A screening failure session must be made in the IWRS. The case book must be signed in the eCRF.

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria; this includes re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters. Re-screening of subjects is allowed ONLY if the screening window of 21 days between screening visit and randomisation visit is exceeded (e.g. due to unforeseen or urgent events which make it impossible for the subject to attend the planned randomisation visit), and ONLY if the subject was eligible for randomisation. No separate informed consent is required, but all assessments and lab samples must be repeated.

Re-sampling of screening parameters is ONLY allowed during an unscheduled visit (see section 8.8) if samples are lost or damaged before arriving at the analysing laboratory, or if the analysis failed at the laboratory.

Premature discontinuation of trial product: If a subject prematurely discontinues trial product, the investigator must undertake procedures similar to those for week 51+4 days as soon as possible, however, the subject should be encouraged to follow all remaining site visits in the trial according to the trial flow chart. The follow-up visit (week 53) must be performed at least two weeks after last administration of somapacitan and at least 8 days after last administration of Norditropin® FlexPro®.

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

Withdrawal from trial: If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for week 51+4 days as soon as possible. If the subject agrees, the follow up visit (week 53) must be performed at least two weeks after last administration of somapacitan and at least 8 days after last administration of Norditropin® FlexPro®.

The end-of-treatment form and the end-of-trial form must be completed, and 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, and in the eCRF it must be specified that the subject will not participate in subsequent visits in the trial. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF system.

Review of diaries, patient reported outcomes (PROs), laboratory reports etc. must be documented either on the documents or in the subject's medical record.

If clarification of entries or discrepancies in the diary or patient reported outcomes is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth
- Sex
- Ethnicity
- Race

8.2.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at screening 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.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.
Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

The following assessments must be recorded in the eCRF:

- History of GHD:
  - Childhood onset (CO): Idiopathic or organic
  - Adulthood onset (AO)
- Concomitant illnesses present at start of the trial
- Relevant medical conditions/illnesses in the past, including history of cancer/intracranial tumour
- Treatment for GHD during the 6 months prior to screening, including type of medication and dose
- Other hormone replacement therapy

The method used for diagnosing GHD should be recorded in the eCRF. The method must be in accordance with the "Guidance of diagnostic criteria and treatment for AGHD (Age ≥ 18): 2013 (Japanese)", or relevant guidelines applicable at the time of GHD diagnosis.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigator's own practice, the investigator must make reasonable effort to obtain a copy of the subject's medical record from the relevant party, e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.2.1 MRI or cranial CT scan

Only for subjects with surgical removal or debulking of pituitary adenoma or other benign intracranial tumour within the last 5 years: The only information collected in the eCRF is whether the subject is eligible for trial participation. MRI or CT scan for screening is accepted if it is performed ≤ 9 months (defined as ≤270 days) prior to randomisation and results are available for evaluation at randomisation.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial products, which is taken during the trial, from screening to the last follow up visit in the trial.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation. For medications containing oestrogen also the route of administration must be recorded.

If a change is due to an AE, then this must be reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Childbearing potential

It must be recorded in the eCRF whether female subjects are of childbearing potential.
Pregnancy testing must be performed on female subjects of childbearing potential as described in Section 8.5.2.7. Female subjects of childbearing potential, and partners of male subjects of reproductive age, must be instructed to use adequate contraceptive methods throughout the trial and until at least 16 days after last trial drug administration.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

8.2.5 Body measurements

8.2.5.1 Height and body weight

The height (in cm, without shoes) and body weight (in kg, without shoes and overcoat) of the subject will be recorded at screening.

Body weight will be measured at regular intervals throughout the trial (see section 2). It is preferable to measure body weight at the same time of day, using the same scale from visit to visit.

8.3 Efficacy assessments

8.3.1 CT scans

Quantitative CT scans will be performed at randomisation (before first trial dose administration) and at week 51+ 4 days to determine cross-sectional TAT, SAT and VAT adipose tissue

compartments. **Note:** This CT scan may be performed at the screening visit instead of at the randomisation visit, if a CT scan is required to confirm eligibility in relation to exclusion criterion # 8.

8.3.2 Patient reported outcomes

Patient reported outcomes (PROs) will be assessed at randomisation and in week 32 and week 51 (see section 2) using the Treatment Satisfaction Questionnaire for Medication - 9 items (TSQM-9)[27]. At randomisation, subjects will state their satisfaction with their pre-trial GH therapy, as they have not yet received trial medication.
The TSQM-9 is a generic questionnaire that measures a subject's satisfaction with medication. Items are rated on a 5- or 7-point scale according to the subject's experience with the medication and the concepts covered are satisfaction with the effect of the medication, convenience, confidence and global treatment satisfaction.
By using the TSQM-9 it will be possible to assess the subjects' satisfaction with medication.

The PRO questionnaire will be a self-administered questionnaire, to be completed by the subject without assistance of the site personnel. The questionnaire should be completed after all fasting related activities are completed but before any other trial related activity at each applicable visit. Written instructions on how to complete the questionnaire will be provided to the subject. Subjects who cannot complete the questionnaire themselves due to physical limitations may receive assistance with completion of the questionnaire. After completion the PRO must be reviewed by the investigator on the same day for potential AEs, including any overall change in health and concomitant medication. When reviewing the PRO questionnaire for AEs the investigator should not influence nor question the subject on the content of the subject's response to PRO questions. Review of the PRO must be documented either on the front page of the documents and/or in the subject's medical record. If clarification of entries in the PRO questionnaire is needed, the subject should be questioned and a conclusion made in the subject's medical record. Only the subject can make changes in the PRO. Care should be taken not to bias the subject. Filled in questionnaires will be sent for central data entry into the clinical database.

8.4 Safety assessments

8.4.1 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.1.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form (medication error form) must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors and reporting timelines, see Section 12.1.4.

8.4.1.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.
In case any of these events fulfil the criteria for a SAE, please report accordingly, see Section 12.
For the following AEs additional data collection is required:

Injection site reactions:
Injection site reactions will be evaluated during the trial (see section 2). If suspicion of an injection site reaction occurs between site visits the subject should be instructed to call the site as soon as possible for further guidance. An unscheduled visit may take place at the investigators discretion.

At all site visits injection site reactions will be evaluated by the investigator by visual and manual inspection of injection sites; at randomisation, injection site reactions will be evaluated after trial drug administration.

If an injection site reaction fulfils the criteria for an AE, it should be reported on the AE form. Additionally, a specific injection site reaction form must be completed in the eCRF.

In the event of an injection site reaction, additional assessments will be performed until resolution, as judged necessary by the investigator. The following results will be recorded in the eCRF:

- Burning
- Pain
- Numbness
- Itching
- Redness
- Induration
- Dimpling (small cavities)
- Swelling
- Macula
- Haematoma
- Bleeding
- Other symptoms/findings

In addition to reporting the site reaction on the AE form and on the injection site reaction form, digital photos must be taken of the injection site at the time of identification and hereafter as often as judged necessary by the investigator. Should injection of trial product require more than one injection, all injections sites should be evaluated. The photos should include trial ID and subject number, as well as date of photo, actual time of photo (24h format) and a ruler for injection site measurement. Copies of all photos will be evaluated by an external dermatologist and subsequently transferred to Novo Nordisk.

8.4.2 ECG

A standard 12-lead ECG will be performed while the subjects are in supine position according to the flow chart (see section 2). The investigator will evaluate the ECG recordings and classify them according to the following categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

At the screening visit, ECGs classified as abnormal and clinically significant will be recorded as concomitant illnesses. Worsening of ECGs will be recorded as AEs if they are evaluated as abnormal and clinically significant at a time point after the screening procedure. If a 12-lead ECG has already been performed and is available ≤ 90 days before randomisation, the procedure need not be repeated. It must be documented in the subject notes that the reason for performing the ECG was not related to the present trial. ECG recordings must be dated and signed by the investigator to document data review.

8.4.3 Physical examination

A physical examination of the following body systems will be performed at screening, randomisation and throughout the trial (see section 2):

- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system, including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation

The investigator will evaluate the findings from the physical examination and classify them as follows:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

At the screening visit, physical examination classified as abnormal and clinically significant will be recorded as concomitant illnesses. Worsening of physical examination findings from the screening visit will be recorded as AEs.

8.4.4 Vital signs

Vital signs will be assessed at screening, randomisation and throughout the trial (see section 2) and will contain:

- Systolic blood pressure (mm Hg), supine after 5 minutes rest
- Diastolic blood pressure (mm Hg), supine after 5 minutes rest
- Pulse (beats per minute), supine after 5 minutes rest

At screening visit, vital signs outside reference range which in the investigator judgement is abnormal and clinically significant should be recorded as concomitant illnesses. Clinically significant worsening of vital signs from the screening visit will be recorded as AEs.

8.5 Laboratory assessments

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 and report these according to section 8.2.2 and section 12.

Antibody samples will be stored as described in section 24.2. All other laboratory samples will be destroyed no later than at finalisation of the clinical trial report.

All lab reports must be dated and signed by the investigator to document data review.

Surveillance of laboratory safety data (with the exception of PK, biomarkers and anti-drug antibody data) will be performed by a medical specialist at least every 2 months based on safety surveillance reports. If a finding is identified, the medical specialist will immediately inform the chairman of the safety committee.

8.5.1 Laboratory assessments for efficacy

Not applicable for this trial.

8.5.2 Laboratory assessments for safety

Biomarkers (IGF-I and IGFBP-3)

When sampling for IGF-I and IGFBP-3, subjects must be fasting 8 hours before sample collection, with only water allowed. If a subject comes non-fasting to visits during the titration periods, the sampling will be re-scheduled according to section 5.3.5.

IGF-I and IGFBP-3 samples will be collected at screening and every second visit during the titration period and throughout the fixed-dose period (see section 2). All samples must be drawn prior to trial drug administration if this is planned on a sampling day. Based on the results, IGF-I SDS values will be calculated by the central lab, transferred to the eCRF and used for dose adjustment during the titration period.

The central laboratory will be responsible for providing age and sex appropriate normal reference ranges of IGF-I and IGFBP-3 and for calculation of IGF-I SDS according to below equation:

$$IGF - I\ SDS\ = \frac{\left(\left(\frac{IGF - I\ value}{Median}\right)^{Skewness}\right) - 1}{Skewness \times Standard\ Deviation}$$

Median, Skewness and Standard Deviation are based on reference data.

IGF-I SDS values will be used for dose titration of somapacitan and Norditropin® FlexPro®. Details of the dose titration are described in section 5.3.1.

8.5.2.1 Glucose metabolism

Fasting plasma glucose, fasting insulin, steady state beta cell function (%B) and insulin resistance (IR) (HOMA estimates), and HbA1c levels will be assessed at screening and during the trial (see section 2). Subjects must be fasting 8 hours before sample collection, with only water allowed. If the subject comes to a fasting visit in a non-fasting state this needs to be recorded in the eCRF.

8.5.2.2 Anti-drug antibodies

Anti-drug antibody samples will be collected prior to trial drug administration at randomisation and at the last visit (follow-up visit).
All subjects who have developed high titre antibody results and/or in vitro neutralising antibody response will be offered an appropriate follow-up period until the antibody response has levelled out, is decreasing or until the investigator and the sponsor decide that further follow-up is not warranted. After individual LSLV, the subjects will be requested to continue to have blood samples drawn every 3 months for follow-up analyses. The investigator will be informed, after a Novo Nordisk safety committee meeting, of any positive antibody results in case of clinically relevant

impact on efficacy and/or safety. The assessment of the impact on efficacy and safety is performed by the Novo Nordisk safety committee (section 12.7.1).

If anti-drug antibody follow up extends beyond the LSLV of the trial period, antibody data will be collected and locked in a separate DBL once follow-up of the last subject with positive antibody test results has been completed. The results will be reported either as an amendment to the Clinical Trial Report or in a separate Clinical Trial Report.

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 drug will be used.
Determination of antibodies against **somapacitan** in subjects randomised to somapacitan will be performed by Novo Nordisk or an appointed special laboratory using validated antibody assays. Confirmed anti-somapacitan antibody positive samples will be further tested for cross-reactivity to hGH and for in vitro neutralising effect.
Determination of **anti-hGH antibodies** in subjects randomised to Norditropin® FlexPro® will be analysed by Novo Nordisk or an appointed special laboratory using validated antibody assays. Confirmed anti-hGH antibodies will be further assessed for neutralising effect of anti-hGH antibodies in a validated cell based neutralising antibody assay.

8.5.2.3 Pharmacokinetics assessments of somapacitan and hGH

Blood samples for determination of somapacitan/hGH from all subjects will be taken at randomisation, at expected peak levels of IGF-I and at pre-dose time points throughout the trial (see section 2). All samples must be drawn prior to trial drug administration if this is planned on a sampling day. The laboratories will provide instructions on sampling, handling of samples, labelling and shipment of samples.

Somapacitan assay: The concentration of somapacitan in serum from subjects randomised to somapacitan will be measured by Novo Nordisk using a validated somapacitan- specific luminescent oxygen channelling immunoassay (LOCI) developed by Novo Nordisk. Validation documentation for the somapacitan analysis method will be available prior to trial start.

hGH assay: The concentration of GH in serum from subjects randomised to Norditropin® FlexPro® will be measured by the responsible special laboratory using a commercially available GH assay validated for Norditropin®.

8.5.2.4 Haematology

Haematology will be assessed at screening and during the trial (see section 2) and will include the following parameters:

- Haemoglobin
- Haematocrit
- Erythrocytes
- Mean corpuscular volume (MCV)
- Mean corpuscular haemoglobin concentration (MCHC)
- Thrombocytes
- Leucocytes

8.5.2.5 Biochemistry

Biochemistry will be assessed at screening and during the trial (see section 2) using serum samples. The assessment will include the following parameters:

- Sodium
- Potassium
- Chloride
- Calcium (total)
- Phosphate (inorganic)
- Creatinine
- Urea
- Uric acid
- Total protein
- Albumin
- Bilirubin (total)
- Creatine Kinase
- Alkaline Phosphatase (AP)
- Gamma-Glutamyltransferase (GGT)
- AST (Aspartate Aminotransferase)
- ALT (Alanine Aminotransferase)
- eGFRcreatinine (CKD-EPI)[28], a derived variable based on s-creatinine and multiplication factors for race and sex, will be calculated by the central laboratory.

8.5.2.6 Hormones

Thyroid function will be assessed at screening and during the trial (see section 2) using serum samples. The assessment will include the following parameters:

- Free T4
- Thyroid Stimulating Hormone (TSH)

If one or more of these parameters are out of normal range, subjects should either receive replacement therapy with thyroid hormone and/or be adjusted as per investigator discretion. For subjects with known TSH deficiency, replacement therapy with thyroid hormone should be adjusted according to the subject's clinical status and free T4, but not TSH.

8.5.2.7 Pregnancy testing

A blood pregnancy test (beta subunit of human chorionic gonadotropin [beta-HCG]) and a urine pregnancy test must be performed at the screening visit in women of childbearing potential (see exclusion criterion 3, section 6.3). At the randomisation visit, a urine pregnancy test must be performed before randomisation. During the trial for all other site visits than screening and randomisation visits, urine pregnancy testing in women of childbearing potential should be performed according to the flow chart.

8.6 Other assessments

8.6.1 Training in the pen-injector and observed trial drug administration

The subjects must be trained in how to handle the pen-injector when handed out the first time. Training must be repeated during the trial at regular intervals in order to ensure correct use of the device. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming the pen to ensure product flow
- 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.

During the trial period all subjects will be trained two times (see section 2) in the use of the pen-injector. After instruction the subject will perform self-injection with trial drug under observation by trial staff. The investigator may choose to perform training with a training pen which should only be injected into a pad or cushion once by the subject (using this test pen is optional).

It is the investigator's or delegated staff's responsibility to assess if the subject is capable of following instructions during training and in the directions for use (DFU), so that the subject can deliver the intended dose in a home setting.

The following will be recorded in the eCRF:

- The subject has received training in use of the pen-injector, including a step-by-step instruction for performing an injection
- The subject has performed an injection of trial product on their own with corrective feedback provided by site staff

8.6.2 Subject diaries

From randomisation a diary will be handed out to the subjects at relevant visits (see section 2, Flow chart). After randomisation, the completed diaries will be collected at regular intervals. The subject should be instructed by the site staff to complete the diary with the following records:

- Drug compliance (from randomisation): The subject will be asked to record date, time and dose of injections and any missed dose
- AEs (incl. injection site reactions)
- Concomitant medication, including changes

Review of diaries must be documented either on the front page of the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject. Data from the subject diaries will be entered in the eCRF by the site staff.

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given, including taking the trial products as prescribed.

Treatment compliance:
During the trial period subjects must record date and time of each dose of trial product in the diary (see section 8.6.2). If a dose is missed during the titration period, the subject must contact the trial site in order to potentially reschedule the next visit (see section 5.3.5).

8.8 Unscheduled visits

Unscheduled visits can be performed at the investigator's discretion if an AE requires additional follow-up, if the previous IGF-I sampling visit was not successful (see section 5.3.5) or if required by the Novo Nordisk department responsible for safety. Further, visits for re-sampling can take place if laboratory samples are lost or damaged before arriving at the analysing laboratory. This re-sampling will be at the discretion of the Novo Nordisk medically responsible person in collaboration with the investigator.

Unscheduled visits can take place at any time during the trial from screening until the last visit, but the eCRF will not include a specific "unscheduled visit" form. Rather, the unscheduled visits will be recorded according to the purpose of the visit, for example AE reporting or re-scheduling a postponed visit.
Visits/contacts to the site not related to the trial do not need to be recorded. Contacts for re-dispensing of trial drug as replacement for lost or damaged trial drug need to be recorded in the IWRS. Only medication allocated/dispensed through the IWRS is to be handed out to the subject.

8.9 Missing data

Investigators should make every effort to ensure all assessments are performed and data are collected. In case of missing data, the reason will be collected via the protocol deviation process described in section 19 and trends will be monitored on an on-going basis throughout the trial followed by appropriate action (e.g. training of site staff).

If an entire visit is missed and it is not possible to re-schedule the visit within the time window allowed, every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to visit schedule.

If a subject is unable/unwilling to attend the subsequent visit(s), procedures described in section 8.1 must be followed.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual (TMM).
Trial products must not be dispensed to any person not included in the trial.

Somapacitan PDS290 10 mg/1.5 ml must not be used if the solution does not appear clear to slightly opalescent, colourless to slightly yellow and essentially free from visible particles. Trial product should not be shaken vigorously at any time.

Norditropin® FlexPro® must not be used if the solution for injection does not appear clear and colourless. Norditropin® FlexPro® should not be shaken vigorously at any time.

9.1 Trial products

The following trial products will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Somapacitan PDS290 10 mg/1.5 ml (NNC0195-0092) (IMP, test product)	10mg/1.5ml	Solution for injection	s.c. injection	PDS290 pen-injector
Norditropin® FlexPro® (IMP, reference therapy)	10mg/1.5ml	Solution for injection	s.c. injection	FlexPro®

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[29], local regulations and trial requirements.

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 enrolment and randomisation.

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (randomisation visit). If applicable, DFUs can be handed out to subjects at subsequent visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Somapacitan PDS290 10 mg/1.5 ml	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Use within 6 weeks
Norditropin® FlexPro®	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Use within 35 days

*In-use time starts when first dose is taken.

The investigator must ensure that subjects are aware of the product in-use time and do not administer product exceeding this time period, but switch to a new pen-injector.

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). 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 must take appropriate action to ensure correct storage.

Responsibility for storage and drug accountability of the trial drug products at the trial site rests with the head of the trial site. The head of the trial site could assign some or all of the responsibilities for accountability of the trial drug products at the sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial drug products in accordance with procedures specified by Novo Nordisk. The head of the trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.
Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.
Non-allocated trial products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.
Drug accountability should be performed at pen level in the IWRS.

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

9.5 Auxiliary supplies

Novo Nordisk Denmark will supply:

- DFUs for somapacitan PDS290 and Norditropin® FlexPro®

Novo Nordisk Pharma Ltd. (Japan) will supply:

- Needles, PenNeedle®
- Test pen for training purposes, if requested

Only needles provided by Novo Nordisk may be used for administration of trial product.

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Dispensing verification (if barcode scanner is used)
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

(Breaking of blinded codes: Not applicable for this trial)

Sixty (60) subjects will be randomised in a 3:1 ratio to receive somapacitan or Norditropin® FlexPro® during a 52 weeks period.

The randomisation will be stratified according to sex (male and female). Discontinued subjects will not be replaced.
The randomisation, stratification and allocation to treatment arm will be handled by the IWRS (see section 10).

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is, according to GCP definition, any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality 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.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or 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.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** – marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** – considerable interference with the subject's daily activities; unacceptable.

- **Causality**
  Relationship between an AE and the relevant trial product*(s)*:
  - **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.

- **Final 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 sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **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 fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the subject is lost to follow-up.

12.1.2 Serious adverse event

A SAE is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

a. The term "life threatening" in the definition of SAE 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 was more severe.

b. The term "hospitalisation" is used when a subject:
  - Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
  - Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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.

[c.] A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE 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).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug. Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. That is a dose higher than 100 % of the intended dose; however, 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.

Medication errors must be reported on an AE form and a specific event form, see section 8.4.1.1.

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product.

In this trial the following AEs require the completion of specific event forms in the eCRF:

- Injection site reactions

For details, see Section 8.4.1.2.

12.1.6 Technical complaints

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:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (week 53). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or the subject, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

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.

Timelines for initial reporting of AEs:
The investigator must complete the following forms in the eCRF within the specified timelines:

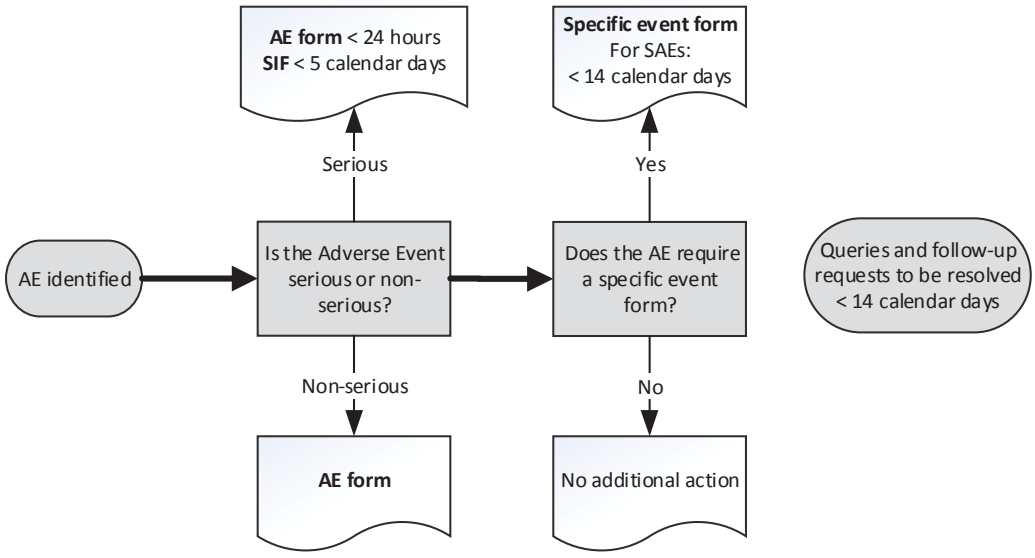
- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form (medication error form and injection site reaction form): In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness.
AEs requiring specific event forms are descibed in Section 12.1.4 *and 12.1.5.*

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- somapacitan IB current version and any updates thereto
- Norditropin® FlexPro®, Company Core Data Sheet (CCDS)-current version and any updates thereto

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.
Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the

information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- somapacitan PDS290 10 mg/1.5 ml
- Norditropin® FlexPro® 10 mg/1.5 ml
- Needles, PenNeedle®

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- Technical complaint on an investigational medical device that could have led to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

If the eCRF 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 eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial products.

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. Reporting of pregnancy information

Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. Reporting of AE information

The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:

Non-serious AEs:

- AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or new-born infant. If the AE occurred in the foetus or new-born infant, the AE can only be reported on paper AE and safety information form.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.5.2 Pregnancies in female partners of male subjects

Male subjects must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period. At the last scheduled visit, male subjects must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male subject and assess, if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the subject's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax:

1. **Reporting of pregnancy information**
   Information from the male subject has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

Initial reporting and follow-up information must be reported within **14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. Reporting of AE information

The following AEs in the foetus and newborn infant have to be reported:

- Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s).
- SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus).

Forms and timelines for reporting AEs:

See Section 12.5.1, point 2, "Forms and timelines for reporting AEs".

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

At present, there is no experience of overdose with somapacitan in humans. In NN8640-3915 healthy male volunteers were dosed with up to 0.32 mg somapacitan /kg (SD up to 0.32 mg/kg and MD up to 0.24 mg/kg). All AEs were mild or moderate and primarily observed at the highest dose levels. Most common AEs were: headache, peripheral oedema, joint pain, muscle pain and increase in blood sugar and insulin levels. In a recent trial in adults with GHD receiving multiple doses of the drug, the same safety profile of AEs were registered. These AEs are similar to those observed for existing growth hormone products on the market. For further details please refer to somapacitan IB[17].

A single overdose with Norditropin® will typically not cause any symptoms. Repeated overdosing may cause headache, oedema, arthralgia, myalgia, paraesthesia, carpal tunnel syndrome, and impaired glucose tolerance (refer to Norditropin® FlexPro® SmPC, version 10 or updates hereof[18]).

Any overdose should be reported as an AE, with or without clinical manifestations. Overdoses are considered medication errors and should be handled as described in section 8.4.1.1.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal somapacitan safety committee to perform review of ongoing safety surveillance.

12.7.2 Data monitoring committee

A data monitoring committee will not be established for the present trial.

12.7.3 Event adjudication committee

An event adjudication committee will not be established for the present trial.

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms (maternal form 1A and 1B, and paper AE- and safety information form related to pregnancies)
- PRO questionnaires

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is 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)

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

Corrections to the data in **paper CRF pages** may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary).

Corrections to the **eCRF data** may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF 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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LSLV at the trial site.

The monitor must be given direct access to all source 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).

All data must be verifiable in source documentation other than the eCRF.
For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original of the completed diaries and/or PROs must not be removed from the trial site, unless they form part of the CRF/eCRF and a copy is kept at the site.

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

The following data will be source data verified for screening failures:
- Date for obtaining informed consent.
- Screen failure reason
- AEs and SAEs

Monitors will review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

Some of the laboratory results (IGF-I SDS values) will be entered manually into the eCRF by Novo Nordisk personnel unrelated to trial conduct. The laboratory will provide all laboratory reports to the investigator for filing at trial site; however, the IGF-I SDS values and actual IGF values will not be available for the site staff until after the end of trial.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

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. In case a SAP is written, it will be finalised before database lock.

17.1 Sample size calculation

PMDA has requested 52 weeks safety data for a total of 60 Japanese GHD subjects previously treated with hGH, to further substantiate the data from the 26 weeks global safety trial NN8640-4043.

The sample size is not based on any formal calculations and does not account for withdrawals in the final sample size. 60 subjects should be randomised in a 3:1 ratio between somapacitan (45 subjects) and Norditropin® FlexPro® (15 subjects).

17.2 Definition of analysis sets

Two analysis sets are defined.

The full analysis set (FAS) used for evaluations of efficacy endpoints includes all randomised subjects that received at least one dose of randomised treatment. Only in exceptional cases may subjects be excluded from the FAS. Subjects will be analysed “as randomised”.

The safety analysis set (SAS) used for evaluations of safety endpoints includes all randomised subjects that received at least one dose of randomised treatment. Subjects will be analysed “as treated”.

The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before DBL. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CTR.

17.3 Primary endpoint

- Incidence of adverse events, including injection site reactions, from first administration of trial product to end of the trial period (53 weeks including follow-up)

The primary objective of the trial is to evaluate the safety of once weekly dosing of somapacitan during 52 weeks of treatment in Japanese GHD subjects previously treated with hGH and analysis of AEs will be the primary tool for achieving this. AEs will be analysed using descriptive statistics. All AEs with onset after the first administration of trial product and up until end of the trial (53 weeks) or 14 days after last trial drug administration, whichever comes first, will be included in the analysis. The AEs 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 AEs, the number of events and rate per 100 person years. AEs will be listed by treatment and subject with information on severity, relationship to trial product and demographics. AEs with onset before first dosing will be reported in a separate listing. AEs with onset 14 days or more after last trial drug administration will be reported in a separate listing.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

- Change from baseline (randomisation) to end of treatment period (52 weeks) in:
    - cross-sectional total adipose tissue compartments (TAT),
    - subcutaneous adipose tissue compartments (SAT), and
    - intra-abdominal or visceral adipose tissue compartments (VAT)

determined by quantitative computed tomography (CT) scans

The change in abdominal adipose tissue compartments (TAT, SAT and VAT) from baseline to week 52 endpoints will be used to address the second objective of evaluating the efficacy of once weekly dosing of somapacitan by measuring the effect on abdominal adipose tissue during 52 weeks of treatment in Japanese GHD subjects previously treated with hGH.
Changes in abdominal adipose tissue compartments (TAT, SAT and VAT) from baseline to week 52 will be analysed using an analysis of covariance (ANCOVA) model with treatment, GHD onset type and sex as factors and baseline value as a covariate. From the model the treatment difference at week 52 between somapacitan and Norditropin® FlexPro® will be estimated and the corresponding 95% confidence interval and p-value will be calculated for each endpoint. Subjects without week 52 data for the analysed endpoint will not be included in the analysis. It is expected that less than 7% of the subjects will not have week 52 data for the CT scan based endpoints.

- Change from baseline (randomisation) to end of treatment period (52 weeks) in Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores for:
    - effectiveness
    - convenience

- global satisfaction

The change from baseline (randomisation) to end of treatment period (52 weeks) in Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores will be used to address the second objective of evaluating the degree of treatment satisfaction of once weekly dosing of somapacitan during 52 weeks of treatment in GHD subjects previously treated with daily hGH.
The change in TSQM-9 scores (effectiveness, convenience and global satisfaction scores) at 32 and 52 week's measurements will be analysed using a mixed model for repeated measurements (MMRM), with treatment, GHD onset type and sex as factors and baseline as a covariate, all nested within week as a factor. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From the MMRM the treatment differences at end of treatment period (52 weeks) between somapacitan and Norditropin® FlexPro® will be estimated and the corresponding 95% CI and p-value will be calculated for each endpoint. Subjects without post-randomisation data for the analysed endpoint will not be included in the analysis.

17.4.1.2 Safety endpoints

- Change from baseline to the end of treatment period (52 weeks) in:
  - Physical examination
  - Body weight
  - Vital signs
  - Electrocardiogram (ECG)
  - Clinical laboratory test results including haematology, biochemistry, fasting glucose, fasting insulin, steady state beta cell function (%B) and insulin resistance (IR) (HOMA estimates) and HbA1c levels
- Occurrence of anti-somapacitan antibodies for subjects randomised to somapacitan from randomisation to end of the trial period (53 weeks including follow-up)
- Occurrence of anti-hGH antibodies for subjects randomised to Norditropin® FlexPro® from randomisation to end of the trial period (53 weeks including follow-up)
- Incidence of clinical technical complaints

All secondary safety endpoints will be analysed using descriptive statistics.

17.4.1.3 Pharmacokinetic endpoints

The somapacitan and hGH serum concentration data will be analysed using descriptive statistics.

17.5 Health economics and/or patient reported outcomes

Results from the PRO questionnaires will be reported in the CTR. See section 17.4.1.1.

18 Ethics

18.1 Benefit-risk assessment of the trial

The non-clinical safety programme of somapacitan reveals no hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity. Non-clinical data is summarised in section 3.1.3.
Currently available data on clinical safety and efficacy of somapacitan is summarised in section 3.1.4. The safety profile of somapacitan has been evaluated in healthy adult subjects receiving single or multiple doses of the drug (NN8640-3915), in subjects with AGHD receiving multiple doses of the drug (NN8640-3947) and in non-naïve subjects with AGHD receiving IGF-I titrated dosing (NN8640-4043). Overall, the drug was well tolerated, and the safety profile of somapacitan observed so far is similar to the existing growth hormone products for daily administration, e.g. Norditropin® FlexPro®.

Additional details on the trial product are described in the IB[17].

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, a revised written subject information must be provided and a new informed consent must be obtained.

18.3 Data handling

If the subject withdraws from the trial or is lost to follow up, then the subject's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit and/or follow up visit will be retained by Novo Nordisk, entered into the database and used for the clinical trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subjects during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters 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 letters 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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

19.1 Protocol deviations

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 eCRF or via listings from the trial database.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

The investigator will make every effort to ensure that all assessments are performed and data is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- Local label for Norditropin® FlexPro®
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP[1] , applicable regulatory requirements and the Declaration of Helsinki[2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

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

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

The investigator will follow instructions from Novo Nordisk when processing data.

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 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).

23 Reports and publications

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 physicians 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. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[30].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[22].

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

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.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[30] (sometimes referred to as the Vancouver Criteria).
Authorship will be appointed based upon the number of recruited subjects and/or significant participation in the analysis and interpretation of data. The investigators offered authorship will be asked to comment on the publication.

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

For a multi-centre 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. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.
Investigators will have access to their own study subjects' data after the Clinical Trial Report is final.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems supplied by Novo Nordisk. These data must be retained by the trial site. If the provided 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

All samples other than antibody samples will be destroyed no later than at the finalisation of the clinical trial report.
Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons.

The samples will be stored at a central bio-repository 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.

The subject's identity will remain confidential and the antibody samples will be identified only by subject number, visit number and trial identification number. No direct identification of the subject will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

The subject may request the stored biosamples to be destroyed by withdrawing consent. The results obtained from any already performed analyses of the samples will still be used.

In the event that the collected antibody samples will be used in the future, the investigator will be directly informed by Novo Nordisk about the results if the findings are deemed clinically relevant. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk.

Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: Updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 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.

27 References

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Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff