Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02229851
Sponsor trial ID:	NN8640-4054
Official title of study:	A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period
Document date:	27 November 2017

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

REAL 1

Trial ID: NN8640-4054

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period

Trial phase: 3a

Protocol originator

Name: [redacted]

Department: [redacted]

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List of abbreviations

AE	adverse event
ACTH	adrenocorticotropic hormone
AGHD	adult growth hormone deficiency
ALT	alanine aminotransferase
AUC	area under the curve
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
CRF	case report form
CTR	clinical trial report
DBL	data base lock
DFU	direction for use
DUN	dispensing unit number
DXA	dual energy x-ray absorptiometry
ecap	electronic pen cap
ECG	electrocardiogram
EOT	end of trial
eCRF	electronic case report form
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	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
hGH	human growth hormone

hsCRP	high-sensitivity C-reactive protein
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
IL-6	interleukin 6
IMP	investigational medicinal product
IRB	Institutional Review Board
IV/WRS	interactive voice/web response system
LBM	lean body mass
LSFV	last subject first visit
LSLV	last subject last visit
MESI	medical event of special interest
MMRM	mixed model for repeated measurements
NNC0195-0092	once weekly growth hormone derivative
NOAEL	no observed adverse event level
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
Sc	subcutaneous
SD	Standard deviation
SDS	standard deviation score
SGA	short for gestational age
SIF	safety information form
SmPC	summary of product characteristics
TSH	thyroid stimulating hormone
UTN	Universal Trial Number
VAT	visceral adipose tissue

1 Summary

NNC0195-0092 is a novel long-acting human growth hormone (hGH) derivative designed for once weekly administration in children with growth hormone deficiency (GHD) and adults with GHD (AGHD). NNC0195-0092 is a hGH derivative, consisting of a growth hormone (GH) back bone with a single point mutation to the amino acid backbone to which a non-covalent albumin binding moiety has been attached.

Objective(s) and endpoint(s):

Primary objective

- To demonstrate the efficacy of once weekly dosing of NNC0195-0092 compared to placebo after 34 weeks of treatment in adults with growth hormone deficiency

Secondary objectives

- To evaluate the clinical safety of once weekly dosing of NNC0195-0092 during 34 weeks of treatment in adults with growth hormone deficiency
- To evaluate the efficacy and safety of NNC0195-0092 for up to 86 weeks of treatment in adults with growth hormone deficiency (i.e. during the main and extension periods of the trial)

Primary endpoint

- Change from baseline to end of main trial period (Week 34) in truncal fat percentage

Key secondary endpoints for efficacy

Changes from baseline to end of main trial period (Week 34) in the following key variables will be used to address the primary objective

- Truncal fat mass (kg)
- Truncal lean body mass (kg)

Key secondary endpoints for safety

The following key endpoints will be used to support the secondary objectives of evaluation of safety in both the main (up to week 35) and extension (up to week 88) trial periods:

- Incidence of adverse events, including injection site reactions
- Occurrence of anti-NNC0195-0092 antibodies

Trial design:

This is a multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial. The trial will compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily dosing of Norditropin®

FlexPro® in adults with GHD during a 35-week period (8 week dose titration, 26 week fixed dose treatment followed by 1 week washout), with a 53-week extension period (8 week dose titration, 44 week fixed dose treatment followed by 1 week washout). After the main trial period placebo subjects will be switched to NNC0195-0092 treatment and Norditropin® FlexPro® subjects will be randomised 1:1 to NNC0195-0092 or Norditropin® FlexPro®.

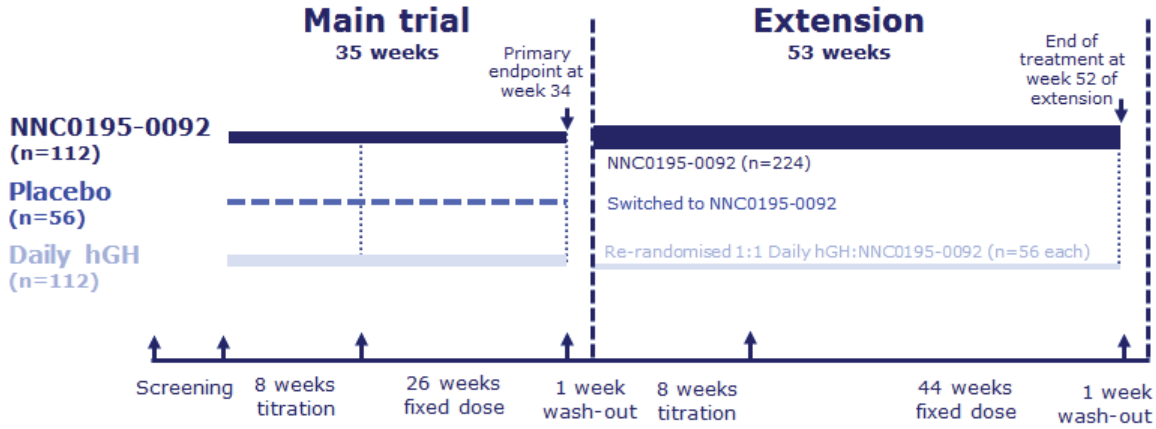

Figure 1–1 Schematic trial overview

Trial population:
Two hundred and eighty will be randomised in a 2:2:1 (NNC0195-0092: Norditropin® FlexPro®: placebo) ratio.

Key inclusion criteria:

- Male or female of at least 23 years of age and not more than 79 years of age at the time of signing informed consent
- hGH treatment naïve or no exposure to hGH or GH secretagogues for at least 180 days prior to randomisation with any registered or investigational hGH or GH secretagogue product (if only used in connection with stimulation tests for diagnosis of GHD, subjects can be included)
- 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

- FOR ALL COUNTRIES EXCEPT JAPAN:
    - Confirmed diagnosis of adult growth hormone deficiency (if a subject satisfies at least one of the following criteria)
        a. Insulin tolerance test (ITT) or glucagon test: a peak GH response of < 3 ng/mL (3 µg/L)
        b. Growth hormone releasing hormone (GHRH) + arginine test according to body mass index (BMI)
            i. BMI< 25 kg/m^2, a peak GH < 11 ng/mL (µg/L)
            ii. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)
            iii. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)
        c. Three or more pituitary hormone deficiencies at screening and IGF-I SDS < -2.0

    FOR JAPAN ONLY: Confirmed diagnosis of adult growth hormone deficiency (subjects with adult onset AGHD need to satisfy at least one of the following criteria, subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria):
        a. ITT test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
        b. glucagon test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
        c. GHRP-2 tolerance test: a peak GH of ≤ 9 ng/mL (assay using recombinant GH standard)

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 file

Assessments:

Assessments for efficacy include: DXA body composition scan, IGF-I and IGFBP-3 (PD), PK, PRO questionnaires (SF-36, TSQM, TRIM-AGHD), body weight and waist circumference.
Assessments for safety include: adverse events including local tolerability, assessment of anti-drug antibodies, thyroid hormones, fasting glucose, insulin and cortisol and HbA1c.

Trial product(s):
All trial products will be administered as subcutaneous injections.

NNC0195-0092 PDS290 10mg/1.5ml
NNC0195-0092 PDS290 Placebo
Norditropin® FlexPro® 10 mg/1.5ml

2 Flow chart

Table 2–1 Trial Flow Chart for the main trial period

Visit	1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Period			**Titration**										**Fixed-dose**			
Time (weeks + days)	**V1b- 1d minimum**	**-3 to -2**	**0**	**1+3d**	**2**	**3+3d**	**4**	**5+3d**	**6**	**7+3d**	**8**	**9+3d**	**16+4d**	**25+4d**	**33+4d**	**35**
Visit type	**IC**	**Screen.**	**Rand.**	**IGF[3]**	**Site**	**IGF**	**Site**	**IGF[3]**	**Phone[3]**	**IGF[3]**	**Site**	**IGF[3]**	**Site**	**Site**	**EOT 1**	**Site**
Visit window (days)					**+1**		**+1**		**+1**		**+1**		**+/- 7[4]**	**+/- 7[4]**	**+/-2**	
Need to be fasting		**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Subject information																
Informed consent	X															
In/exclusion criteria		X	X													
Demography		X														
Medical history		X														
Concomitant illness		X														
Concomitant medication		X	X		X		X		X		X		X	X	X	X
MRI/ CT[15]		X														
Height		X														
Pregnancy test[5]		X	X		X						X		X	X	X	X
Randomisation			X													
Withdrawal criteria					X						X		X	X		X*
Efficacy																
DXA		X[6]													X	
IGF-I and IGFBP-3		X	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]*
PK-Sampling			X[7]	X[7]	X[7]	X[7]	X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X
PRO questionnaires[8]			X											X	X	
Lipids		X													X	
hsCRP and IL-6		X									X		X	X	X	
Body weight		X	X		X						X		X	X	X	X*
Waist circumference			X												X	
Safety																
Adverse Events			X		X		X		X		X		X	X	X	X

Visit	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**[1]	**15**[2]
Period			**Titration**										**Fixed-dose**			
Time (weeks + days)	**V1b- 1d minimum**	**-3 to -2**	**0**	**1+3d**	**2**	**3+3d**	**4**	**5+3d**	**6**	**7+3d**	**8**	**9+3d**	**16+4d**	**25+4d**	**33+4d**	**35**
Visit type	**IC**	**Screen.**	**Rand.**	**IGF**[3]	**Site**	**IGF**	**Site**	**IGF**[3]	**Phone**[3]	**IGF**[3]	**Site**	**IGF**[3]	**Site**	**Site**	**EOT 1**	**Site**
Visit window (days)					**+1**		**+1**		**+1**		**+1**		**+/- 7**[4]	**+/- 7**[4]	**+/-2**	
Need to be fasting		**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Haematology		X									X		X	X	X	
Biochemistry,		X									X		X	X	X	
Thyroid function		X									X		X	X	X	
Testosterone[9]		X														
Fasting plasma glucose		X									X		X	X	X	
Fasting insulin		X									X		X	X	X	
HbA1c		X									X		X	X	X	
Fasting serum cortisol		X									X		X	X	X	
ACTH stimulation test		X[10]									X[11]					X[11]*
ECG		X									X				X	
Vital signs		X	X		X						X		X	X	X	X*
Physical examination		X	X		X						X		X	X	X	X*
Local tolerability			X[12]		X						X		X	X	X	X*
Anti-NNC0195-0092 + anti hGH antibodies			X[7]		X[7]		X[7]				X[7]		X[7]	X[7]	X	X[7]
Eye examination (fundos-photo.)[13]		X														X
Trial material																
ecap dispensing and training																X*
Dose adjustment[14]					X		X		X		X					X*
Dispensing visit			X		X		X				X		X	X		X*
Dosing (Observed trial drug administration)			X		X						X					X*
Drug accountability			X		X		X				X		X	X		X
Hand out + instruct in diary			X		X		X				X		X	X		X*
Diary returning					X		X				X		X	X		X
Compliance					X						X		X	X	X	

Visit	1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Period			**Titration**									**Fixed-dose**				
Time (weeks + days)	**V1b- 1d minimum**	**-3 to -2**	**0**	**1+3d**	**2**	**3+3d**	**4**	**5+3d**	**6**	**7+3d**	**8**	**9+3d**	**16+4d**	**25+4d**	**33+4d**	**35**
Visit type	**IC**	**Screen.**	**Rand.**	**IGF[3]**	**Site**	**IGF**	**Site**	**IGF[3]**	**Phone[3]**	**IGF[3]**	**Site**	**IGF[3]**	**Site**	**Site**	**EOT 1**	**Site**
Visit window (days)					**+1**		**+1**		**+1**		**+1**		**+/- 7[4]**	**+/- 7[4]**	**+/-2**	
Need to be fasting		**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Other																
EOT Form																
IV/WRS call		X	X		X		X		X		X		X	X		X

1. If a subject discontinues treatment prematurely during the 34-week period, procedures for treatment discontinuation described in section 8.2 must be followed.
2. All assessments marked with * do not need to be performed if a subject withdraws from the trial up to and including visit 15.
3. All IGF visits may be performed by local sampling services as directed by Novo Nordisk if permitted by the investigator and local requirements. The phone visits can be site visits instead if required by local practice or regulation or at investigator's discretion.
4. Visits 12 and 13 can be moved either one whole week earlier or one whole week later.
5. To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample At V2 the test is mandatory and needs to be performed from a urine sample. If required locally this may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than V1b and V2, optional urine pregnancy testing may be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements.
6. Baseline DXA should be obtained at Visit 1b however if it is not possible, it should be performed within 4 calendar days from Visit 1b since the quality of the scanned image must be confirmed by the imaging laboratory before the subject can be randomised.
7. Before trial drug administration (if dosing planned on visit day) and in a fasting state for all IGF-I samples
8. The PRO questionnaires must be performed after all fasting related activities and before all other trial-related activity at each applicable visit. TSQM is not assessed at screening.
9. Testosterone is assessed only in subjects receiving testosterone replacement therapy
10. If subject is not being treated with glucocorticoid replacement and has not had adrenocorticotropic hormone (ACTH) stimulation test within past 3 months, perform ACTH stimulation test.
11. If subject is not being treated with glucocorticoid replacement, perform ACTH stimulation test.
12. After trial drug administration.
13. Fundusphotography performed in subjects diagnosed with diabetes mellitus only (see inclusion criterion 10). Fundusphotography performed ≤ 90 days prior to randomisation is acceptable if results are available for evaluation at randomisation.
14. Besides the IGF-I based dose adjustment during the titration period, dose reduction can be considered during the entire study period (including the two titration periods) 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 dose reduction takes place during the titration periods or for deviations to the titration schedule see section 5.3.5.

15. Only for subjects with a history of pituitary adenoma or other benign intracranial tumour. MRI/CT if an MRI or CT scan has not been performed ≤ 9 months (defined as ≤ 270 days) prior to randomisation (results must be available for evaluation at randomisation).

Table 2–2 Trial Flow Chart for the Extension Period

Visit	16	17	18	19	20	21	22	23	24	25	26	27	28[1]	29[1]
	Titration period								Fixed-dose period					
Time (week)	36+3d	37	38+3d	39	40+3d	41	42+3d	43	44+3d	53+4d	64+4d	75+4d	86+4d	88
Visit type	IGF[2]	Site	IGF[2]	Site	IGF[2]	Phone[2]	IGF[2]	Site	IGF[2]	Site	Site	Site	EOT 2	Site
Visit window (days)		+1		+1		+1		+1		+/- 7[3]	+/- 7[3]	+/- 7[3]	+/- 2	+/- 2
Need to be fasting	X	X	X	X	X		X	X	X	X	X	X	X	X
Concomitant medication		X		X		X		X		X	X	X	X	X
Pregnancy test[4]		X						X		X	X	X	X	X
Withdrawal criteria		X						X		X	X	X		
Efficacy														
DXA													X	
IGF-I and IGFBP-3	X[5]	X[5]	X[5]	X[5]	X[5]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
PK sampling	X[5]	X[5]	X[5]	X[5]	X[5]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
PRO questionnaires[6]											X		X	
Lipids													X	
hsCRP and IL-6								X		X	X	X	X	
Body weight		X						X		X	X	X	X	X
Waist circumference													X	
Safety														
Adverse events		X		X		X		X		X	X	X	X	X
Haematology								X		X	X	X	X	
Biochemistry								X		X	X	X	X	
Thyroid function								X		X	X	X	X	
Fasting plasma glucose								X		X	X	X	X	
Fasting insulin								X		X	X	X	X	
HbA1c								X		X	X	X	X	
Fasting serum cortisol[7]								X		X	X	X	X	
ACTH stimulation test								X[7]						
ECG								X			X		X	
Vital signs		X						X		X	X	X	X	X
Physical examination		X						X		X	X	X	X	X

Visit	16	17	18	19	20	21	22	23	24	25	26	27	28[1]	29[1]
	Titration period								Fixed-dose period					
Time (week)	36+3d	37	38+3d	39	40+3d	41	42+3d	43	44+3d	53+4d	64+4d	75+4d	86+4d	88
Visit type	IGF[2]	Site	IGF[2]	Site	IGF[2]	Phone[2]	IGF[2]	Site	IGF[2]	Site	Site	Site	EOT 2	Site
Visit window (days)		+1		+1		+1		+1		+/- 7[3]	+/- 7[3]	+/- 7[3]	+/- 2	+/- 2
Need to be fasting	X	X	X	X	X		X	X	X	X	X	X	X	X
Local tolerability		X						X		X	X	X	X	X
Anti-NNC00195-0092 + anti hGH antibodies		X[5]		X[5]				X[5]		X[5]	X[5]	X[5]	X	X
Eye examination (fundos-photo.)[8]														X
Trial material														
ecap dispensing and training										X				
Dose adjustment[9]		X		X		X		X						
Dispensing visit		X		X				X		X	X	X		
Dosing (observed trial drug administration)		X						X						
Drug and ecaps accountability		X		X				X		X	X	X		X
Hand out and instruct in diary		X		X				X		X	X	X		
Diary returning		X		X				X		X	X	X		X
ecap returning										X				X
Compliance		X						X		X	X	X	X	
Other														
EOT Form														X
Contact IV/WRS		X		X		X		X		X	X	X		X

1. If a subject withdraws prematurely during the 53-week extension period, procedures for treatment discontinuation described in section 8.2 must be followed.
2. All IGF visits may be performed by local sampling services as directed by Novo Nordisk if permitted by the investigator and local requirements. The phone visits can be site visits instead if required by local practice or regulation or at investigator's discretion.
3. Visits 25-27 can be moved either one whole week earlier or one whole week later.
4. Optional urine pregnancy testing in women of childbearing potential may be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements.
5. Before trial drug administration if dosing planned on visit day and in a fasting state for all IGF-I samples.
6. The PRO questionnaires must be performed after all fasting related activities and before all other trial-related activity at each applicable visit.
7. If subject is not being treated with glucocorticoid replacement, perform ACTH stimulation test.
8. Fundusphotography is performed in subjects diagnosed with diabetes mellitus only (see inclusion criterion 10)

9. Besides the IGF-I based dose adjustment during the titration period, dose reduction can be considered during the entire study period (including the two titration periods) 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 dose reduction takes place during the titration periods or for deviations to the titration schedule see section 5.3.5.

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

Information about the risks and benefits for a subject participating in the trial are described in section 3.1.5

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 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 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 GH treatment has proved both efficacious and safe, one major drawback of the treatment has been the need for daily 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 NNC0195-0092

NNC0195-0092 is human growth hormone with a single point mutation in the amino acid backbone to which a non-covalent albumin binding moiety has been attached. NNC0195-0092 will be provided in a liquid formulation in a pen system.

The primary pursued therapeutic indications considered for NNC0195-0092 are GHD in children and adults.

3.1.3 Non-clinical data

The PD profile of NNC0195-0092 has been investigated in the standard GHD animal model – the hypophysectomised rat, where once weekly s.c. injection of NNC0195-0092 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 NNC0195-0092 can induce increased and sustained levels of IGF-1 for 4−10 days, thus supporting a once weekly dosing schedule.

NNC0195-0092 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, NNC0195-0092 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 NNC0195-0092.

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), subcutaneous 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 monkey, 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. local tolerability reactions), PK and PD of s.c. doses of NNC0195-0092 (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. NNC0195-0092 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 local tolerability issues identified. No differences in $AUC_{(0\text{-}tau)}$ and C_{max} 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 NNC0195-0092.

In the trial NN8640-3947 multiple doses of NNC0195-0092 administered s.c. to AGHD patients were 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 local tolerability issues identified. The observed adverse events (AE) are overall similar to AEs seen in trials with daily hGH treatment. No anti NNC0195-0092 antibodies or anti hGH antibodies were detected.

The IGF-I response after once-weekly NNC0195-0092 (0.02 and 0.04 mg/kg) and once-daily Norditropin appear similar. The IGF-I profiles indicate that NNC0195-0092 may be suitable for once weekly dosing, with a clinical relevant dose range ≤0.08 mg/kg for AGHD.

3.1.5 Risks and benefits

The non-clinical safety programme of NNC0195-0092 reveals no special 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 NNC0195-0092 is summarised in section 3.1.4. The safety profile of NNC0195-0092 has been evaluated in healthy adult subjects receiving single or multiple doses of the drug (NN8640-3915). Overall, the drug was well tolerated. All adverse events were mild, or moderate and primarily observed at the highest dose levels. Most common adverse events were: headache, peripheral oedema, joint pain, muscle pain, transient increase in blood sugar and insulin levels. In a recent trial in patients with adults with GHD (NN8640-3947) receiving multiple doses of the drug, the same safety profile of adverse events were registered. Overall, the safety profile of NNC0195-0092 observed so far is similar to the existing growth hormone products for daily administration e.g. Norditropin®.

Additional details on the trial product are described in the Investigator's Brochure (IB)[17].

3.1.6 Norditropin® FlexPro®

Norditropin® is the registered trademark for Novo Nordisk's recombinant human GH 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 prepubertal 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 a safe and efficacious but has greater convenience and thus potentially better compliance compared to standard once daily GH treatment.

The aim of the trial is to investigate efficacy, safety and tolerability of multiple once weekly s.c. dosing of NNC0195-0092 in adults with GHD. This trial is a pivotal trial required for application for marketing authorisation for NNC0195-0092 in adults with GHD.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary objective

- To demonstrate the efficacy of once weekly dosing of NNC0195-0092 compared to placebo after 34 weeks of treatment in adults with growth hormone deficiency

Secondary objectives

- To evaluate the clinical safety of once weekly dosing of NNC0195-0092 during 34 weeks of treatment in adults with growth hormone deficiency
- To evaluate the efficacy and safety of NNC0195-0092 for up to 86 weeks of treatment in adults with growth hormone deficiency (i.e. during the main and extension periods of the trial)

4.2 Primary endpoint

- Change from baseline to end of main trial period (Week 34) in truncal fat percentage.

Body composition is measured by DXA; truncal fat percentage is defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass (kg) and truncal lean body mass (kg)

4.3 Supportive secondary endpoints

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov are marked below.

4.3.1 Supportive secondary efficacy endpoints

Changes from baseline to end of main trial period (Week 34) in the following variables will be used to address the primary objective:

- Truncal fat mass*
- Truncal lean body mass*
- Total fat mass
- Visceral adipose tissue (VAT)
- Android fat mass
- Gynoid fat mass
- Appendicular skeletal muscle mass (ASMM)
- Lean body mass

- IGF-I SDS
- IGFBP-3 SDS
- Scores of the following PRO questionnaires:
    - TRIM-AGHD (total and domain scores)
    - SF-36v2 (summary and domain scores)
- Lipid profile (total cholesterol, HDL- cholesterol, LDL-cholesterol and triglycerides)
- Cardiovascular parameters (hsCRP and IL-6)
- Body weight
- Waist circumference

Changes from baseline to end of extension period (Week 87) in all of the above mentioned variables as well as bone mineral content (BMC) and bone mineral density (BMD) will be used to support the secondary objective regarding evaluation of efficacy during the extension period.

- Compliance with treatment will be evaluated based on time stamps from the electronic pen caps (ecaps) in the extension period and based on diary data in the main trial and the extension period. The endpoint is defined as percentage of doses taken as prescribed.
- Scores of PRO questionnaire TSQM (domain scores) will be evaluated at weeks 34 and 87

Visceral adipose tissue and android and gynoid fat mass will be assessed only if the DXA scanner permits.

4.3.2 Supportive secondary safety endpoints

The following endpoints will be used to support the secondary objectives of evaluation of safety in both the main (up to week 35) and extension (up to week 88) trial periods:

- Incidence of adverse events, including injection site reactions*
- Occurrence of anti-NNC0195-0092 antibodies*
- Incidence of technical complaints
- Changes from baseline in physical examination, ECG results and vital signs
- Changes from baseline in 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

5 Trial design

5.1 Type of trial

This is a multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily dosing of Norditropin® FlexPro® in adults with GHD during a 35-week period, with a 53-week extension period.

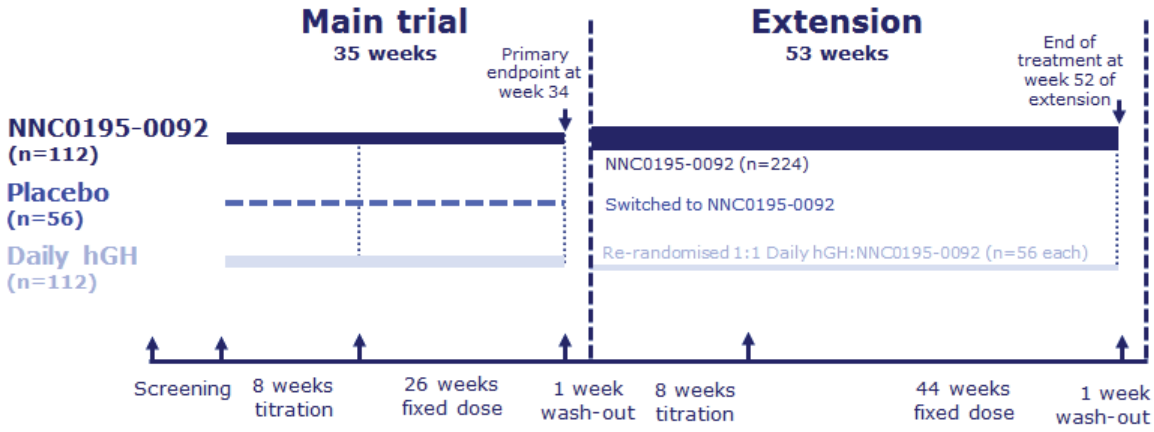

Figure 5–1 Trial design

Two hundred and eighty (280) subjects will be randomised in a 2:2:1 ratio to receive NNC0195-0092, Norditropin® FlexPro® or placebo during a 35-week period (8 weeks of titration, followed by 26 weeks of treatment and 1 week of washout). The randomisation will be stratified according to two region levels (Japan and all other countries), sex (male and female) and diabetic status (diagnosed with diabetes mellitus vs. not diagnosed with diabetes mellitus). All subjects completing the 35-week period will continue their active treatment with NNC0195-0092 weekly injection or Norditropin® FlexPro® daily injection in a non-placebo-controlled design for an additional 53-week extension period (8 weeks of titration, followed by 44 weeks of treatment and 1 week of washout). Placebo subjects will be switched to NNC0195-0092 treatment and Norditropin® FlexPro® subjects will be re-randomised 1:1 to NNC0195-0092 or Norditropin® FlexPro® within the same strata as used for the first randomisation. During the extension period subjects will be seen on a regular basis for adverse events, safety laboratory measurements, and efficacy.

The trial flow is depicted in Table 2–1 (main trial period) and Table 2–2 (extension period).

A blinded interim reporting of all safety parameters as described in sections 8.5 and 17.5 is planned to be done when 50 subjects randomised to NNC0195-0092 have completed the main trial. Data for

all subjects up to week 35 (see Table 2–1) who have completed the main trial at this time will be included.

5.2 Rationale for trial design

The randomised, placebo-controlled, partly double-blind, active controlled, multicentre design is based on regulatory scientific advices. The inclusion of the active controlled arm in an open design is to compare efficacy and safety including local tolerability of NNC0195-0092 to daily Norditropin® FlexPro® treatment. A multinational approach has been chosen to address that the results are applicable for subjects with different demographic characteristics. The parallel design has been chosen instead of a cross-over design as a cross-over trial would not be possible due to carry-over effects on e.g. body composition. The titration period allows for four opportunities to adjust the dose of NNC0195-0092 to achieve an optimal targeted serum IGF-I concentration. The 26-week fixed dose treatment period is the expected minimal time needed for changes of body composition to develop. The washout periods are included to confirm the antibody response.

The extension period is an outcome of HA interactions and allows for longer-term evaluation of efficacy and safety of NNC0195-0092. Subjects treated with Norditropin® FlexPro® during the main trial are re-randomised to NNC0195-0092 and Norditropin® FlexPro® at the beginning of the extension to obtain additional safety data for once weekly treatment and still compare efficacy and safety between the active treatments.

5.3 Treatment of subjects

Subjects will be randomised in a 2:2:1 ratio to receive either NNC0195-0092 (approximately 112 subjects), Norditropin® FlexPro® (approximately 112 subjects, open label towards both other arms) or placebo (approximately 56 subjects, double blind towards NNC0195-0092).

Time of injections:

- NNC0195-0092 and placebo 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 12:00 PM (noon). Trial drug must 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 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.

For the first 35-week treatment period, the first dose will be administered by the subject on Day 0 (randomisation), and the last dose will be administered by the subject at home during Week 33. For the extension period, the first dose will be administered in the beginning of Week 35, and the last

dose will be administered by the subject at home during Week 86. No drug will be administered at the Week 34 and Week 87. The maximal treatment duration for a single subject is 86 weeks.

Subjects in all three arms will be trained in the use of the pen-injector and inject themselves under the supervision of the site staff at the visit and will inject themselves at home (see sections 2 and 8.7).

Weight loss medications known to affect body weight substantially are not allowed during the trial.

5.3.1 Dose titration

During the first 8 weeks the dose will be titrated every second week starting from Week 2. The last dose adjustment in the main trial period will be done at Week 8. This allows four opportunities for dose adjustment (Week 2, 4, 6, and 8). Dose titration is based on blinded insulin like growth factor-I standard deviation score (IGF-I SDS) values which will be uploaded from the central laboratory to the interactive voice/web response system (IV/WRS) which calculates the next dose. Subjects will come to the clinic 1 week 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. Dose adjustments are performed at Week 0 (starting dose) 2, 4, 6, and 8, i.e. four days after the IGF-I titration samples have been collected. The blood draw 1 week and 3 days after the dose adjustment visit at week 8 is to record the IGF-I level attained following the last dose adjustment at Week 8. Dose adjustment at Week 6 will be instructed over the phone. After last dose adjustment (if any) at Week 8, 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 study period (including the two titration periods) at the investigator's discretion for safety concerns. If adverse events with an 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. The procedure for dose reduction is described in section 6.5.

If a subject reports symptoms of GH related AEs at a dose adjustment visit, the dose adjustment call in the IV/WRS must be performed prior to potentially reducing the dose by 25% as the IGF-I based titration might reduce the dose.

5.3.2 Dose titration algorithm

The titration algorithm depends on the obtained difference in IGF-I SDS between the value at any time during the titration period and the IGF-I SDS value at randomisation. In order to accommodate subjects requiring a high dose, the increments can be higher if only a small change from randomisation has been observed (see Table 5–2 and Table 5–4).

The size of the dose adjustments in Table 5–2 was derived based on PK/PD analysis of data from previous trials with NNC0195-0092. The dose titration of Norditropin® FlexPro® (Table 5–4) is designed based on clinical experience, interim results from NN8640-3947 which contained a comparator arm with daily Norditropin® FlexPro® doses and also in alignment with a titration algorithm from literature[12].

5.3.3 Titration for subjects treated with either NNC0195-0092 or Placebo

The starting doses of NNC0195-0092 at Visit 2 (Day 0) are described in table 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 NNC0195-0092 or placebo subjects

Group	**Starting dose of NNC0195-0092***	Starting dose converted to daily exposure
Subjects between 23 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 8 weeks.

Table 5–2 Dose Titration Algorithm for NNC0195-0092 or placebo subjects

IGF-I SDS Interval (1 week and 3 days after last dose adjustment)	**Increment/reduction of weekly dose**	
	Change IGF-I SDS from screening > 1	**Change IGF-I SDS from screening ≤ 1**
IGF-I SDS > 3	-1 mg	
1.75 < IGF-I SDS ≤ 3	-0.5 mg	
-0.5 < IGF-I SDS ≤ 1.75	-	+0.5 mg
-2 < IGF-I SDS ≤ -0.5	+0.5 mg	+0.5 mg
IGF-I SDS ≤ -2	+1 mg	+1.5 mg

The minimum weekly dose of NNC0195-0092 is 0.1 mg. If the algorithm returns a dose of less than 0.1mg, the weekly dose of NNC0195-0092 must be 0.1 mg. The maximum weekly dose of NNC0195-0092 is 8 mg.

If NNC0195-0092 or placebo 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, they should contact the trial site since the blood

sampling and subsequent visit will potentially have to be rescheduled (see section 5.3.5). Injections must remain in the body areas of thighs and/or abdomen with rotation within these body areas.

Titration of placebo subjects will mirror titration of NNC0195-0092 subjects to avoid un-blinding. Subjects in the placebo group will also receive instructions on dose adjustment to mimic the pattern of dose adjustment in subjects receiving NNC0195-0092 treatment.

5.3.4 Titration for subjects treated with daily Norditropin® FlexPro®

The starting doses of Norditropin® FlexPro® given daily from Visit 2 (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 23 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 8 weeks.

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

IGF-I SDS Interval (1 week and 3 days after last dose adjustment)	Increment/reduction of daily dose	
	Change IGF-I SDS from screening > 1	Change IGF-I SDS from screening ≤ 1
IGF-I SDS > 3	-0.1 mg/day	
1.75 < IGF-I SDS ≤ 3	-0.05 mg/day	
-0.5 < IGF-I SDS ≤ 1.75	-	+0.05 mg/day
-2 < IGF-I SDS ≤ -0.5	+0.05 mg/day	+0.05 mg/day
IGF-I SDS ≤ -2	+0.1 mg/day	+0.2 mg/day

The minimum daily dose of Norditropin® FlexPro® is 0.05 mg. If the algorithm returns a dose of less than 0.05mg, the weekly dose of Norditropin® FlexPro® must be 0.05 mg. The maximum daily dose of Norditropin® FlexPro® is 1.1mg.

If Norditropin® FlexPro® subjects forget or are unable to give 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 visit, the subject should contact the trial site since the IGF visit and subsequent visits will have to be rescheduled, i.e. postponed two weeks.

5.3.5 Deviations from titration schedule

The dose titration schedule in the protocol must be followed in order to allow titration to an optimal therapeutic dose for all subjects. Four 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),

- the **previous IGF-I sampling visit** will, depending on whether the visit has taken place or not,
  - be repeated two weeks later as an unscheduled if the visit has already taken place
  - **or** be rescheduled to two weeks later if it has not taken place
- the **affected dose adjustment visit** will be rescheduled to two weeks later
- all **subsequent visits** during the titration periods will be rescheduled to two weeks later
- the **fixed dose IGF-I sample visits** (i.e. V11 and V24, respectively) will be rescheduled to two weeks later.

Subsequent trial visits after V11 and 24 respectively will not be postponed.

As an exception visits may be rescheduled up to two times during each titration period (allowing for a maximum of 6 opportunities for dose adjustment evaluation). If a subject has not completed at least 3 dose adjustment evaluations, this will be considered a PD as fewer than three completed dose adjustment evaluations are not expected to be sufficient to achieve therapeutic doses in a majority of subjects.

Deviations from the IV/WRS based dose titration other than those described above and dose reduction in steps of 25% will not be considered protocol deviations, however the reason for deviating must be recorded. Based on this information it may be decided to ask for additional information regarding the deviation (see section 14.1). If the answer explains the deviation no further action will be taken.

5.3.6 Treatment during the extension period

After the main trial period NNC0195-0092 subjects will continue once weekly treatment. Placebo subjects will be switched to NNC0195-0092 treatment and Norditropin® FlexPro® subjects will be randomised 1:1 to NNC0195-0092 or Norditropin® FlexPro®. The extension period consist of treatment for 52 weeks (followed by 1 week washout). Dose titration will be repeated for all subjects during the first 8 weeks of the extension period as described for the main trial period. All subjects will start on the starting doses as described in section 5.3.3.

The extension period is considered as open label but blinding between NNC0195-0092 and Placebo during the 35-week main trial will be maintained throughout the trial. After database lock of the extension period the trial sites will be informed about the subject's treatment allocation during the 35-week treatment period.

5.4 Treatment after end of trial

No treatment will be offered after end of trial unless required in accordance with local law or regulation. When discontinuing trial products 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 NNC0195-0092 when marketed.

The dosing regimen is once weekly for NNC0195-0092 and placebo as the compound is developed as a once weekly therapy for adults with GHD to provide improved convenience/compliance over normal hGH, which must be dosed daily. A healthy subject study (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. Trial product in these two trials was given in the morning, therefore morning injection for NNC0195-0092 and placebo has been chosen 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].

An individualised dose titration regimen rather than a fixed body weight based regimen has been chosen for this trial. Clinical studies have found that adverse effects were less frequent in subjects receiving dose-titration as compared to the weight-based dosing[11]. As IGF-I is a biomarker of GH mediated effects[4], IGF-I has been chosen as a titration target. The dose titration is described in detail in section 5.3.

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 NNC0195-0092. Dose reduction in steps of 25% has been selected as lowest anticipated reduction with significant change in GH related AEs.

A 6-month maintenance period has been chosen to allow adequate time to observe the effect of NNC0195-0092 on truncal fat percentage change from baseline. Observations from other studies with longer term efficacy results indicate that the maximum effect of GH on body fat is achieved at approximately 6 months[12,19].

The extension period of 53 weeks in a non-placebo-controlled design allows for longer-term evaluation of efficacy and safety of NNC0195-0092.

The placebo arm is included due to a health authority requirement. Norditropin® FlexPro® was chosen as active comparator as once daily hGH treatment is standard therapy in the present subject population.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be started on trial products: 280

Number of subjects expected to complete the main trial period: 260

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 of at least 23 years of age and not more than 79 years of age 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. **FOR ALL COUNTRIES EXCEPT JAPAN:** Confirmed diagnosis of adult growth hormone deficiency (if a subject satisfies at least one of the following criteria)
    a. Insulin tolerance test (ITT) or glucagon test: a peak GH response of < 3 ng/mL (3 µg/L)
    b. Growth hormone releasing hormone (GHRH) + arginine test according to body mass index (BMI)
        a. BMI< 25 kg/m^2, a peak GH < 11 ng/mL (µg/L)
        b. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)
        c. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)
    c. Three or more pituitary hormone deficiencies at screening and IGF-I SDS < -2.0

    FOR JAPAN ONLY: Confirmed diagnosis of adult growth hormone deficiency (subjects with adult onset AGHD need to satisfy at least one of the following criteria, subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria):
    a. ITT test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
    b. glucagon test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
    c. GHRP-2 tolerance test: a peak GH of ≤ 9 ng/mL (assay using recombinant GH standard)
5. IGF-I SDS < -0.5 at screening relative to the mean of the age and sex normal ranges according to the central laboratory measurements

6. hGH treatment naïve or no exposure to hGH or GH secretagogues for at least 180 days prior to randomisation with any registered or investigational hGH or GH secretagogue product (if only used in connection with stimulation tests for diagnosis of GHD, subjects can be included)
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
8. Subjects must have serum levels of total testosterone (males only) and free T4 within normal limits according to the central laboratory measurements
9. Adequate adrenal function (confirmed with ACTH stimulation test within the last 90 days prior to randomisation; if no result is available, ACTH stimulation test will be performed as part of the screening procedure after the informed consent is signed) or adequate and stable replacement therapy (as judged by the investigator) for at least 90 days prior to randomisation
10. Subjects without diabetes mellitus; or subjects diagnosed with diabetes mellitus provided that ALL the following criteria are met:
    –diabetes mellitus (diagnosed clinically) ≥ 6 months prior to screening
    –stable oral anti-diabetic (OAD) treatment, defined as unchanged medication and unchanged dose for ≥ 90 days prior to screening
    –no history of use of injectable anti-diabetic agents
    –HbA1c <7.0% at screening according to central laboratory
    –no diabetes related co-morbidities (as judged by the investigator) at screening
    –fundusphotography performed ≤ 90 days prior to randomisation without proliferative retinopathy or severe non-proliferative diabetic retinopathy

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 informed consent
   BRAZIL ONLY: Participation in other trials within one year (defined as 365 days) prior to screening visit (Visit 1b) unless there is a direct benefit to the research subject at the investigator´s discretion
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)
   a. **FOR BRAZIL ONLY**: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory
   b. **FOR GERMANY ONLY**: Adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal IUD, sexual abstinence or vasectomised partner
   c. **FOR SWEDEN ONLY**: Adequate contraceptive measures are:
      i. oral (except low-dose gestagen (lynestrenol and norestisteron))

ii. injectable, or implanted hormonal contraceptives
iii. intrauterine device, intrauterine system (for example, progestin-releasing coil)
iv. vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate)

d. **FOR THE UK ONLY**: Contraception requirements as per the at any time applicable MHRA guidelines

4. Male of reproductive age who or whose partner(s) is not using adequate contraceptive methods (adequate contraceptive measures, as required by local regulation or practice)
5. Receipt of any investigational medicinal product within 180 days before screening or participation in another 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. Anticipated change in lifestyle (eating, exercise or sleeping pattern) during the trial. Exclusion based on this criterion is at the investigator's discretion
8. 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 file
9. For subjects with a history of pituitary adenoma or other benign intracranial tumour:
    a. Surgical removal of pituitary adenoma or other benign intracranial tumour within 12 months (defined as ≤ 365 days) before randomisation.
    b. 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.
10. Clinically significant hepatic disease defined as alanine aminotransferase (ALT) level greater than 3 times upper normal limit according to the central laboratory measurements
11. Clinically significant chronic renal impairment defined as creatinine level greater than 1.5 times upper normal limit according to the central laboratory measurements
12. History of positive results of tests for hepatitis B and/or C
13. History of positive result of test for human immunodeficiency virus (HIV) antibodies
14. Acute severe illness associated with weight loss in the last 180 days prior to randomisation (defined as a loss of more than 5.0% of the total body weight)
15. Active Cushing's syndrome within the last 24 months prior to randomisation
16. FOR JAPAN ONLY: Diabetes mellitus
17. Heart insufficiency, NYHA class >2

18. Use of weight loss medications within the last 12 months (defined as 365 days) known to affect body weight substantially. Exclusion based on this criterion is at the investigator's discretion
19. History of acromegaly
20. Systemic corticosteroids other than in replacement doses within 90 days before randomisation
21. 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
22. Inability to undergo DXA whole body scanning due to a body weight or size which exceeds the limit of the DXA scanner. Weight and size limits differ between scanner types. Details about weight and size limits are described in the image acquisition guideline from the imaging laboratory
23. Female subject who plans to change estrogen therapy during the trial

6.4 Randomisation criteria

1. The quality evaluation of the baseline DXA scan needs to be performed by the imaging laboratory prior to randomisation

6.5 Dose reduction criteria

If adverse events with an probable relationship to the trial drug are persistent (e.g. oedema, hypertension, arthralgia, carpal tunnel syndrome, and/or GH induced hyperglycaemia) but allow continuation in the trial as judged by the investigator and subject, dose reduction in consecutive steps of 25% of the current dose can be considered at the investigator's discretion. If after consecutive dose reduction steps AEs still persist the subject's treatment may be discontinued or the subject may be withdrawn according to treatment discontinuation/withdrawal criterion number 2.

6.6 Treatment discontinuation and withdrawal criteria

Efforts should be made for subjects to attend and complete scheduled visit procedures. There will be a clear distinction between treatment discontinuation and subject withdrawal.

If any of the below treatment discontinuation or withdrawal criteria apply, treatment may be discontinued or the subject must be withdrawn (see section 8.2 for detailed instructions).

6.6.1 Treatment discontinuation

1. The subject may discontinue treatment at will at any time.
2. Treatment may be discontinued at the discretion of the investigator due to a safety concern or if the subject is judged non-compliant with trial procedures.

Treatment must be discontinued if the following applies:

3. Adverse Event: 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
4. Any other condition develops that is cited in exclusion criteria (except for development of diabetes mellitus during the course of the trial that can be controlled with standard therapy)
5. Development of neutralising antibodies to NNC0195-0092 defined by 2 consecutive samples found positive for *in vitro* neutralising antibodies and an influence on PK as described in section 8.5.13. The investigator will be notified by the sponsor if a subject has had 2 samples positive for *in vitro* neutralising antibodies immediately after obtaining knowledge of the results.
6. Pregnancy*
7. Intention of becoming pregnant during the trial, including the extension period*
   *No DXA scans can be performed on these subjects

6.6.2 Withdrawal criteria

1. The subject may withdraw at will at any time.

The subject must be withdrawn if the following applies

2. Included in the trial in violation of the inclusion and/or exclusion criteria
3. Use of weight loss medications known to affect body weight substantially. Withdrawal based on this criterion is at the investigator's discretion.

6.7 Subject replacement

Subjects who discontinue treatment or are withdrawn will not be replaced.

6.8 Rationale for trial population

One of the expected target populations for NNC0195-0092 are adults with GHD. Therefore adults with GHD have been chosen as trial population to support marketing authorization for NNC0195-0092.

Subjects who are hGH treatment naïve or have not been exposed to hGH within the last 6 months prior to randomisation and have AGHD beyond transition (at least 23 years of age) are chosen as this is a pre-requisite for evaluating the primary endpoint; change in truncal fat percentage.

Both male and female adults with GHD are chosen to be enrolled in this trial, to obtain information on the efficacy and safety of the drug product in both sexes.

7 Milestones

Planned duration of recruitment period i.e. FSFV – LSFV: 18 months

End of trial is defined as LSLV of the extension period

Recruitment:

The screening and randomisation rate will be followed closely via the IV/WRS 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 IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation will be randomised.

Trial registration:

Information about the trial will be disclosed on clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[20], the Food and Drug Administration Amendment Act (FDAAA)[21], European Commission Regulation for EudraCT[22] 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).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list.

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) 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.

All laboratory analyses in this trial will be performed by the central laboratory unless stated otherwise for the single parameter. Urine pregnancy tests will be performed at the sites with test material supplied by the central laboratory.

Laboratory values outside reference ranges will be marked on the laboratory reports. All results will be faxed or electronically transferred to the investigator. The investigator must assess all results outside the reference ranges as either clinically significant or not clinically significant and sign and date each page of the lab report. For parameters which are not blinded this review needs to be documented prior to the subject's next site visit.

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 must be reported to the investigator.

The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Surveillance of laboratory safety data (with the exception of anti-drug antibody data) will be performed by a medical specialist at least every 2 months based on safety surveillance reports. The medical specialist will evaluate the laboratory safety data and look for potential safety signals or issues (safety surveillance). If a signal or alert is identified, the medical specialist will immediately inform the chairman of the safety committee.

8.2 Handling of Screening failures, re-screening, treatment discontinuation and withdrawals

Screening failures

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

A screening failure session must be made in the IV/WRS. The eCRF case book must be signed.

Re-screening and re-sampling

Re-screening of subjects is allowed ONLY if the screening window of 21 days between visit 1b and 2 is exceeded. No separate informed consent is required. Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria related to any laboratory parameters with exception of free T4 and/or testosterone.

Subjects with pituitary deficiencies referred to specialists treating GHD are not always sufficiently replaced with thyroxines and/or testosterone, evidenced by a low free T4 or testosterone. These subjects can be re-screened once when appropriate replacement therapy has been instituted and stable for at least three months at the discretion of the investigator.

Re-sampling is allowed during an unscheduled visit (section 8.6) if samples are lost or damaged before arriving at the analysing laboratory.

Treatment discontinuation

If a subject discontinues treatment in the trial, the investigator must aim to undertake all procedures in the trial after treatment discontinuation except trial drug administration.

Pregnant subjects or subjects with the intention to become pregnant must not undergo additional DXA scans.

A treatment discontinuation session must be made in the IV/WRS and in the eCRF it must be specified if the subject will participate in subsequent visits or withdraw from the trial. Final drug accountability must be performed.

Withdrawal

If the subject does not participate in all visits (withdrawal), the investigator must aim to perform procedures similar to those for the respective end of trial (EOT) visits (V14 or V28) as soon as possible and a post-treatment follow-up visit (V15 or V29, at least two weeks after last treatment with NNC0195-0092 and at least 8 days after last treatment with Norditropin® FlexPro®).

A treatment discontinuation session must be made in the IV/WRS and in the eCRF it must be specified if the subject will participate in subsequent visits or withdraw from the trial. The end-of-trial form must be completed, and final drug accountability must be performed . The eCRF case book must be signed.

Although a subject is not obliged to give his/her reason(s) for discontinuing treatment or for withdrawing from the trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Attempts to contact the subject must be documented in the subject file. Where the reasons are obtained, the primary reason for not completing the trial or for discontinuation of treatment must be specified on the end-of-trial form in the eCRF.

8.3 Subject related information

8.3.1 Demography

Information about date of birth and sex will be captured in IV/WRS according to the local regulations. Race and ethnicity will be recorded in the eCRF according to the local regulations.

8.3.2 Concomitant illness and medical history

Medical history includes medical events which the subject has experienced in the past. At least history of cancer/intracranial tumour, history of GHD, growth hormone treatment, other hormone replacement therapy, and other conditions that the investigator considers relevant to this trial must be recorded.

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
- Treatment for GHD in the past including type of medication and dose

The GHD diagnostic method should be recorded in the eCRF.

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit). Concomitant illness will be recorded at Visit 1b.

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.

8.3.3 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, dose, 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.

8.3.4 MRI and CT

An MRI or CT scan can be performed at screening if required to confirm eligibility in relation to exclusion criterion 9. The only information collected in the eCRF is whether the subject is eligible for trial participation.

8.3.5 Subject diaries

From randomisation a diary will be dispensed to subjects at every site visit and it will be returned at the next site visit (visits marked as site visits in the flowchart, see section 2). The subject should be instructed by the site staff to complete the diary with the following records:

- Drug compliance: The subject will be asked to record date, time and dose of injections and any missed dose
- Adverse events
- Concomitant medication

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 or PRO 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.

8.3.6 Body measurements

The height (in cm, without shoes) and body weight (in kg, without shoes and overcoat) of the subject will be recorded at screening. BMI will be calculated during analysis as: BMI = weight (kg)/[height (m)]^2. Body weight is assessed at least every 2-3 months throughout the trial.

8.3.7 Pregnancy test

A blood pregnancy test (beta subunit of human chorionic gonadotropin [beta-HCG]) will be performed at Screening in women of childbearing potential (refer to exclusion criterion 0). At visit 2 a urine pregnancy test will be performed before randomisation. During the trial for all other site visits, urine pregnancy testing may be performed at the investigator's discretion, such as for a missed menstrual cycle, or according to local requirements.

8.4 Assessments for efficacy

8.4.1 DXA body composition measurement

Body composition will be measured using dual energy x-ray absorptiometry (DXA) whole body scans. The overall process of image acquisition, transfer, central analysis, reporting of results and archiving is described in an **Imaging Charter** prepared by the imaging laboratory. The DXA scan will be performed at Screening (however if it is not possible, it must be performed within 4 calendar days after the screening visit) at the end of the main trial period and at the end of the extension period (see section 2).

The quality of the baseline DXA scan obtained at Visit 1b must be confirmed by the imaging laboratory before the subject can be randomised. The DXA scans will be provided to the imaging laboratory designated by Novo Nordisk for reading in a blinded manner. If a subject withdraws prematurely from the trial, an end-of trial DXA will be performed.

Processes for image acquisition are outlined in an **image acquisition guideline (IAG)**: A single whole body DXA scan will be acquired with the subjects positioned supine, with their arms near their sides on the scanner table. Subjects should be normally hydrated, are not permitted to eat for at least 2 hours prior to the scan, must empty their bladder preceding the scan, and are not allowed to wear any metal or plastic (zippers, snaps, fasteners, grommets, belts, and under-wire bras etc.) or compressive clothing during the scan. Besides the three scans per subject described in this protocol a limited number of repeat scans might be acquired if required due to technical reasons.

Each trial site DXA scanner will need to be qualified by the imaging laboratory prior to scanning subjects. DXA scanner qualification will require submitting baseline DXA instrument local spine phantom quality control (QC) scan results and a whole body DXA scan test transfer. During the trial, all sites must continue to acquire spine phantom QC scans at least three times per week and submit a copy of their QC database (once a month) to the imaging laboratory. Each subject must be

scanned using the same DXA scanner for the duration of the trial. The imaging laboratory must be informed of any scanner software or hardware upgrades. If scanning on the same scanner is not possible or software or hardware upgrades occur, procedures as outlined in the IAG must be followed.

A cross calibration using a cross calibration phantom will be performed at least once at each site prior to the second partial database lock (DBL) of the main trial period.

Each trial site will further receive an **imaging manual** prepared and distributed by the imaging laboratory which will include machine specific instructions for acquiring DXA scans. The manual will serve as a reference tool for use during the trial and in training technologists. DXA technologist training will occur at the start of the trial and at any time deemed necessary to assure proper scan acquisition.

Following DXA scan acquisition each trial site will be responsible for transferring each DXA scan to the imaging laboratory for quality review and analysis. DXA analysis data will include:

- Truncal fat mass (g)
- Truncal lean body mass (g)
- Total fat mass (g)
- Visceral adipose tissue (VAT, cm2)*
- Android fat mass (g)*
- Gynoid fat mass (g)*
- Appendicular skeletal muscle mass (ASMM)
- Lean body mass (g)
- Bone parameters (BMC (g) and BMD (g/cm2)

*analyses marked with an asterisk will be performed only if the scanner permits as evaluated by the imaging laboratory.

DXA analysis data will be transferred from the imaging laboratory to Novo Nordisk immediately prior to the DBLs of the main and extension periods. The investigators will receive the results from the analysis only after LSLV of the extension period in order to avoid un-blinding.

8.4.2 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 this might extend the titration period (see section 5.3.5).

IGF-I and IGFBP-3 samples will be collected at screening, randomisation, every second week during the titration periods and at least every 3rd month throughout the trial (see section 2). All

samples must be drawn prior to trial drug administration if this is planned on a sampling day. Results will be uploaded to the IV/WRS and are used for dose adjustment during the titration periods.

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 a reference range.

The investigators will receive the results from the analysis only after LSLV of the extension period in order to avoid un-blinding.

IGF-I values will be used for dose titration of NNC0195-0092, placebo and Norditropin® FlexPro®. Details of the dose titration are described in section 5.3

8.4.3 Pharmacokinetics assessments of NNC0195-0092 and hGH

In order to test for changes in pharmacokinetics (PK) induced by anti-NNC0195-0092/ hGH antibodies, blood samples for determination of NNC0195-0092/hGH from all subjects will be taken at randomisation and expected peak levels of IGF-I at least every second month 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 investigators will not be informed of the results of PK assessments during the trial to maintain blinding.

After trial completion a detailed description of both assay methods, validation documentation and bioanalytical reports for the assays will be submitted with the final clinical trial report (CTR) according to FDA requirements[23,24].

NNC0195-0092 assay

The concentration of NNC0195-0092 in serum from subjects randomised to NNC0195-0092 will be measured by Novo Nordisk using a validated NNC0195-0092 specific luminescent oxygen channelling immunoassay (LOCI) developed by Novo Nordisk. Validation documentation for the NNC0195-0092 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 assay.

8.4.4 Lipids

The following lipids will be measured at screening and at the end of the main and extension trial periods (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.

- cholesterol (total)
- HDL cholesterol
- LDL cholesterol
- triglycerides

8.4.5 Cardiovascular parameters

The following cardiovascular parameters will be assessed at screening and every 2 to 3 months throughout the trial (see section 2).

- hsCRP
- IL-6

8.4.6 Body weight

Body weight will be measured in kg with one decimal as one observation (without shoes and overcoat) at screening, randomisation and every 2 to 3 months throughout the trial (see section 2). It is preferable to measure body weight at the same time of day and preferably using the same scale from visit to visit.

8.4.7 Waist circumference

The waist circumference will be measured in cm at randomisation and at the end of the main and extension trial periods (see section 2) and is defined as the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest.

Three consecutive measurements of waist circumference should be performed and recorded in the eCRF. The waist circumference will be measured in cm to the nearest ½ cm using a non-stretchable measuring tape (measuring tapes will be provided to the sites).

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue and twists in the tape should

be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

8.4.8 Patient reported outcomes

PRO will be assessed at randomisation, at several occasions during trial conduct and at the two EOT visits (see section 2) using four questionnaires: TRIM-AGHD[25], SF-36v2[26], TSQM[27].

By choosing these questionnaires it will be possible to assess the improvements in health related quality of life (HRQoL) as well as overall improvements in health status in relation to the results of the trial.

The PRO questionnaires will be self-administered questionnaires, to be completed by the subject without assistance of the site personnel and should preferably be completed after all fasting related activities but before any other visit related procedures are conducted. Written instructions on how to complete the questionnaires will be provided to the subject. Subjects who cannot complete the questionnaires themselves due to physical limitations may receive assistance with completion of the questionnaires. After completion the PROs 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 questionnaires 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 PROs 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 questionnaires 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.

TRIM-AGHD

The Treatment Related Impact Measure-Adult Growth Hormone Deficiency (TRIM-AGHD) is a disease specific questionnaire which measures the impact of growth hormone treatment on the functioning and well-being of adults with GHD[25]. The four concepts covered by the questionnaire is physical health, energy levels, cognitive ability and psychological health. TRIM-AGHD has 27 items and a total score as well as domain specific scores can be derived. TRIM-AGHD is scored so that a lower score indicates a better health state.

SF-36

The Short Form 36 (SF-36v2) is a health survey which assesses the functional status and well-being of the subject utilizing 36 questions covering selected concepts. The concepts cover physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional and mental health over the previous 4 weeks. Scores for each concept and overall scores for the physical and the mental components are calculated

according to the SF-36 manual[26]. Higher scores indicate a better health state. SF-36v2 data will also be used to calculate the subject's utility values.

TSQM

The Treatment Satisfaction Questionnaire for Medication - 9 items (TSQM-9) is a generic questionnaire that measures a subjects' satisfaction with medication. Items are rated on a 5- or 7-point scale according to subjects' experience with the medication and the concepts covered are satisfaction with the effect of the medication, convenience, confidence and global treatment satisfaction.

8.5 Assessments for safety

8.5.1 Adverse events

Please refer to section 12 Adverse Events and pregnancies for more details.

8.5.2 Haematology

Haematology will be assessed at screening and every 2 to 3 months throughout 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

8.5.3 Biochemistry

Biochemistry will be assessed at screening and every 2 to 3 months throughout 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)

8.5.4 Thyroid function

Thyroid function will be assessed at screening and every 2 to 3 months throughout the trial (see section 2) using serum samples. The assessment will include the following parameters:

- Total T3
- Total T4
- 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 per investigator discretion.

8.5.5 Testosterone

Testosterone will be assessed at the screening visit in subjects receiving testosterone replacement therapy.

8.5.6 Fasting plasma glucose, fasting insulin, and HbA1c

Fasting plasma glucose, fasting insulin, and HbA1c tests will be assessed at screening and every 2 to 3 months throughout 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.

Rescue criterion for subjects diagnosed with diabetes mellitus before inclusion into the trial: If the HbA1c increases clinically significantly during the trial, the investigator should consider adjusting the anti-diabetic medication according to local practice.

8.5.7 Fasting serum cortisol

For general monitoring of adrenal glucocorticoid function, fasting serum cortisol will be assessed at screening and every 2 to 3 months throughout 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. For subjects with fasting serum cortisol below normal range, who are not currently receiving glucocorticoid replacement therapy, a

confirmatory ACTH stimulation test, additional to the ACTH stimulation testing outlined in Section 8.5.8, should be performed and appropriate treatment initiated.

8.5.8 Adrenocorticotropic hormone (ACTH) stimulation test

Cortisol levels will be assessed at screening, at the end of the two titration periods and at the start of the extension period (see section 2). If a subject is not treated with glucocorticoid replacement an ACTH stimulation test will be performed at screening if not performed within 3 months prior to planned randomisation, at the end of the two titration periods and at the start of the extension period.

8.5.9 ECG

A standard 12-lead ECG will be performed while the subjects are in supine position at screening and regularly during the entire trial (see section 2). The investigator will evaluate the ECG recordings and classify them as either: "normal", "abnormal, not clinically significant" or "abnormal, clinically significant". At the screening visit, ECGs classified as "abnormal, clinically significant" will be recorded as concomitant illnesses. Worsening of ECGs will be recorded as AEs if they are evaluated as "abnormal, clinically significant" at a time point after the screening procedure.

8.5.10 Vital signs

Vital signs will be assessed at screening, randomisation and at least every 2 to 3 months 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

The investigator will evaluate the vital signs and classify them as either: "normal", "abnormal, not clinically significant" or "abnormal, clinically significant". At screening visit, vital signs outside reference range classified as "abnormal, clinically significant" will be recorded as concomitant illnesses. Clinically significant worsening of vital signs from the screening visit will be recorded as AEs.

8.5.11 Physical examination

A physical examination of the following body systems will be performed at screening, randomisation and at least every 2 to 3 months (see section 2) throughout the trial:

- Head, neck, eyes, nose
- 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 either: “normal”, “abnormal, not clinically significant” or “abnormal, clinically significant”. At the screening visit, physical examination classified as “abnormal, clinically significant” will be recorded as concomitant illnesses. Worsening of physical examination findings from the screening visit will be recorded as AEs.

8.5.12 Local tolerability

Local tolerability will be evaluated on a regular basis at visits to the trial site (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 or specific unscheduled visits local tolerability will be evaluated by the investigator by visual and manual inspection of injection sites.

If a local tolerability reaction is identified the following results will be recorded in the eCRF:

- Pain
- Itching
- Swelling (in mm)
- Redness (in mm)
- Induration (in mm)
- Palpation for signs of skin dimpling (small cavities, in mm)
- Others

Each assessment will be reported on a scale from 0 (none), 1 (mild), 2 (moderate), or 3 (severe). For redness, dimpling and induration, the affected area should also be evaluated in mm using a ruler. Assessments will be performed by the investigator. In the event of a local reaction, additional assessments will be performed until resolution, as judged necessary by the investigator. Under circumstances where the adult with GHD reports subjective symptoms, the reaction will also be noted as an AE.

In case of clinically significant findings at the local tolerability assessments, the finding must be reported as an AE and digital photos must be taken of the injection site at the time of identification and hereafter as often as judged by the investigator. Should injection of trial product require more than one injection all injections sites should be evaluated. The pictures should include trial ID, subject number, date of photo, actual time of photo (24h format) and a ruler for injection site measurement. All pictures will be transferred to Novo Nordisk.

8.5.13 Anti-drug antibodies

Anti-drug antibodies will be assessed at randomisation, 2, 4, 8 and 16 weeks after randomisation and thereafter every two to three months throughout the trial and at EOT and follow-up (see section 2). All samples must be drawn prior to trial drug administration if this is planned on a sampling day. Samples will be analysed up to all three DBLs in the trial, i.e. after 50 subjects randomised to NNC0195-0092 have completed the main trial period, after all subjects have completed the main trial period and after completion of the extension period.

All subjects who have had a positive antibody test result (high titre antibodies and/or persistent 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. The investigator will be informed of positive antibody results in case of clinically relevant impact on efficacy and/or safety. The process for assessing the impact on efficacy and safety is described in section 12.7.1. If anti-drug antibody follow up extends beyond the LSLV of the extension period of the trial, 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 may be reported as an amendment to the 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.

To evaluate the impact of antibody formation, results of antibody and *in vitro* neutralising antibody analyses will be compared to PK by collecting samples to assess serum concentrations of NNC0195-0092 for days after last dosing and 3 days prior to antibody sampling takes place.

To ensure further assessment of the antibody responses if requested by regulatory authorities, antibody samples will be stored by Novo Nordisk for a longer period until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA). See section 24.2 for further information.

NNC0195-0092 antibodies
Determination of antibodies against NNC0195-0092 in subjects randomised to NNC0195-0092 will be performed by Novo Nordisk using a validated antibody binding assay. The assay is a bridging

enzyme-linked immuno-sorbent assay (ELISA) developed by Novo Nordisk to specifically determine antibody levels against NNC0195-0092. Confirmed anti-NNC0195-0092 antibody positive samples will be further tested for cross-reactivity to hGH and for *in vitro* neutralising effect. The *in vitro* neutralising effect of anti-NNC0195-0092 antibodies will be evaluated in a validated cell-based neutralising antibody assay and by correlation to PK/PD.

hGH antibodies
Anti-hGH antibodies in subjects randomised to Norditropin® FlexPro® will be analysed by Novo Nordisk using a validated antibody binding assay. The assay is a bridging ELISA developed by Novo Nordisk to specifically determine antibody levels against hGH. Confirmed anti-hGH antibodies will be further assessed for neutralising effect of anti-hGH antibodies in a validated cell based neutralising antibody assay and by correlating to PK/PD.

8.5.14 Assessments in case of suspicion of severe hypersensitivity

If a severe immediate hypersensitivity reaction to the trial product is suspected, blood will be sampled for assessment of anti-drug antibodies including IgE isotype of these after a suitable washout period (minimum 2 weeks). In these cases, it is also recommended to test for tryptase (total and/or mature tryptase) within 3 hours of the reaction if practically feasible. If tryptase is measured, an additional baseline tryptase sample should be taken at the same time as the IgE sample is obtained. Tryptase concentrations (if measured) as well as results of anti-drug antibodies and IgE-isotype antibodies will be collected by Novo Nordisk and included in the final SAE report.

8.5.15 Eye examination

Fundusphotography will be performed in subjects diagnosed with diabetes mellitus before inclusion into the trial (see exclusion criterion 16). It can be performed by the Investigator or a local Ophthalmologist according to local practice at screening and at the end of the main and extension periods. Result of the fundusphotography will be interpreted locally by the Investigator in relation to the trial. To document this, the Investigator must sign and date the result page. The interpretation must follow the categories:

- "Normal"
- "Abnormal, not clinically significant"
- "Abnormal, clinically significant"

In the case of an "abnormal, clinically significant" fundusphotography, the Investigator must comment in the subject notes and, if it occurs at the screening visit, record this on the medical history/concomitant illness form. If the fundusphotography shows proliferative retinopathy or severe non-proliferative diabetic retinopathy the subject must be excluded (see section 6.3).

If a fundusphotography has already been performed no longer than 90 days before randomisation and if the results are available the procedure does not need to be repeated. The Investigator must still interpret, sign and date the fundusphotography. If the fundusphotography was performed before the subject has signed the informed consent Form, it must be documented in the subject notes that the reason for performing the procedure was not related to this trial.

Any clinically significant worsening of the fundusphotography result from baseline must be reported as an AE.

Fundusphotography performed within the 3 weeks before Visits 15 and 29 respectively are acceptable as Visit 15 or Visit 29 data.

8.6 Unscheduled visit

Unscheduled visits can be performed at the investigators discretion if an AE requires additional follow-up or if required by the Novo Nordisk department responsible for safety. Unscheduled visits can take place at any time during the trial from screening until the last visit in the trial. Further, unscheduled 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.

All assessments performed at any time during the trial can be performed during unscheduled visits with the exception of DXA body composition scan (only permitted if required due to DXA technical reasons), waist circumference and PROs.

Visits/contacts to the site not related to the trial do not need to be reported as an unscheduled visit. Contacts for re-dispensing of trial drug as replacement for lost or damaged trial drug do not need to be recorded as unscheduled visits but need to be recorded in the IV/WRS.

8.7 Observed trial drug administration, pen-injector and ecap training

During each of the titration periods all subjects will be trained three times (see section 2) in the use of the pen-injector. After instruction the subject will inject him/herself under observation by trial staff. This can be preceded by injection with a training pen (see section 9.2) which can be administered by the subject into a pad or cushion once (using this test pen is optional).

It is the investigators or delegated staffs 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.

During the ecap dispensing and training (see section 2) site staff will instruct the subject in the use of the ecap in accordance with the ecap info card and make sure to replace the injection pen cap with an ecap.

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 on his/her own with corrective feedback provided by site staff
- The subject has received training in the use of the ecap
- Date and time of ecap training
- unique ID of dispensed ecap

8.8 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.

During the main and extension trial periods subjects must record date and time of each dose of trial product in the diary (see section 8.3.5). 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). Compliance will be further evaluated based on time stamps from electronic pen caps (ecap) throughout the extension period. Details about the ecaps and required procedures are described in section 9.5. Compliance data will not be made available to investigators and subjects during the trial.

8.9 Missing data

Investigators will make every effort to ensure all assessments are performed and data are collected. If missing data do occur the reason will be collected via the PD 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 taken 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 8.2 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.

NNC0195-0092 PDS290 10mg/1.5ml and NNC0195-0092 PDS290 Placebo 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 product

Trial product	Strength	Dosage form	Route of administration
NNC0195-0092 PDS290 10 mg/1.5 ml	10 mg/1.5 ml	PDS290	s.c.
NNC0195-0092 PDS290 Placebo	0 mg/1.5 ml		
Norditropin® FlexPro®	10 mg/1.5 ml	FlexPro®	s.c.

9.2 Labelling

Labelling of the trial products will be in accordance with Annex 13[28], local regulations and trial requirements.

Trial product for the main part of the trial

- NNC0195-0092 PDS290 10 mg/1.5 ml and NNC0195-0092 PDS290 Placebo pens will be visually identical and labelled blinded
- Norditropin® FlexPro® will be open labelled

Trial product for the extension part of the trial

- NNC0195-0092 PDS290 10 mg/1.5 ml will be open labelled
- Norditropin® FlexPro® will be open labeled

Each investigator site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS. Dispensing unit numbers (DUNs) will be distributed to the sites according to enrolment and randomisation.
The investigator must document on the IV/WRS dispensing record that direction for use is given to the subject orally and in writing at each dispensing visit.

Placebo or test pen for training purpose

NNC0195-0092 PDS290 Placebo or test medium will be labelled for training purposes. The pen injectors used in all three trial arms are identical, accordingly the same test pen can be used for all subjects. The test pen contains NNC0195-0092 PDS290 Placebo. For the use of the test pen refer to section 8.7.

9.3 Storage

Table 9–2 Trial product storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
NNC0195-0092 PDS290 10 mg/1.5 ml	Store in a refrigerator (2-8°C) in the outer carton, in order to protect from light. Do not freeze.	2-8°C in between injections Do not freeze.	Use within 4 weeks
NNC0195-0092 PDS290 Placebo			
Norditropin® FlexPro®	According to label : Store in a refrigerator (2-8°C) in the outer carton, in order to protect from light. Do not freeze.	2-8°C Below 25^{0}C Do not freeze	28 days 21 days
FOR JAPAN ONLY: Norditropin® FlexPro®	Store in a refrigerator (2-8°C) in the outer carton, in order to protect from light. Do not freeze.	2-8°C Do not freeze	35 days

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

The investigator must ensure the availability of proper storage conditions, 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). Trial product that has been stored improperly must not be dispensed to any subject before it has been re-evaluated and

approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

For Japan only: 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 (e.g. a pharmacist). The trial product storage manager should control and take accountability of the trial drug products in accordance with procedures specified by Novo Nordisk A/S. 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 is the responsibility of the investigator. Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.

Destruction of used and unused trial product(s) after drug accountability can be performed on an on-going basis and at the latest upon completion of the trial. The monitor will arrange for destruction. This will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented. Drug accountability must be performed on DUN level and recorded in IV/WRS. Drug accountability will be performed in accordance with the flow charts, see section 2.

9.5 Auxiliary supplies

- Needles, NovoFine®
- ecap
- DFU for PDS290 and FlexPro®
- ecap info card

All auxiliary supplies will be provided by Novo Nordisk.

ecaps will be used in this trial in the extension period. The ecap is going to replace the pen cap of pens in both treatment arms and is intended to be used as a normal pen cap. The ecap is a non-interventional device with a separate electronic data logger to register occurrences of cap removal and cap mounting in an electronic memory. For more information about the ecap please refer to the ecap info card.

The subject will receive one ecap for the first half of the extension trial and another for the second half and should be properly instructed on how to replace the original cap with the ecap and to return it at the appropriate visits. The ecaps will be shipped by Novo Nordisk to affiliates/local depots or directly to the trial sites.

The site staff will enter the unique number of the ecap dispensed to the subject in the eCRF. The site staff will perform ecap accountability in the eCRF. Once the returned ecaps have been accounted and reconciled by the monitor they should be shipped in batches to a central reading facility designated by Novo Nordisk.

10 Interactive voice/web response system

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

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Drug Dispensing
- Dose titration
- Dose reduction
- Treatment discontinuation
- Completion
- Code break
- Drug accountability
- Data change

Dose adjustment will be handled by IV/WRS according to the algorithm described in section 5.3. Placebo doses will be adjusted to mimic dose titration for NNC0195-0092 treatment. IV/WRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

Two hundred and eighty subjects will be randomised in a 2:2:1 ratio to receive NNC0195-0092, Norditropin® FlexPro® or placebo during a 35-week period. The randomisation will be stratified according to two region levels (Japan and all other countries), sex (Male and Female) and diabetic status (diagnosed with diabetes mellitus vs. not diagnosed with diabetes mellitus). The randomisation and stratification will be handled by the IV/WRS (see section 10).

All subjects completing the 35 weeks will continue on active treatment in a non-placebo-controlled design for an additional 53-week extension period.

11.1 Breaking of blinded codes

The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IV/WRS, record the reason, and sign and date the document.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS vendor helpdesk should be contacted. Contact details are listed in Attachment I.

If the code has been broken the subject can continue in the trial.

The central laboratory responsible for measurements of IGF-I and IGFBP-3 (PD) and the special laboratories analysing PK and antibody samples will have access to or receive a report from the IV/WRS listing the assigned treatment for each subject.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a 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 procedures (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 assessment**

–**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 assessment**

The following terms are used when assessing the 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 of an AE**

–**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.

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]. Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.

–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:

a. Is admitted to a hospital or in-subject, irrespective of the duration of physical stay, or
b. 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 dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse event

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

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Medication errors concerning trial products:
   –Administration of wrong drug.
   –Wrong route of administration, such as intramuscular instead of subcutaneous.
   –Administration of an overdose with the intention to cause harm (eg suicide attempt).
   –Accidental administration of a higher dose than intended. 'That is a dose higher than 100%' more than 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 not necessarily did happen.

Technical complaint

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)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- 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 (i.e. Visit 29 or Visit 15 if a subject does not wish to participate in the extension part of the trial). 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 subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents: IB[17] and the Company Core Data Sheet (CCDS), current version or updates hereof.

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

MESIs, regardless of seriousness, must be reported using both the AE form and the SIF.

The AE form for a non-serious AE should be signed when the event is resolved or at the end of the trial.

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 SIF **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.

- **Non-serious AE fulfilling the MESI criteria:** The AE form, and SIF **within 14 calendar days** of the investigator's first knowledge of the event.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms 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 re-enter the information on the appropriate forms in the eCRF. Contact details (fax, telephone, e-mail and address) are provided in the investigators trial file.

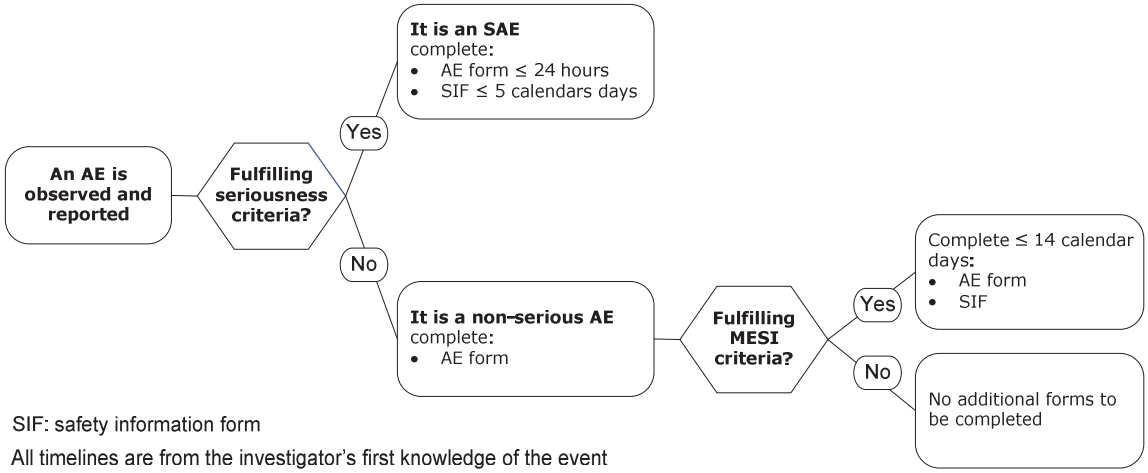

Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by the sponsor:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and 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 GCP[1], unless locally this is an obligation of the investigator.

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.
- **Non-serious AE fulfilling the MESI criteria:** Follow-up information on MESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

The investigator must ensure that 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.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- NNC0195-0092 PDS290 10mg/1.5ml
- NNC0195-0092 PDS290 Placebo
- Norditropin® FlexPro® 10 mg/1.5ml
- Needles, NovoFine® 32G Tip
- ecap

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, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form for each product listed. If the technical complaint involves more than one batch number or more than one DUN, a technical complaint form for each batch number or for each DUN 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**
- 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.

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 print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch number and, if available, the DUN. 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. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9).

12.5 Pregnancy

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 product(s). Treatment with trial product must be discontinued immediately (see section 6.6.1).

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:

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

SAEs*:*

–Paper AE form* **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.

* 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.

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 new-born 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:

Please 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 NNC0195-0092 in humans. In NN8640-3915 healthy male volunteers were dosed with up to 0.32 mg NNC0195-0092/kg (SD up to 0.32 mg/kg and MD up to 0.24 mg/kg). All adverse events were mild or moderate and primarily observed at the highest dose levels. Most common adverse events 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 adverse events were registered. These adverse events are similar to those observed for existing growth hormone products on the market. For further details please refer to IB[17].

Any overdose should be reported as an AE, with or without clinical manifestations. Overdoses are considered medication errors and thus MESIs.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal NNC0195-0092 safety committee to perform ongoing safety surveillance according to the NNC0195-0092 safety committee guideline. The NNC0195-0092 safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

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 supplied by a vendor.

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 (including AE forms and SIF in relation to pregnancy)

In addition paper AE forms, safety information forms and technical complaint forms will be provided. These must be used when access to the eCRF is revoked.

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 CRF data may be made by the investigator or the investigator's authorised staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's authorised 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 and ecap accountability. The first monitoring visit will be performed as soon as possible after FSFV and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site with the protocol and GCP, but will not exceed 12 weeks. If no subjects are enrolled at a site the monitoring visit interval will not exceed 18 weeks.

The monitor must be given direct access to 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 CRF. The only exceptions are race and ethnicity and the unique number of ecaps dispensed to a subject which can be recorded directly in the eCRF. History of GHD and diagnosis must be source data verifiable and reasonable efforts must be put into acquiring medical records from primary physicians or other hospitals or departments.

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 monitor will ensure that the CRFs are completed, diaries entered in the eCRF and that paper PROs are collected. The original diaries and PROs must not be removed from the trial site.

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

The monitor will collect CRF pages and other trial related forms containing data from screening failures. The existence of the subject and the reason for screening failure must be source data verifiable.

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

14.1 Titration surveillance

Surveillance of trial product titration will be performed centrally by an independent Novo Nordisk Titration Group not otherwise involved in the conduct of the trial. Surveillance will be performed on an on-going basis throughout both the main and extension trial until all subjects have completed dose titration. The titration group reviews the information provided by the investigator in case of deviations and follows up accordingly. The titration group will be blinded towards treatment allocation.

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 from the laboratory performing the analyses. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial identification number. 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.

Two partial database locks are planned to be done during the trial (facilitating interim safety reporting and analysis of main trial period data, respectively) as well as a database lock after the extension period of the trial is completed. For details please refer to section 17.5.

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. The SAP will be finalised before database lock.

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

All statistical tests conducted will be two sided on the 5% level. Region is defined as a factor with 2 levels: Japan and all other countries.

17.1 Sample size calculation

Under the assumption of a true mean difference of 2.5% between NNC0195-0092 and placebo and a standard deviation (SD) of 4.5% for the primary endpoint and based on a two-sided, two-sample t-test with a significance level of 5% and a 2:1 randomisation ratio between NNC0195-0092 and placebo, 104 subjects in the NNC0195-0092 treated group and 52 subjects in the placebo treated group completing the main trial should ensure 90% power for detecting a difference between NNC0195-0092 and placebo. The assumptions of a true mean difference of 2.5% between active treatment and placebo and a SD of 4.5% is slightly conservative to what is observed in similar trials. In a secondary comparison of the primary endpoint, it will be possible to expect with probability 0.87 that half the length of the 95% confidence interval (CI) constructed for the difference between NNC0195-0092 and Norditropin® FlexPro® will be at most 1.3% if additional 104 subjects are enrolled in the Norditropin® FlexPro® treated group, resulting in a total of 260 subjects to be included in the trial. Expecting at most 7% drop-out from the trial, 280 subjects should be included in the trial.

Simulations (10000 samples, analysis based on multiple imputation technique as described in section 17.3) under the the assumption of a drop-out rate of 7% and an additional assumption that 50% of the subjects who do not complete the main trial contribute to the primary analysis with post-randomisation DXA data, gives 89% power for detecting a difference between NNC0195-0092 and placebo with 112 subjects in the NNC0195-0092 treated group and 56 subjects in the placebo treated group. If the assumptions are changed to a drop-out rate of 15% and all subjects who do not complete the main trial will have no post-randomisation DXA data, then simulations gives 78% power for detecting a difference between NNC0195-0092 and placebo.

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".

A partial database lock of all data obtained up to Week 35 is planned to take place shortly after the last dosed subject has passed the assessments of Week 35 (main trial). The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

In the extension trial period the data for the efficacy analysis will be analysed using the randomized treatment from the start of the main trial period in combination with the allocated/randomized treatment in the extension phase. There will thus be four groups in the extension trial: NNC0195-0092 /NNC0195-0092, placebo/NNC0195-0092, Norditropin® FlexPro®/Norditropin® FlexPro® and Norditropin® FlexPro®/NNC0195-0092. Subjects not participating in the extension trial will be included based on their main trial randomization with a special case for Norditropin® FlexPro® subjects who will be included in the Norditropin® FlexPro® /Norditropin® FlexPro® group. For the safety endpoints the actual treatment (main trial period) in combination with the actual treatment (extension trial period) will be used for the analysis.

17.3 Primary endpoint

The primary endpoint is change from baseline (randomisation) to end of main trial period (Week 34) in truncal fat percentage.

The primary objective of the trial is to demonstrate the efficacy of once weekly dosing of NNC0195-0092 after 34 weeks of treatment in adults with GHD and the primary analysis of the primary endpoint will be the primary tool for achieving this. Body composition is measured by DXA and truncal fat percentage is defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass (kg) and truncal lean body mass (kg).

Truncal fat percentage as a function of time since baseline is expected to be monotone if the subject stays on the randomised treatment in the main trial period. Based on this assumption, the primary analysis of the primary endpoint will be conducted using a multiple imputation technique where the trajectory after a withdrawn subject's last observation is imputed based on data from the placebo arm, thus mimicking an intention to treat (ITT) scenario where withdrawn subjects are assumed to be switched to no treatment (placebo) after withdrawal. For each of 100 copies of the dataset (seed=34247), an analysis of covariance (ANCOVA) model with GHD onset type (adult or child), sex, region, DM (diabetic status) and sex by region by DM interaction as factors and baseline truncal fat (%) as a covariate. is fitted to the change in truncal fat percentage from baseline to 34 weeks data for the placebo group only. The estimated parameters, and their variances, from this model are used to impute missing values at 34 weeks for subjects in all treatment groups, based on

their sex, region, DM, GHD onset type and baseline truncal fat values. If a truncal fat assessment for a subject has been performed after baseline at intermediate time t (e.g. in connection with the end-of-trial visit for withdrawn subjects, section 8.2) this information will be combined with the time-normalized model based estimate so that the final imputed value for the subject is a sum of the observed value at time t and the model based estimated change multiplied by (34 weeks-t)/(34 weeks) minus the baseline value.

For each of the complete data sets, the change from baseline to 34 weeks is analysed using an ANCOVA model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and the baseline truncal fat value as a covariate.

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

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

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

From m_{MI} and SD_{MI}, the treatment difference at Week 34 between NNC0195-0092 and placebo will be estimated and the corresponding 95% CI and p-value will be calculated. As a secondary comparison, the treatment difference at Week 34 between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CI will be calculated.

Superiority of NNC0195-0092 over placebo will be considered confirmed if the upper boundary of the two-sided 95% CI of the treatment difference (NNC0195-0092 – placebo) is below 0 (i.e. greater reduction from baseline in truncal fat percentage in the NNC0195-0092 treated group than in the placebo treated group).

The secondary comparison, comparison of NNC0195-0092 with Norditropin® FlexPro®, will be used to assist the clinical judgment of the clinical relevance of the estimated treatment difference between NNC0195-0092 and placebo.

A secondary analysis of the primary endpoint based on an assumption of missing at random (MAR) will be done using an ANCOVA model with treatment (i.e. NNC0195-0092, placebo and once-daily Norditropin® FlexPro®), GHD onset type (adult or child), sex, region, DM and sex by region by DM interaction as factors and baseline truncal fat (%) as a covariate. From the model the treatment difference at Week 34 between NNC0195-0092 and placebo will be estimated and the corresponding 95% CI and p-value will be calculated. Subjects without Week 34 data for the

endpoint will not be included in the analysis. As a secondary comparison, the treatment difference at Week 34 between NNC0195-0092 and Norditropin® FlexPro® will be estimated from the model and the corresponding 95% CI will be calculated.

An additional supportive analysis of the primary endpoint will be done using the same model as were used for the secondary analysis of the primary endpoint. Only subjects who have completed at least 3 dose adjustment evaluations (see section 5.3.1) and have Week 34 data for the endpoint will be included in this analysis.

The secondary analysis of the primary endpoint is based on the assumption of missing at random (MAR). For this trial the missing data are expected to be mainly due to subjects that are withdrawn from the trial. The possible withdrawal reasons and criteria are described in section 6.6. Up to 7% of the subjects are expected to drop-out from the main part of this trial. Data from subjects who withdraw from the trial due to withdrawal criterion 2 and treatment discontinuation criteria 6 and 7 can reasonably be assumed to be missing completely at random (MCAR). It is expected that a limited amount of the missing data will be due to these criteria. For most of the expected missing data, due to the other withdrawal criteria and subjects withdrawing at own will the MAR assumption may be questionable. Therefore, the sensitivity analyses described below will be used to investigate whether the results from the secondary analysis are robust against departures from the assumption of MAR.

Sensitivity analyses

Let δ be defined as the difference between the mean of the observed data and the mean of the unobserved data μ_{unobs}-μ_{obs}, adjusted for other observed data. Under an MAR analysis, δ is assumed to be 0. Positive values of δ indicate that subjects with missing endpoint values have smaller reductions from baseline than subjects with observed endpoint values. If subjects primarily withdraw due to perceived lack of efficacy then this could be the most likely direction of departure from MAR though change in truncal fat percentage may not be a parameter that is linked in a simple way to the perceived efficacy level of the individual subject. Let f_1 and f_0 be the fractions of subjects with unobserved endpoint data in the NNC0195-0092 and placebo arms, respectively. The sensitivity analysis is done by adding a quantity Δ to the treatment effect estimate under the MAR assumption (i.e. treatment effect estimate from the secondary analysis of the primary endpoint), where $\Delta = f_1\delta$ if data depart from MAR in the NNC0195-0092 arm only, $\Delta = -f_0\delta$ if data depart from MAR in the placebo arm only, and $\Delta = (f_1-f_0)\delta$ if data depart from MAR in the same way in both arms. The calculations will use a range of δ values going from 0 to 2% and the approximation that the standard error of the treatment difference is unaffected by the sensitivity analysis[29]. All subjects from the FAS can be viewed as included in this analysis as subjects with missing endpoint data will be contributing to one of the fraction values f_1 and f_0. A similar sensitivity analysis will be made for the secondary comparison between NNC0195-0092 and Norditropin® FlexPro®.

Other exploratory analysis of the primary endpoint

Using the same model as were used for the primary analysis of the primary endpoint, additional exploratory analysis will be done by including treatment by sex, treatment by region and treatment by GHD onset type interaction terms, one at a time, to the model. For region, sub group analysis will also be done based on the primary analysis model.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

Changes from baseline to end of main trial period (Week 34) in the following variables will be used to address the primary objective:

- Truncal fat mass
- Truncal lean body mass
- Total fat mass
- Visceral adipose tissue
- Android fat mass
- Gynoid fat mass
- appendicular skeletal muscle mass (ASMM)
- Lean body mass
- Bone mineral content (extension part only)
- Bone mineral density (extension part only)
- IGF-I SDS
- IGFBP-3 SDS
- Scores of the following PRO questionnaires:
    - TRIM-AGHD
    - SF-36v2

- Lipid profile (total cholesterol, HDL- cholesterol, LDL-cholesterol and triglycerides)
- Cardiovascular parameters (hsCRP and IL-6)
- Body weight
- Waist circumference

Changes in total fat mass, truncal fat mass, visceral adipose tissue, android and gynoid fat mass, appendicular skeletal muscle mass, lean body mass, truncal lean body mass, waist circumference and lipids (total cholesterol, HDL- cholesterol, LDL-cholesterol and triglycerides) from baseline to Week 34 will be analysed using an ANCOVA model with treatment, GHD onset type, sex, region,

DM and sex by region by DM interaction as factors and baseline value as a covariate. The lipids data will be log transformed before analysis, both baseline and Week 34 values. From the model the treatment differences (for lipids the treatment differences will be reported as ratios) at Week 34 between NNC0195-0092 and placebo and between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CIs and p-values will be calculated for each endpoint based on the same multiple imputation technique as was used in the primary analysis of the primary endpoint.

Changes in IGF-I SDS and IGFBP-3 SDS from baseline to the 1, 3, 5, 7, 9, 16, 25, 33 and 35 week's measurements will be analysed using a mixed model for repeated measurements (MMRM), with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline value as a covariate, all nested within week as a factor. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From the MMRM the treatment differences at Week 34 between NNC0195-0092 and placebo and between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CIs and p-values will be calculated for each endpoint. Subjects without post-randomisation data for the analysed endpoint will not be included in the analysis.

Changes in scores of TRIM-AGHD (total and individual domain scores), SF-36 (physical and health component summary scores and individual domain scores) from baseline to the 8, 25, and 34 week's measurements will be analysed using a mixed model for repeated measurements (MMRM), with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline value as a covariate, all nested within week as a factor. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From the MMRM the treatment differences at Week 34 between NNC0195-0092 and placebo and between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CIs and p-values will be calculated for each endpoint. Subjects without post-randomisation data for the analysed endpoint will not be included in the analysis.

Changes in cardiovascular parameters (hsCRP and IL-6) from baseline to the 8, 16, 25, and 34 week's measurements will be analysed using a MMRM, with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline value 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. The data will be log transformed before analysis, both baseline value and values assessed at post-randomization visits. From the MMRM the treatment differences (ratios) at Week 34 between NNC0195-0092 and placebo and between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CIs and p-values will be calculated for each endpoint. Subjects without post-randomisation data for the analysed endpoint will not be included in the analysis.

- Scores of PRO questionnaire TSQM at Week 34

The scores of PRO questionnaire TSQM at Week 34 will be used to address the primary objective.

The TSQM scores (effectiveness, convenience and global satisfaction scores) at 8, 25, and 34 week's measurements will be analysed using a mixed model for repeated measurements (MMRM), with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors, all nested within week as a factor. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From the MMRM the treatment differences at Week 34 between NNC0195-0092 and placebo and between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CIs and p-values will be calculated for each endpoint. Subjects without post-randomisation data for the analysed endpoint will not be included in the analysis.

Changes from baseline to end of extension period (Week 87) in all of the above mentioned variables in 17.3 and 17.4.1 (not TSQM) as well as bone mineral content (BMC) and bone mineral density (BMD) will be used to support the secondary objective regarding evaluation of efficacy during the extension period. For TSQM the analogous endpoints to support this secondary objective will be scores assessed at Week 87.

The data will be analysed using descriptive statistics. This analysis will be supplemented with exploratory analysis on changes from baseline to end of extension period (Week 87) data based on MMRM analysis models similar to the main trial period data analysis, where NNC0195-0092/NNC0195-0092 and Norditropin® FlexPro®/Norditropin® FlexPro® arms will be compared. For TSQM scores the analysis will be made on Week 87 data and not change from baseline data. The interpretation of these analysis results should take into account the added complications inherent in analysing data from an extension period, including selection bias.

The NNC0195-0092 and hGH serum concentration data will be analysed using descriptive statistics. The data will also be used in the population PK analysis described in section 17.6.

Compliance with treatment will be evaluated based on time stamps from the ecaps in the extension period and diary data in the main trial period and the extension period. The data will be analysed using descriptive statistics.

A Kaplan-Meier plot of the time-to-withdrawal will be presented by treatment arm and the implication on the efficacy analysis of any marked differences will be commented upon in the clinical trial report.

17.4.1.2 Safety endpoints

The following endpoints will be used to support the secondary objectives of evaluation of safety in both the main (up to week 35) and extension (up to week 88) trial periods:

- Incidence of adverse events, including injection site reactions
- Incidence of clinical technical complaints
- Occurrence of anti-NNC0195-0092 antibodies
- Changes from baseline in physical examination, ECG results and vital signs
- Changes from baseline in 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

Adverse events will be analysed using descriptive statistics. All adverse events with onset after the first administration of trial product and up until Week 34 will be included in the main trial period analysis. The adverse events will be summarised by treatment, MedDRA (Medical Dictionary for Regulatory Activities) system organ class and MedDRA preferred term. The descriptive statistics will include the number and percentage of subjects who experienced adverse events and the number of events. Adverse events will be listed by treatment and subject with information on severity, relationship to trial product and demographics. Adverse events with onset before first dosing will be reported in a separate listing.

All other safety endpoints will be analysed using descriptive statistics. Additionally, an exact logistic regression analysis on the event of experiencing at least one injection site reaction during the main trial period will be done with treatment, GHD onset type , sex, region, DM and sex by region by DM interaction as factors included in the model as factors and number of injections taken in the main trial period included as offset.

17.5 Interim reporting, reporting of main and extension periods of the trial

Two partial database locks are planned during the trial (facilitating interim safety reporting and analysis of main trial period data, respectively) as well as a database lock after the extension period of the trial is completed (facilitating the analysis of the extension trial data).

First partial DBL

A blinded interim safety reporting will be performed when 50 subjects randomised to NNC0195-0092 have completed the main trial.

Data for all subjects up to and including V15 who have completed the main trial at this time will be included in a partial database lock (first partial database lock of trial data) with the following exceptions:

- Data derived from the DXA body composition measurement will not be included (see section 8.4.1)
- Antibody samples will be fully analysed but not be loaded in the clinical database to avoid unblinding
    - Anti-drug antibody data for non-neutralising antibodies against NNC0195-0092 and hGH not classified as high titre antibodies (see section 8.5.13) will be reported as a tabulated summary in a blinded manner. This will include number of subjects with antibodies in the once weekly arms (NNC0195-0092 + placebo) versus number of subjects with antibodies in the once daily arm (hGH) including antibody titres and results for in vitro neutralising effect. Handling of data and report preparation is the responsibility of the analysing laboratory
    - Should any subjects develop high titre and/or persistent in vitro neutralising antibodies (see section 8.5.13) the safety committee might recommend unblinding of specific data for further analysis and an independent ad hoc safety group (see section 12.7.1) will be established. The purpose of an ad hoc safety group is to review unblinded data and based on analyses recommend further action to the safety committee. This ad hoc group will be able to report relevant data in an unblinded manner. Ad hoc safety group members must NOT be involved in daily project activities
        - Data for PK, IGF-I, IGFBP-3 will be fully analysed to support the independent ad hoc safety group if needed but data will not be loaded in the clinical database to avoid unblinding.

Data will be analysed using descriptive statistics and will support the future phase 3 trial programme in children with GHD (regulatory requirement). As the safety data will be reported in a blinded manner (once weekly arms combined (NNC0195-0092 or placebo) versus Norditropin® FlexPro®) no impact is expected on the remainder of the trial.

Second partial DBL (main trial)

Data for all subjects up to and including V15 who have completed or discontinued the main trial will be included in a partial database lock (second partial database lock of trial data). After the second partial DBL the sponsor will become unblinded while the subjects and site personnel will remain blinded regarding the NNC0195-0092 versus Placebo allocation during the main period.

Final DBL (extension)

The extension trial is open-label after the main trial period and the data from the extension period will support the secondary objective of evaluating the efficacy and safety of NNC0195-0092 for up to 86 weeks of treatment in adults with GHD, but will not contribute with confirmatory results.

17.6 Population PK analysis

A population pharmacokinetic analysis (POP-PK) will be used to evaluate the effect of anti-NNC0195-0092 antibodies on the PK of NNC0195-0092. All values from samples taken 3 days after the last trial drug administration will be used for the analysis and relevant covariates that could influence the PK will be included in the analysis.

A more technical and detailed elaboration of the population pharmacokinetic analysis will be done in the modelling analysis plan (MAP) which will be finalised before the second DBL. Results will be reported in a report separate from the CTR.

17.7 Health economics and/or subject reported outcomes

Please refer to 17.4.1.1. Results from the PROs will be reported in the CTRs.

18 Ethics

Please refer to section 3.1.5 for a description of the risks and benefits.

18.1 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 task may be delegated by the investigator 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, and a revised written subject information must be provided and a new informed consent must be obtained.

18.2 Data handling

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

- Data already collected and data collected at the end-of-trial and follow up visits will be retained by Novo Nordisk, entered into the database and used for the 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.

18.3 Information to subject 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 letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subjects by discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank for your participation letter" at the end of the trial. Further the subject may receive trial letters during the trial period.

All information to the subjects will be submitted to the health authorities and IECs/IRBs for approval.

18.4 Premature termination of the trial and/or trial site

Novo Nordisk, the investigator, 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 a 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 IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

If, after the termination of the trial, the risk/benefit 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

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 clinical database.

Documentation on protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

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, 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
- 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
- Signed and dated agreement on the final protocol
- Signed and dated agreement on protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement
- Signed and dated Investigator Agreement
- Financial disclosure form from investigator and sub-investigator(s)
- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by each investigator
    - FDA form 1572:
        - For US sites:
            - Intended for US sites
            - Conducted under the IND
            - All US investigators, as described above, will sign FDA Form 1572
        - For sites outside the US:
            - Intended for participating sites outside of the US
            - Not conducted under the IND
            - All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together.

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

By signing the protocol, each investigator also agrees to allow Novo Nordisk making 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. If any tasks are delegated, the investigator must maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator must ensure that there is adequate 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 must ensure adequate supervision of the conduct of the trial at the trial site.

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's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject identification code list must be kept securely and separate from the personal 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 Novo Nordisk for regulatory purposes and 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.

One Principal Investigator will be appointed 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.

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 principal 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 for publication of such primary policy 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.

Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation and human biospecimens

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 Novo Nordisk 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 as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biospecimens

Antibody samples will be stored by Novo Nordisk until marketing authorisation by regulatory authorities (in USA, EU, Japan) but no longer than 15 years after end of trial. Only Novo Nordisk will have access to these samples. Further characterisation of the antibody response may be requested by the health authorities. Biological samples of subjects from Brazil will not be stored after the end of the trial.

None of the data will be identified by name. Antibody samples will be identified only by a subject number, a visit number and a trial identification number. In the event that the collected antibody samples will be used in the future, the investigator will become 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.

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 sponsor, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: 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 risk/benefit 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 CTR 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's trial 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.

Novo Nordisk accepts liability in accordance with:

FOR POLAND: Novo Nordisk accepts liability for the trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the trial, Novo Nordisk and investigator are covered by the Insurance Policy issued according to applicable Polish law.

FOR RUSSIA: Novo Nordisk accepts liability for the trial in accordance with Federal Law of 12 April 2010 No. 61-FZ "On Medicinal Drugs' Cerculation"

FOR SPAIN: Novo Nordisk accepts liability for the trial in accordance with Royal decree 223/2004, of 6th February, establishing the requisites concerning clinical trials.

FOR GERMANY: Novo Nordisk accepts liability for the trial in accordance with the drug law dated August 24, 1976 last amended by Article 1 of the Law of 10th October 2013 (Federal Law Gazette I p. 3183).

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

Protocol Amendment

no 1
to Protocol, final version 1.0
dated 25 March 2014

Trial ID:NN8640-4054

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period

Trial phase: 3a

Applicable to all countries

Amendment originator:

[redacted]

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Page

1 Introduction including rationale for the protocol amendment

This amendment is based on consultations with the Food and Drug Administration (FDA) in the US and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

1.1 The changes required by the FDA and PMDA

- FDA: The primary analysis of the primary endpoint will be changed to an analysis based on the ITT principle rather than on an assumption of missing at random. The former primary analysis will be used as a secondary analysis (section 17)
- FDA: A general focus on the avoidance of missing data (sections 6, 8.2 and 8.6, introduction of the SI/IC)
- FDA: Additional antibody and PK sampling will be added to align with the time points for immunogenicity assessments as recommended in the FDA Immunogenicity guideline of February 2013 (sections 2, 8.4.3 and 8.5.14)
- FDA: Inclusion of subjects with diabetes mellitus in order to understand the effect of the drug in this subgroup of subjects. As a result of including subjects with diabetes mellitus fundusphotography of these subjects will be performed as safety precaution. An additional stratum for subjects with diabetes mellitus will be added to randomisation (sections 2, 6.2, 6.3, 8.5.15 and 17)
- PMDA: At sites in Japan subjects with diabetes mellitus will be excluded (section 6.3)
- PMDA: Application of Japanese guidelines for the diagnosis of adult growth hormone deficiency for subjects included at sites in Japan (sections 1 and 6.2)

1.2 Additional changes and clarifications

Changes

- Urinalysis will be removed. Based on recently available data it has been evaluated that the urinalysis does not provide additional or important information on the efficacy or safety of NNC0195-0092 that is not covered by the blood tests planned.

Clarifications

Clarifications will be implemented in sections 1, 2, 4, 5, 6, 8, 9, 10, 11 14 and 17 of the protocol.

In this protocol amendment:

- Any new text is written ***in italics.***

- Any text deleted from the protocol is written using ~~strike through~~.
- Changes in the flowcharts are further highlighted in red

2 Changes to protocol version 1

2.1 Changes to section 1 of the protocol

Key inclusion criteria

FOR ALL COUNTRIES EXCEPT JAPAN: Confirmed diagnosis of adult growth hormone deficiency (if a subject satisfies at least one of the ~~four~~ following criteria)

a. ~~For the i~~*I*nsulin tolerance test (ITT) or glucagon test: ~~the validated cut-off for GHD in adults is~~ a peak GH response of < 3~~.0~~ ng/mL (3 µg/L)
b. ~~For g~~*G*rowth hormone releasing hormone (GHRH) +Arginine test~~: for those subjects with~~ a*ccording to* body mass index (BMI)
    i. BMI < 25 kg/m^2, a peak GH < 11 ng/mL (µg/L)*; for*
    ii. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)~~; for~~
    iii. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)
c. Three or more pituitary hormone deficiencies at screening and ~~a low IGF-I (~~IGF-I SDS < -2.0~~)~~

~~d~~ **FOR JAPAN ONLY:** ~~GHRP-2 tolerance test: a peak GH response of ≤9 ng/mL~~

- *Confirmed diagnosis of adult growth hormone deficiency (subjects with adult onset AGHD need to satisfy at least one of the following criteria, subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria):*
    - *ITT test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)*
    - *glucagon test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)*
    - *GHRP-2 tolerance test: a peak GH of ≤ 9 ng/mL (assay using recombinant GH standard)*

2.2 Changes to section 2 of the protocol

Table 2–1 Trial Flow Chart for the main trial period

Visit	1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Period			Titration									Fixed-dose				
Time (weeks + days)	V1b- 1d minimum	-3 to -2	0	1+3d	2	3+3d	4	5+3d	6	7+3d	8	9+3d	16+~~3~~4 d	25+~~3~~4d	33+~~3~~4d	35
Visit type	IC	Screen.	Rand.	IGF[3]	Site	IGF	~~Phone~~[3] *Site*	IGF[3]	Phone[3]	IGF[3]	Site	IGF[3]	Site	Site	EOT 1	Site
Visit window (days)					+1		+1		+1		+1		+/- 7[4]	+/- 7[4]	+/-2	~~+/- 2~~
Need to be fasting		X	X	X	*X*	X	*X*	X		X	X	X	X	X	X	X
Subject information																
Informed consent	X															
In/exclusion criteria		X	X													
Demography		X														
Medical history		X														
Concomitant illness		X														
Concomitant medication		X	X		X		X		X		X		X	X	X	X
MRI/ CT[15]		*X*														
Height		X														
Pregnancy test[5]		X	X		X						X		X	X	X	X
Randomisation			X													
Withdrawal criteria			~~X~~		X						X		X	X		X*
Efficacy																
DXA		X[6]													X	
IGF-I and IGFBP-3		X	X[7]	X[7]	*X*[7]	X[7]	*X*[7]	X[7]		X[7]	*X*[7]	X[7]	X[7]	X[7]	X[7]	X[7]*
PK-Sampling			X[7]	X[7]	*X*[7]	X[7]	*X*[7]	X[7]		X[7]	*X*[7]	X[7]	X[7]	X[7]	X[7]	X
PRO questionnaires[8]			X											X	X	
Lipids		X													X	
hsCRP and IL-6		X									X		X	X	X	
Body weight		X	X		X						X		X	X	X	X*
Waist circumference			X												X	
Safety																

Visit	1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Period			**Titration**										**Fixed-dose**			
Time (weeks + days)	**V1b- 1d minimum**	**-3 to -2**	**0**	**1+3d**	**2**	**3+3d**	**4**	**5+3d**	**6**	**7+3d**	**8**	**9+3d**	**16+~~3~~4 d**	**25+~~3~~4d**	**33+~~3~~4d**	**35**
Visit type	**IC**	**Screen.**	**Rand.**	**IGF[3]**	**Site**	**IGF**	**~~Phone[3]~~ *Site***	**IGF[3]**	**Phone[3]**	**IGF[3]**	**Site**	**IGF[3]**	**Site**	**Site**	**EOT 1**	**Site**
Visit window (days)					+1		+1		+1		+1		+/- 7[4]	+/- 7[4]	+/-2	~~+/- 2~~
Need to be fasting		**X**	**X**	**X**	***X***	**X**	***X***	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events			X		X		X		X		X		X	X	X	X
Haematology		X									X		X	X	X	
Biochemistry,		X									X		X	X	X	
Thyroid function		X									X		X	X	X	
Testosterone[9]		X														
~~Urinalysis~~		~~X~~									~~X~~		~~X~~	~~X~~	~~X~~	
Fasting plasma glucose		X									X		X	X	X	
Fasting insulin		X									X		X	X	X	
HbA1c		X									X		X	X	X	
Fasting serum cortisol		X									X		X	X	X	
ACTH stimulation test		X[10]									X[11]					X[11]*
ECG		X									X				X	
Vital signs		X	X		X						X		X	X	X	X*
Physical examination		X	X		X						X		X	X	X	X*
Local tolerability			X[12]		X						X		X	X	X	X*
Anti-NNC0195-0092 + anti hGH antibodies			X[7]		X[7]		*X*[7]				X[7]		X[7]	X[7]	X	X[7]
Eye examination (fundus-photo)[13]		*X*														*X*
Trial material																
ecap dispensing and training																X*
Dose adjustment[13~~,4~~]					X		X		X		X					X*
Dispensing visit			X		X		*X*				X		X	X		X*
Dosing (Observed trial drug administration)			X		X						X					X*
Drug accountability			*X*		X		*X*				X		X	X	~~X~~	X

Visit	1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Period			**Titration**									**Fixed-dose**				
Time (weeks + days)	**V1b- 1d minimum**	**-3 to -2**	**0**	**1+3d**	**2**	**3+3d**	**4**	**5+3d**	**6**	**7+3d**	**8**	**9+3d**	**16+~~3~~4 d**	**25+~~3~~4d**	**33+~~3~~4d**	**35**
Visit type	**IC**	**Screen.**	**Rand.**	**IGF[3]**	**Site**	**IGF**	**~~Phone~~[3] *Site***	**IGF[3]**	**Phone[3]**	**IGF[3]**	**Site**	**IGF[3]**	**Site**	**Site**	**EOT 1**	**Site**
Visit window (days)					**+1**		**+1**		**+1**		**+1**		**+/- 7[4]**	**+/- 7[4]**	**+/-2**	**~~+/- 2~~**
Need to be fasting		**X**	**X**	**X**	***X***	**X**	***X***	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Hand out + instruct in diary			X		X		*X*				X		X	X	~~X~~	X*
Diary returning					X		*X*				X		X	X	~~X~~	X
Compliance					X						X		X	X	X	
Other																
EOT Form															~~X~~	
IV/WRS call		X	X		X		X		X		X		X	X	~~X~~	X

74 *13. Fundusphotography performed in subjects diagnosed with diabetes mellitus only (see inclusion criterion 10). Fundusphotography performed ≤ 90 days prior to*
75 *randomisation is acceptable if results are available for evaluation at randomisation.*
76 ~~13~~*14. B*esides the IGF-I based dose adjustment during the titration period, dose reduction can be considered during the entire study period (including the two titration
77 periods) 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
78 acceptable as judged by the investigator and subject, dose reduction in steps of 25% can be considered. If dose reduction takes place during the titration periods or for
79 deviations to the titration schedule see section 5.3.5.
80 *15. Only for subjects with a history of pituitary adenoma or other benign intracranial tumour. MRI/CT if an MRI or CT scan has not been performed ≤ 9 months (defined*
81 *as ≤ 270 days) prior to randomisation (results must be available for evaluation at randomisation).*

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84 **Table 2–2 Trial Flow Chart for the Extension Period**

Visit	16	17	18	19	20	21	22	23	24	25	26	27	28[1]	29[1]
	Titration period								Fixed-dose period					
Time (week)	36+3d	37	38+3d	39	40+3d	41	42+3d	43	44+3d	53+~~3~~4d	64+~~3~~4d	75+~~3~~4d	86+~~3~~4d	88
Visit type	IGF[2]	Site	IGF[2]	~~Phone[2]~~ *Site*	IGF[2]	Phone[2]	IGF[2]	Site	IGF[2]	Site	Site	Site	EOT 2	Site
Visit window (days)		+1		+1		+1		+1		+/- 7[3]	+/- 7[3]	+/- 7[3]	+/- 2	+/- 2
Need to be fasting	X	*X*	X	*X*	X		X	X	X	X	X	X	X	X
Concomitant medication		X		X		X		X		X	X	X	X	X
Pregnancy test[4]		X						X		X	X	X	X	X
Withdrawal criteria		X						X		X	X	X		
Efficacy														
DXA													X	
IGF-I and IGFBP-3	X[5]	*X*[5]	X[5]	*X*[5]	X[5]		X[5]	*X*[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
PK sampling	X[5]	*X*[5]	X[5]	*X*[5]	X[5]		X[5]	*X*[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
PRO questionnaires[6]											X		X	
Lipids													X	
hsCRP and IL-6								X		X	X	X	X	
Body weight		X						X		X	X	X	X	X
Waist circumference													X	
Safety														
Adverse events		X		X		X		X		X	X	X	X	X
Haematology								X		X	X	X	X	
Biochemistry								X		X	X	X	X	
Thyroid function								X		X	X	X	X	
~~Urinalysis~~													~~X~~	
Fasting plasma glucose								X		X	X	X	X	
Fasting insulin								X		X	X	X	X	
HbA1c								X		X	X	X	X	
Fasting serum cortisol[7]								X		X	X	X	X	
ACTH stimulation test								X[7]						
ECG								X			X		X	
Vital signs		X						X		X	X	X	X	X

Visit	16	17	18	19	20	21	22	23	24	25	26	27	28[1]	29[1]
	Titration period								Fixed-dose period					
Time (week)	36+3d	37	38+3d	39	40+3d	41	42+3d	43	44+3d	53+~~3~~4d	64+~~3~~4d	75+~~3~~4d	86+~~3~~4d	88
Visit type	IGF[2]	Site	IGF[2]	~~Phone[2]~~ *Site*	IGF[2]	Phone[2]	IGF[2]	Site	IGF[2]	Site	Site	Site	EOT 2	Site
Visit window (days)		+1		+1		+1		+1		+/- 7[3]	+/- 7[3]	+/- 7[3]	+/- 2	+/- 2
Need to be fasting	X	*X*	X	*X*	X		X	X	X	X	X	X	X	X
Physical examination		X						X		X	X	X	X	X
Local tolerability		X						X		X	X	X	X	X
Anti-NNC00195-0092 + anti hGH antibodies		X[5]		*X*[5]				X[5]		X[5]	X[5]	X[5]	X	X
Eye examination (fundus-photo.)[8]														*X*
Trial material														
ecap dispensing and training										X				
Dose adjustment[~~8~~9]		X		X		X		X						
Dispensing visit		X		*X*				X		X	X	X		
Dosing (observed trial drug administration)		X						X						
Drug and ecaps accountability		X		*X*				X		X	X	X	~~X~~	X
Hand out and instruct in diary		X		*X*				X		X	X	X	~~X~~	
Diary returning		X		*X*				X		X	X	X	~~X~~	X
ecap returning										X			~~X~~	*X*
Compliance		X						X		X	X	X	X	
Other														
EOT Form													~~X~~	*X*
Contact IV/WRS		X		X		X		X		X	X	X	~~X~~	*X*

8. Fundusphotography is performed in subjects diagnosed with diabetes mellitus only (see inclusion criterion 10)

~~8~~9.Besides the IGF-I based dose adjustment during the titration period, dose reduction can be considered during the entire study period (including the two titration periods) 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 dose reduction takes place during the titration periods or for deviations to the titration schedule see section 5.3.5

2.3 Changes to section 4 of the protocol

4.3.2 Supportive secondary safety endpoints

The following endpoints will be used to support the secondary objectives of evaluation of safety in both the main (up to week 35) and extension (up to week 88) trial periods:

- Incidence of adverse events, including injection site reactions*
- Occurrence of anti-NNC0195-0092 antibodies*
- Incidence of technical complaints
- Changes from baseline in physical examination, ECG results and vital signs
- Changes from baseline in clinical laboratory test results including haematology, biochemistry, ~~urine analysis,~~ fasting glucose, fasting insulin, steady state beta cell function (%B) and insulin resistance (IR) (HOMA estimates), and HbA1c levels

2.4 Changes to section 5 of the protocol

5.1 Type of trial

Two hundred and eighty (280) subjects will be randomised in a 2:2:1 ratio to receive NNC0195-0092, Norditropin® FlexPro® or placebo during a 35-week period (8 weeks of titration, followed by 26 weeks of treatment and 1 week of washout). The randomisation will be stratified according to two region levels (Japan and all other countries) ~~and,~~ sex (male and female) *and diabetic status (diagnosed with diabetes mellitus vs. not diagnosed with diabetes mellitus)*. All subjects completing the 35-week period will continue their active treatment with NNC0195-0092 weekly injection or Norditropin® FlexPro® daily injection in a non-placebo-controlled design for an additional 53-week extension period (8 weeks of titration, followed by 44 weeks of treatment and 1 week of washout). Placebo subjects will be switched to NNC0195-0092 treatment and Norditropin® FlexPro® subjects will be re-randomised 1:1 to NNC0195-0092 or Norditropin® FlexPro® *within the same strata as used for the first randomisation*. During the extension period subjects will be seen on a regular basis for adverse events, safety laboratory measurements, and efficacy.

5.3 Treatment of subjects

Time of injections:

- NNC0195-0092 and placebo 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 12:00 PM (noon). *Trial drug must 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 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.*

5.3.1 Dose titration

During the first 8 weeks the dose will be titrated every second week starting from Week 2. The last dose adjustment in the main trial period will be done at Week 8. This allows four opportunities for dose adjustment (Week 2, 4, 6, and 8). Dose titration is based on blinded insulin like growth factor-I

standard deviation score (IGF-I SDS) values which will be uploaded from the central laboratory to the interactive voice/web response system (IV/WRS) which calculates the next dose. Subjects will come to the clinic 1 week 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. Dose adjustments are performed at Week 0 (starting dose) 2, 4, 6, and 8, i.e. four days after the IGF-I titration samples have been collected. The blood draw 1 week and 3 days after the dose adjustment visit at week 8 is to record the IGF-I level attained following the last dose adjustment at Week 8. Dose adjustment at Week ~~4 and~~ 6 will be instructed over the phone. After last dose adjustment (if any) at Week 8, the individual dose level is fixed.

5.3.3 Titration for subjects treated with either NNC0195-0092 or Placebo

~~The minimum weekly dose of NNC0195-0092 is 0.1 mg. The maximum weekly dose of NNC0195-0092 is 7 mg.~~

The minimum weekly dose of NNC0195-0092 is 0.1 mg. If the algorithm returns a dose of less than 0.1mg, the weekly dose of NNC0195-0092 must be 0.1 mg. The maximum weekly dose of NNC0195-0092 is 8 mg.

5.3.4 Titration for subjects treated with daily Norditropin® FlexPro®

~~The minimum daily dose of Norditropin® FlexPro® is 0.05 mg. The maximum daily dose of Norditropin® FlexPro® is 1mg.~~

The minimum daily dose of Norditropin® FlexPro® is 0.05 mg. If the algorithm returns a dose of less than 0.05mg, the weekly dose of Norditropin® FlexPro® must be 0.05 mg. The maximum daily dose of Norditropin® FlexPro® is 1.1mg.

If Norditropin® FlexPro® subjects forget or are unable to give the dose in the evening they should skip the dose and continue on the next evening with the next scheduled dose. If ~~they~~ *a subject* failed to inject the trial product the evening before a planned IGF visit, the~~y~~ *subject* should contact the trial site since the IGF visit and subsequent visits will ~~potentially~~ have to be rescheduled, i.e. *postponed* ~~moved one or~~ two weeks.

5.3.5 Deviations from titration schedule

The dose titration schedule in the protocol must be followed in order to allow titration to an optimal therapeutic dose for all subjects. Four 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, patient comes for IGF-I sampling in a non-fasting state, dose reduction), all subsequent visits during the titration periods plus the fixed dose IGF-I sample visits (i.e. V11 and V24, respectively) will be postponed by two weeks. Subsequent trial visits after V11 and 24, respectively will not be postponed.~~

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),

- *the **previous IGF-I sampling visit** will, depending on whether the visit has taken place or not,*
    - *be repeated two weeks later as an unscheduled if the visit has already taken place*
    - ***or** be rescheduled to two weeks later if it has not taken place*
- *the **affected dose adjustment visit** will be rescheduled to two weeks later*
- *all **subsequent visits** during the titration periods will be rescheduled to two weeks later*
- *the **fixed dose IGF-I sample visits** (i.e. V11 and V24, respectively) will be rescheduled to two weeks later.*

Subsequent trial visits after V11 and 24 respectively will not be postponed.

As an exception visits may be rescheduled up to two times during each titration period (allowing for a maximum of 6 opportunities for dose adjustment evaluation). If a subject has not completed at least 3 dose adjustment evaluations, this will be considered a PD as fewer than three completed dose adjustment evaluations are not expected to be sufficient to achieve therapeutic doses in a majority of subjects.

Deviations from the IV/WRS based dose titration other than those described above and dose reduction in steps of 25% will not be considered protocol deviations, however the reason for deviating must be ~~entered in the IV/WRS~~*recorded*. Based on this information it may be decided to ask for additional information regarding the deviation (see section 14.1). If the answer explains the deviation no further action will be taken.

2.5 Changes to section 6 of the protocol

6.2 Inclusion criteria

4. ***FOR ALL COUNTRIES EXCEPT JAPAN:*** Confirmed diagnosis of adult growth hormone deficiency (if a subject satisfies at least one of the ~~four~~ following criteria)

a. ~~For the i~~*I*nsulin tolerance test (ITT) or glucagon test: ~~the validated cut-off for GHD in adults is~~ a peak GH response of < 3~~.0~~ ng/mL (3 µg/L)
b. ~~For g~~*G*rowth hormone releasing hormone (GHRH) +Arginine test~~: for those subjects with~~ a*ccording to* body mass index (BMI)
   i. BMI < 25 kg/m^2, a peak GH < 11 ng/mL (µg/L)*; for*
   ii. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)~~; for~~
   iii. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)
c. Three or more pituitary hormone deficiencies at screening and ~~a low IGF-I (~~IGF-I SDS < -2.0~~)~~

~~d~~ **FOR JAPAN ONLY:** ~~GHRP-2 tolerance test: a peak GH response of ≤9 ng/mL~~

- *Confirmed diagnosis of adult growth hormone deficiency (subjects with adult onset AGHD need to satisfy at least one of the following criteria, subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria):*
  - *ITT test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)*
  - *glucagon test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)*
  - *GHRP-2 tolerance test: a peak GH of ≤ 9 ng/mL (assay using recombinant GH standard)*

5. IGF-I SDS < -0.5 at screening *relative to the mean* of the age and sex normal ranges according to the central laboratory measurements

10 Subjects without diabetes mellitus; or subjects diagnosed with diabetes mellitus provided that ALL the following criteria are met:

- *diabetes mellitus (diagnosed clinically) ≥ 6 months prior to screening*
- *stable oral anti-diabetic (OAD) treatment, defined as unchanged medication and unchanged dose for ≥ 90 days prior to screening*

- *no history of use of injectable anti-diabetic agents*
- *HbA1c <7.0% at screening according to central laboratory*
- *no diabetes related co-morbidities (as judged by the investigator) at screening*
- *fundusphotography performed ≤ 90 days prior to randomisation without proliferative retinopathy or severe non-proliferative diabetic retinopathy*

6.3 Exclusion criteria

2. Previous participation in this trial. Participation is defined as informed consent

BRAZIL ONLY: *Participation in other trials within one year (defined as 365 days) prior to screening visit (Visit 1b) unless there is a direct benefit to the research subject at the investigator´s discretion*

7. Anticipated change in lifestyle (eating, exercise or sleeping pattern) during the trial. *Exclusion based on this criterion is at the investigator's discretion*

~~9. Evidence of growth of pituitary adenoma or other benign intracranial tumour within the last 12 months (defined as 365 days) before randomisation (determined by comparing a previous MRI or CT to a new MRI or CT obtained no more than 9 months (defined as 270 days) prior to randomisation). If MRI or CT results are not available these can be performed at screening. Only confirmation of tumour stability will be recorded in the electronic case report form (eCRF)~~

9. For subjects with a history of pituitary adenoma or other benign intracranial tumour:

- *Surgical removal of pituitary adenoma or other benign intracranial tumour within 12 months (defined as ≤ 365 days) before randomisation.*
- *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.

~~16. Diabetes mellitus (including currently treated, well-controlled DM) defined by at least one of the following criteria:~~

- ~~HbA1c ≥7.0%~~
- ~~Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)~~
- ~~Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT)~~

16. ***FOR JAPAN ONLY:*** *Diabetes mellitus*

~~24~~ ~~**BRAZIL ONLY:** Participation in other trials within one year (defined as 365 days) prior to screening visit (Visit 1b) unless there is a direct benefit to the research subject at the investigator´s discretion~~

6.4 Randomisation criteria

1. The quality *evaluation* of the baseline DXA scan needs to be performed by the im~~i~~*a*ging laboratory prior to randomisation

6.6 Treatment discontinuation and withdrawal criteria

Efforts should be made for subjects to attend and complete scheduled visit procedures. There will be a clear distinction between treatment discontinuation and subject withdrawal.

If any of the below treatment discontinuation or withdrawal criteria apply, treatment may be discontinued or the subject must be withdrawn (see section 8.2 for detailed instructions).

6.6.1 Treatment discontinuation

*6. Pregnancy**
*7. Intention of becoming pregnant during the trial, including the extension period**
**No DXA scans can be performed on these subjects*

6.6.2 Withdrawal

1. The subject may withdraw at will at any time.

~~2. The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures.~~

The subject must be withdrawn if the following applies

~~3.~~ *2.* Included in the trial in violation of the inclusion and/or exclusion criteria

~~4. Pregnancy~~

~~5. Intention of becoming pregnant during the trial, including the extension period~~

~~6.~~ *3* Use of weight loss medications known to affect body weight substantially. *Withdrawal based on this criterion is at the investigator's discretion*

~~If treatment is discontinued or a subject is withdrawn, the procedures described in section 8.2 must be followed.~~

2.6 Changes to section 8 of the protocol

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).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list.

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) 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.

All laboratory analyses in this trial will be performed by the central laboratory unless stated otherwise for the single parameter. U~~rinalysis and u~~rine pregnancy tests will be performed at the sites with test material supplied by the central laboratory.

Laboratory values outside reference ranges will be marked on the laboratory reports. All results will be faxed or electronically transferred to the investigator. The investigator must assess all results outside the reference ranges as either clinically significant or not clinically significant and sign and date each page of the lab report. For parameters which are not blinded this review needs to be documented prior to the subject's next site visit.

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 must be reported to the investigator.

The investigator must review all laboratory results ~~including urinalysis~~ for concomitant illnesses and AEs and report these according to this protocol.

8.2 Handling of Screening failures, re-screening,~~and~~ treatment discontinuation *and withdrawals*

Treatment discontinuation

If a subject discontinues treatment in the trial, the investigator must aim to undertake all procedures in the trial after treatment discontinuation except trial drug administration.

Pregnant subjects or subjects with the intention to become pregnant must not undergo additional DXA scans.

A treatment discontinuation session must be made in the IV/WRS and in the eCRF it must be specified if the subject will participate in subsequent visits or withdraw from the trial. Final drug accountability must be performed.

Withdrawal

If the subject does not participate in all visits (withdrawal), the investigator must aim to perform procedures similar to those for the respective end of ~~treatment~~*trial* (EOT) visits (V14 or V28) as soon as possible and a post-treatment follow-up visit (V15 or V29, at least two weeks after last treatment with NNC0195-0092 and at least 8 days after last treatment with Norditropin® FlexPro®).

A treatment discontinuation session must be made in the IV/WRS and in the eCRF it must be specified if the subject will participate in subsequent visits or withdraw from the trial. 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~~. The eCRF case book must be signed.

Although a subject is not obliged to give his/her reason(s) for discontinuing treatment or for withdrawing from the trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. *Attempts to contact the subject must be documented in the subject file.* Where the reasons are obtained, the primary reason for not completing the trial or for discontinuation of treatment must be specified on the end-of-trial form in the eCRF.

8.3.5 Subject diaries

From randomisation a diary will be dispensed to subjects at every site visit and it will be returned at the next site visit *(visits marked as site visits in the flowchart, see section 2)*. The subject should be instructed by the site staff to complete the diary with the following records:

8.4.3 Pharmacokinetics assessments of NNC0195-0092 and hGH

In order to test for changes in pharmacokinetics (PK) induced by anti-NNC0195-0092/ hGH antibodies, blood samples for determination of NNC0195-0092/hGH from all subjects will be taken at randomisation and expected peak levels of IGF-I at least every second month throughout the trial (~~single sample 3 days after dosing,~~ see section 2. All samples must be drawn prior to trial drug administration if this is planned on a sampling day.

~~8.5.6 Urinalysis~~

~~Urinalysis will be performed at screening and every 2 to 3 months during the main trial and at the end of the extension trial (see section 2) from a sample of mid-stream urine by means of a stick test assessing the following parameters:~~

- ~~Protein~~
- ~~Glucose~~
- ~~Erythrocytes~~
- ~~Leukocytes~~
- ~~pH~~
- ~~Bilirubin~~
- ~~Specific gravity~~

~~If urine glucose is positive proper tests following the current guidelines should be performed at the investigator's discretion in order to confirm the diagnosis of diabetes mellitus (DM). If confirmed, DM should be reported as an AE and treatment should be considered for DM at investigator's discretion. Discontinuation of the trial drug should only be considered if continued treatment is judged by the investigator to be a hazard for the subject. Increase in glucose is observed when starting GH replacement in some subjects and is often transient.~~

~~8.5.7~~ *8.5.6* Fasting plasma glucose, fasting insulin, and HbA1c

Fasting plasma glucose, fasting insulin, and HbA1c tests will be assessed at screening and every 2 to 3 months throughout 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.

Rescue criterion for subjects diagnosed with diabetes mellitus before inclusion into the trial: If the HbA1c increases clinically significantly during the trial, the investigator should consider adjusting the anti-diabetic medication according to local practice.

~~8.5.9~~ *8.5.8* Adrenocorticotropic hormone (ACTH) stimulation test

Cortisol levels will be assessed at screening, at the end of the two titration periods and at the start of the extension period (see section 2). If a subject is not treated with glucocorticoid replacement an ACTH stimulation test will be performed at screening if not performed within 3 months prior to planned randomisation, at the end of the two titration periods and at the ~~end of the main trial~~ *start of the extension period.*

~~8.5.13~~ *8.5.12* Local tolerability

Local tolerability will be evaluated on a regular basis at visits to the trial site (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 or specific unscheduled visits l~~L~~ocal tolerability will be evaluated by the investigator by visual and manual inspection of injection sites.

If a local tolerability reaction is identified ~~based on the following assessments, and~~ the following results will ~~also~~ be recorded in the eCRF:

~~8.5.14~~ *8.5.13* Anti-drug antibodies

Anti-drug antibodies will be assessed at randomisation, 2, *4,* 8 and 16 weeks after randomisation and thereafter every two to three months throughout the trial and at EOT and follow-up (see section 2). All samples must be drawn prior to trial drug administration if this is planned on a sampling day. Samples will be analysed up to all three DBLs in the trial, i.e. after 50 *subject*~~patient~~s randomised to NNC0195-0092 have completed the main trial period, after all *subject*~~patient~~s have completed the main trial period and after completion of the extension period.

8.5.15 Eye examination

Fundusphotography will be performed in subjects diagnosed with diabetes mellitus before inclusion into the trial (see exclusion criterion 16). It can be performed by the Investigator or a local Ophthalmologist according to local practice at screening and at the end of the main and extension periods. Result of the fundusphotography will be interpreted locally by the Investigator in relation to the trial. To document this, the Investigator must sign and date the result page. The interpretation must follow the categories:

- *"Normal"*
- *"Abnormal, not clinically significant"*
- *"Abnormal, clinically significant"*

In the case of an "abnormal, clinically significant" fundusphotography, the Investigator must comment in the subject notes and, if it occurs at the screening visit, record this on the medical history/concomitant illness form. If the fundusphotography shows proliferative retinopathy or severe non-proliferative diabetic retinopathy the subject must be excluded (see section 6.3).

If a fundusphotography has already been performed no longer than 90 days before randomisation and if the results are available the procedure does not need to be repeated. The Investigator must still interpret, sign and date the fundusphotography. If the fundusphotography was performed before the subject has signed the informed consent Form, it must be documented in the subject notes that the reason for performing the procedure was not related to this trial.

Any clinically significant worsening of the fundusphotography result from baseline must be reported as an AE.

Fundusphotography performed within the 3 weeks before Visits 15 and 29 respectively are acceptable as Visit 15 or Visit 29 data.

8.7 Observed trial drug administration, pen-injector and ecap training

During each of the titration periods all subjects will be trained three times (see section 2) in the use of the pen-injector. After instruction the subject will inject him/herself under observation by trial staff. This can be preceded by injection with a training pen (see section 9.2) which can be administered by the ~~patient~~ *subject into a pad or cushion* once (using this test pen is optional).

8.9 Missing data

Investigators will make every effort to ensure all assessments are performed and data are collected. If missing data do occur the reason will be collected via the PD 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 taken 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 8.2 must be followed.

2.7 Changes to section 9 of the protocol

9 Trial supplies

NNC0195-0092 PDS290 10mg/1.5ml and NNC0195-0092 PDS290 Placebo 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 must not be shaken.~~ *Trial product should not be shaken vigorously at any time.*

9.3 Trial product storage conditions

Table 9.2 Trial product storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
NNC0195-0092 PDS290 10 mg/1.5 ml	Store in a refrigerator (2-8°C) in the outer carton, in order to protect from light.	2-8°C in between injections	~~Up to 6 weeks~~ *Use within 4 weeks*
NNC0195-0092 PDS290 Placebo	Do not freeze.	Do not freeze.	
Norditropin® FlexPro®	According to label : Store in a refrigerator (2-8°C) in the outer carton, in order to protect from light. Do not freeze.	2-8°C Below 25^{0}C Do not freeze	28 days 21 days

FOR JAPAN ONLY: Norditropin® FlexPro®	Store in a refrigerator (2-8°C) in the outer carton, in order to protect from light. Do not freeze.	2-8°C Do not freeze	35 days

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

For Japan only: *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 (e.g. a pharmacist). The trial product storage manager should control and take accountability of the trial drug products in accordance with procedures specified by Novo Nordisk A/S. 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.*

9.5 Auxiliary supplies

- Needles, NovoFine® ~~32G Tip~~
- ecap
- DFU for PDS290 and FlexPro®
- ecap info card

2.8 Changes to section 10 of the protocol

10 Interactive voice/web response system

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Drug Dispensing (including ecap dispensing in the extension period)
- Dose titration
- *Dose reduction*
- Treatment discontinuation
- Completion
- Code break
- Drug accountability ~~(including ecap accountability in the extension period)~~
- Data change

2.9 Changes to section 11 of the protocol

Two hundred and eighty subjects will be randomised in a 2:2:1 ratio to receive NNC0195-0092, Norditropin® FlexPro® or placebo during a 35-week period. The randomisation will be stratified according to two region levels (Japan and all other countries)*,* ~~and~~ sex (Male and Female) *and diabetic status (diagnosed with diabetes mellitus vs. not diagnosed with diabetes mellitus).* The randomisation and stratification will be handled by the IV/WRS (see section 10).

2.10 Changes to section 14 of the protocol

14.1 Titration surveillance

Surveillance of trial product titration will be performed centrally by an independent Novo Nordisk Titration Group not otherwise involved in the conduct of the trial. Surveillance will be performed on an on-going basis throughout *both* the *main and extension* trial *until all subjects have completed dose titration*. The titration group reviews the information provided by the investigator in case of deviations and follows up ~~on significant deviations~~*accordingly*. The titration group will be blinded towards treatment allocation.

2.11 Changes to section 17 of the protocol

Throughout section 17 '~~sex, region and sex by region~~' and '~~region, sex and region by sex~~' will be changed to '*sex, region, DM and sex by region by DM interaction'*.

17.1 Sample size calculation

Under the assumption of a true mean difference of 2.5% between NNC0195-0092 and placebo and a standard deviation (SD) of 4.5% for the primary endpoint and based on a two-sided, two-sample t-test with a significance level of 5% and a 2:1 randomisation ratio between NNC0195-0092 and placebo, 104 subjects in the NNC0195-0092 treated group and 52 subjects in the placebo treated group completing the main trial should ensure 90% power for detecting a difference between NNC0195-0092 and placebo. The assumptions of a true mean difference of 2.5% between active treatment and placebo and a SD of 4.5% is slightly conservative to what is observed in similar trials. In a secondary comparison of the primary endpoint, it will be possible to expect with probability 0.87 that half the length of the 95% *confidence interval (*CI*)* constructed for the difference between NNC0195-0092 and Norditropin® FlexPro® will be at most 1.3% if additional 104 subjects are enrolled in the Norditropin® FlexPro® treated group, resulting in a total of 260 subjects to be included in the trial. Expecting at most 7% drop-out from the trial, 280 subjects should be included in the trial.

Simulations (10000 samples, analysis based on multiple imputation technique as described in section 17.3) under the assumption of a drop-out rate of 7% and an additional assumption that 50% of the subjects who do not complete the main trial contribute to the primary analysis with post-randomisation DXA data, gives 89% power for detecting a difference between NNC0195-0092 and placebo with 112 subjects in the NNC0195-0092 treated group and 56 subjects in the placebo treated group. If the assumptions are changed to a drop-out rate of 15% and all subjects who do not complete the main trial will have no post-randomisation DXA data, then simulations gives 78% power for detecting a difference between NNC0195-0092 and placebo.

17.3 Primary endpoint

The primary endpoint is change from baseline (randomisation) to end of main trial period (Week 34) in truncal fat percentage.

The primary objective of the trial is to demonstrate the efficacy of once weekly dosing of NNC0195-0092 after 34 weeks of treatment in adults with GHD and the primary analysis of the primary endpoint will be the primary tool for achieving this. Body composition is measured by DXA and truncal fat percentage is defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass (kg) and truncal lean body mass (kg).

Truncal fat percentage as a function of time since baseline is expected to be monotone if the subject stays on the randomised treatment in the main trial period. Based on this assumption, the primary analysis of the primary endpoint will be conducted using a multiple imputation technique where the trajectory after a withdrawn subject's last observation is imputed based on data from the placebo arm, thus mimicking an intention to treat (ITT) scenario where withdrawn subjects are assumed to be switched to no treatment (placebo) after withdrawal. For each of 100 copies of the dataset (seed=34247), an analysis of covariance (ANCOVA) model with GHD onset type (adult or child), sex, region, DM (diabetic status) and sex by region by DM interaction as factors and baseline truncal fat (%) as a covariate. is fitted to the change in truncal fat percentage from baseline to 34 weeks data for the placebo group only. The estimated parameters, and their variances, from this model are used to impute missing values at 34 weeks for subjects in all treatment groups, based on their sex, region, DM, GHD onset type and baseline truncal fat values. If a truncal fat assessment for a subject has been performed after baseline at intermediate time t (e.g. in connection with the end-of-trial visit for withdrawn subjects, section 8.2) this information will be combined with the time-normalized model based estimate so that the final imputed value for the subject is a sum of the observed value at time t and the model based estimated change multiplied by (34 weeks-t)/(34 weeks) minus the baseline value.

For each of the complete data sets, the change from baseline to 34 weeks is analysed using an ANCOVA model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and the baseline truncal fat value as a covariate.

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

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

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

From m_{MI} and SD_{MI}, the treatment difference at Week 34 between NNC0195-0092 and placebo will be estimated and the corresponding 95% CI and p-value will be calculated. As a secondary comparison, the treatment difference at Week 34 between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CI will be calculated.

~~Changes in truncal fat percentage from baseline to Week 34 will be analysed using an ANCOVA model with treatment (i.e. NNC0195-0092, placebo and once daily Norditropin® FlexPro®), GHD onset type (adult or child), sex, region and sex by region interaction as factors and baseline truncal~~

~~fat (%) as a covariate. From the model the treatment difference at Week 34 between NNC0195-0092 and placebo will be estimated and the corresponding 95% CI and p-value will be calculated. Subjects without Week 34 data for the endpoint will not be included in the analysis. As a secondary comparison, the treatment difference at Week 34 between NNC0195-0092 and Norditropin® FlexPro® will be estimated from the model and the corresponding 95% CI and p-value will be calculated.~~

Superiority of NNC0195-0092 over placebo will be considered confirmed if the upper boundary of the two-sided 95% CI of the treatment difference (NNC0195-0092 – placebo) is below 0 (i.e. greater reduction from baseline in truncal fat percentage in the NNC0195-0092 treated group than in the placebo treated group).

The secondary comparison, comparison of NNC0195-0092 with Norditropin® FlexPro®, will be used to assist the clinical judgment of the clinical relevance of the estimated treatment difference between NNC0195-0092 and placebo.

A secondary analysis of the primary endpoint based on an assumption of missing at random (MAR) will be done using an ANCOVA model with treatment (i.e. NNC0195-0092, placebo and once-daily Norditropin® FlexPro®), GHD onset type (adult or child), sex, region, DM and sex by region by DM interaction as factors and baseline truncal fat (%) as a covariate. From the model the treatment difference at Week 34 between NNC0195-0092 and placebo will be estimated and the corresponding 95% CI and p-value will be calculated. Subjects without Week 34 data for the endpoint will not be included in the analysis. As a secondary comparison, the treatment difference at Week 34 between NNC0195-0092 and Norditropin® FlexPro® will be estimated from the model and the corresponding 95% CI will be calculated.

An *additional supportive* ~~secondary~~ analysis of the primary endpoint will be done using the same model as were used for the *secondary* ~~primary~~ analysis of the primary endpoint. Only subjects who have completed at least 3 dose adjustment evaluations (see section 5.3.1) *and have Week 34 data for the endpoint* will be included in this analysis.

The *secondary* ~~primary~~ analysis of the primary endpoint is based on the assumption of missing at random (MAR). For this trial the missing data are expected to be mainly due to subjects that are withdrawn from the trial. The possible withdrawal reasons and criteria are described in section 6.5. Up to 7% of the subjects are expected to drop-out from the main part of this trial. Data from subjects who withdraw from the trial due to withdrawal criteri~~a~~*on* 2~~, 3 and 4~~ *and treatment discontinuation criteria 6 and 7* can reasonably be assumed to be missing completely at random (MCAR). It is expected that a limited amount of the missing data will be due to these criteria. For most of the expected missing data, due to the other withdrawal criteria and subjects withdrawing at own will the MAR assumption may be questionable. Therefore, the sensitivity analyses described

below will be used to investigate whether the results from the *secondary* ~~primary~~ analysis are robust against departures from the assumption of MAR.

Sensitivity analyses

Let δ be defined as the difference between the mean of the observed data and the mean of the unobserved data μ_{unobs}-μ_{obs}, adjusted for other observed data. Under an MAR analysis, δ is assumed to be 0. Positive values of δ indicate that subjects with missing endpoint values have smaller reductions from baseline than subjects with observed endpoint values. If subjects primarily withdraw due to perceived lack of efficacy then this could be the most likely direction of departure from MAR though change in truncal fat percentage may not be a parameter that is linked in a simple way to the perceived efficacy level of the individual subject. Let f_1 and f_0 be the fractions of subjects with unobserved endpoint data in the NNC0195-0092 and placebo arms, respectively. The sensitivity analysis is done by adding a quantity Δ to the treatment effect estimate under the MAR assumption *(i.e. treatment effect estimate from the secondary analysis of the primary endpoint)*, where $\Delta = f_1\delta$ if data depart from MAR in the NNC0195-0092 arm only, $\Delta = -f_0\delta$ if data depart from MAR in the placebo arm only, and $\Delta = (f_1-f_0)\delta$ if data depart from MAR in the same way in both arms. The calculations will use a range of δ values going from 0 to 2% and the approximation that the standard error of the treatment difference is unaffected by the sensitivity analysis[32]. All subjects from the FAS can be viewed as included in this analysis as subjects with missing endpoint data will be contributing to one of the fraction values f_1 and f_0. A similar sensitivity analysis will be made for the secondary comparison between NNC0195-0092 and Norditropin® FlexPro®.

~~Truncal fat percentage as a function of time since baseline is expected to be monotone if the subject stays on the randomised treatment in the main trial period. Based on this assumption, a sensitivity analysis using a multiple imputation technique will also be conducted where the trajectory after a withdrawn subject's last observation is imputed based on data from the placebo arm, thus mimicking an intention to treat (ITT) scenario where withdrawn subjects are assumed to be switched to no treatment (placebo) after withdrawal. For each of 100 copies of the dataset (seed=34247), an analysis of covariance model with GHD onset type, sex and region as factors, and baseline truncal fat percentage as covariate is fitted to the change in truncal fat percentage from baseline to 34 weeks data for the placebo group only. The estimated parameters, and their variances, from this model are used to impute missing values at 34 weeks for subjects in all treatment groups, based on their sex, region, GHD onset type and baseline truncal fat values. If a truncal fat assessment for a subject has been performed after baseline at intermediate time t (e.g. in connection with the end-of-trial visit for withdrawn subjects, section 0) this information will be combined with the time-normalized model based estimate so that the final imputed value for the subject is a sum of the observed value at time t and the model based estimated change multiplied by (34 weeks-t)/(34 weeks) minus the baseline value.~~

~~For each of the complete data sets, the change from baseline to 34 weeks is analysed using an analysis of covariance model with treatment, GHD onset type, region, sex and region by sex as factors and the baseline truncal fat value as a covariate.~~

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

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

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

~~From m_{MI} and SD_{MI}, the 95% CI for the treatment difference and the associated p-value are calculated.~~

17.4.1.1 Efficacy endpoints

Changes from baseline to end of main trial period (Week 34) in the following variables will be used to address the primary objective:

- Truncal fat mass
- Truncal lean body mass
- Total fat mass
- Visceral adipose tissue
- Android fat mass
- Gynoid fat mass
- appendicular skeletal muscle mass (ASMM)
- Lean body mass
- Bone mineral content (extension part only)
- Bone mineral density (extension part only)
- IGF-I SDS
- IGFBP-3 SDS
- Scores of the following PRO questionnaires:
    - TRIM-AGHD

- SF-36v2
- ~~QoL-AGHDA~~
- Lipid profile (total cholesterol, HDL- cholesterol, LDL-cholesterol and triglycerides)
- Cardiovascular parameters (hsCRP and IL-6)
- Body weight
- Waist circumference

Changes in total fat mass, truncal fat mass, visceral adipose tissue, android and gynoid fat mass, appendicular skeletal muscle mass, lean body mass, truncal lean body mass, waist circumference and lipids (total cholesterol, HDL- cholesterol, LDL-cholesterol and triglycerides) from baseline to Week 34 will be analysed using an ANCOVA model with treatment, GHD onset type, ~~sex, region and sex by region~~ *sex, region, DM and sex by region by DM interaction* as factors and baseline value as a covariate. The lipids data will be log transformed before analysis, both baseline and Week 34 values. From the model the treatment differences (for lipids the treatment differences will be reported as ratios) at Week 34 between NNC0195-0092 and placebo and between NNC0195-0092 and Norditropin® FlexPro® will be estimated and the corresponding 95% CIs and p-values will be calculated for each endpoint *based on the same multiple imputation technique as was used in the primary analysis of the primary endpoint.* ~~Subjects without Week 34 data for the analysed endpoint will not be included in the analysis.~~

17.4.1.2 Safety endpoints

The following endpoints will be used to support the secondary objectives of evaluation of safety in both the main (up to week 35) and extension (up to week 88) trial periods:

- Incidence of adverse events, including injection site reactions
- Incidence of clinical technical complaints
- Occurrence of anti-NNC0195-0092 antibodies
- Changes from baseline in physical examination, ECG results and vital signs
- Changes from baseline in clinical laboratory test results including haematology, biochemistry, ~~urine analysis,~~ fasting glucose, fasting insulin, steady state beta cell function (%B) and insulin resistance (IR) (HOMA estimates), and HbA1c levels

2.12 General corrections

- ~~Derivate~~ is changed to *derivative* throughout.
- ~~Estrogen~~ is changed to *oestrogen* throughout
- ~~Patient~~ is changed to *subject* throughout where applicable
- ~~QoL-AGHDA~~ and all related text is removed throughout the protocol as this questionnaire is not used in the trial.
- Minor typos have been corrected throughout

3 Changes to Subject information/informed consent for version 1

Trial title:

~~Safety and efficacy of once weekly liquid growth hormone (NNC0195-0092) in adults with growth hormone deficiency~~

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period

Introduction

You are invited to take part in a voluntary research study (clinical trial) because you have been diagnosed with growth hormone deficiency. Before you decide if you want to participate in the clinical trial, it is important that you have understood why the clinical trial is being conducted and what your participation will mean for you. You will be asked to read this information carefully.

This document includes a "subject information" and an "informed consent form". The subject information provides information about the clinical trial you are invited to take part in and what will happen if you participate. It also provides information about the purpose of the clinical trial and the involved benefits, as well as information about the possible risks and discomforts that may be associated with participating in the clinical trial. *This trial can only deliver a meaningful conclusion if long-term health and vital status are collected from all participants until the end of the trial irrespective of whether or not they have been on trial drug throughout the trial or only part of it.* You are asked to give your consent to participate by signing the "informed consent form" at the end of this document. You will also have the opportunity to discuss information about the clinical trial with the trial doctor and to ask any questions you may have.

This trial is initiated by the pharmaceutical company Novo Nordisk A/S, which is the clinical trial "sponsor". The protocol (a document that describes why and how to conduct the trial) and this subject information sheet have obtained a favorable opinion from an independent Ethics Committee and national and international regulatory authorities. If you agree to take part in the clinical trial you will be provided with a signed copy of this subject information and the informed consent form.

Clinical trial, trial drugs and treatments

Information on handling, administration and storage will be given to you when you receive the trial drug from your trial doctor. Please handle and store the trial drug according to the instructions

(label and direction for use). ~~It is very important that you do not inject the trial drug if it does not appear clear and colourless.~~

Examinations and analyses

Main trial period

Visit No.	1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Time of visit	1 day prior to visit 1b	2-3 weeks prior to visit 2	Week 0	Week 1 + 3 days	Week 2	Week 3 + 3 days	Week 4	Week 5 + 3 days	Week 6	Week 7 + 3days	Week 8	Week 9 + 3 days	Week 16 + 3 days	Week 25 + 3 days	Week 33 + 3 days	Week 35
Visit type	a	a	a	b	a	b	*a*~~e~~	b	c	b	a	b	a	a	a	a
Fasting no / yes	no	yes	yes	yes	~~no~~*yes*	yes	~~no~~*yes*	yes	no	yes	yes	yes	yes	yes	yes	yes
Informed consent	x															
Demographic information		x														
Medical history		x														
Concomitant medication		x	x		x		x		x		x		x	x	x	x
Body measurements		x	x		x						x		x	x	x	x
Patient diary			x		x						x		x	x	x	x
X-ray scan		x													x	
Questionnaires			x											x	x	
Side effects			x		x		x		x		x		x	x	x	x
ECG		x									x				x	
Physical examination/ vital signs		x	x		x						x		x	x	x	x
~~Urine sample~~		~~x~~									~~x~~		~~x~~	~~x~~	~~x~~	
Pregnancy test		x	x		x						x		x	x	x	x
Blood sample		x	x		x		*x*				x		x	x	x	x
Special blood sample		x	x	x	*x*	x	*x*	x		x	*x*	x	x	x	x	x
ACTH test		x									x					x

ecap																x
Dose adjustment					x		x		x		x					x
Drug dispensing			x		x						x		x	x		x
Eye examination			*x*													*x*

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Visit No.	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Time of visit	Week 36 + 3 days	Week 37	Week 38 + 3 days	Week 39	Week 40 + 3 days	Week 41	Week 42 + 3 days	Week 43	Week 44 + 3 days	Week 53 + 3 days	Week 64 + 3 days	Week 75 + 3 days	Week 86 + 3 days	Week 88
Visit type	b	a	b	*~~a~~e*	b	c	b	a	b	a	a	a	a	d
Fasting no / yes	yes	*~~no~~yes*	yes	*~~no~~yes*	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Concomitant medication		x		x		x		x		x	x	x	x	x
Body measurements		x						x		x	x	x	x	x
Patient diary		x						x		x	x	x	x	
X-ray scan													x	
Questionnaires											x		x	
Side effects		x		x		x		x		x	x	x	x	x
ECG								x			x		x	
Physical examination/ vital signs		x						x		x	x	x	x	x
Pregnancy test		x						x		x	x	x	x	x
~~Urine sample~~													~~x~~	
Blood sample		x		*x*				x		x	x	x	x	x
Special blood sample	x	*x*	x	*x*	x		x	*x*	x	x	x	x	x	x
ACTH test								x						
ecap										x				
Dose adjustment		x		x		x		x						
Drug dispensing		x						x		x	x	x		
Eye examination														*x*

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- *Eye examination:*

You will be asked to undergo an eye examination several times during the trial. This is done to avoid including patients with certain eye diseases into the trial and to check if these eye diseases develop in included patients.

- ~~**Urine sample:**~~

~~To determine your general health and disease status a urine sample will be analysed.~~

Blood and urine samples

The lab equipment may provide standard analyses not requested for this clinical trial but produced automatically in connection with the requested analyses. Such data will not be provided to Novo Nordisk A/S but provided to and reviewed by the trial doctor.

Only results from routine blood samples and urine analyses will be available to you through your trial doctor during the trial.

During the entire trial, approximately ~~350~~*400* mL of blood will be collected from you (less than a single blood donation of 500 ml). The blood volume collected at each visit ranges from approximately ~~7.5~~*6* to 30 mL of blood (½ - 2 tablespoons).

~~**Early termination of the trial**~~

~~If you decide to stop your participation in the clinical trial before completion (withdrawal) you need to inform the trial doctor immediately. If you are in the main trial period when you decide to withdraw from the clinical trial, you will be asked to come in for clinic visit 14 and visit 15 . Alternatively, you will be asked to come in for clinic visit 28 and final visit 29 if you withdraw from the clinical trial in the extension trial period. Visit 15 and visit 29 should occur at least 8 days or 14 days after last treatment depending on the treatment you have received during the clinical trial. It would be very important that you attend these visits.~~

~~If you decide to discontinue drug treatment but you are still willing to participate in the clinical trial, you will be asked by your trial doctor to attend all remaining visits and have the corresponding assessments performed except trial drug administration.~~

~~The trial doctor may terminate your participation in the clinical trial if your medical condition changes so that the doctor believes that your health status no longer allows you to take part in the clinical trial, or if you do not follow the instructions given by the trial doctor.~~

~~The sponsor also reserves the right to end the clinical trial early at any time for safety or other reasons. If this happens, you will be informed by your trial doctor.~~

~~The reason for terminating your participation will be explained in detail to you by your trial doctor and arrangements made for you to continue on an alternative treatment.~~

Discontinuation of trial drug

You may decide to stop your trial drug treatment at any time during the trial. The trial doctor may also discontinue your treatment with trial drug if your medical condition changes so that the doctor believes that your health status no longer allows you to take part in the clinical trial, or if you do not follow the instructions given by the trial doctor.

If you or your trial doctor decide to discontinue drug treatment but you are still willing to participate in the clinical trial, you will be asked by your trial doctor to attend all remaining visits and have the corresponding assessments performed except trial drug administration.

Withdrawal and termination of the trial

If you decide to stop your participation in the clinical trial before completion (withdrawal) you need to inform the trial doctor immediately. You can also be withdrawn from the trial if you are included on a wrong background or use weight loss medications.

If you are in the main trial period when you (or your trial doctor) decide to withdraw from the clinical trial, you will be asked to come in for clinic visit 14 and visit 1. Alternatively, you will be asked to come in for clinic visit 28 and final visit 29 if you withdraw from the clinical trial in the extension trial period. Visit 15 and visit 29 should occur at least 8 days or 14 days after last treatment depending on the treatment you have received during the clinical trial. It would be very important that you attend these visits.

The reason for terminating your participation will be explained in detail to you by your trial doctor and arrangements made for you to continue on an alternative treatment.

The sponsor also reserves the right to end the clinical trial early at any time for safety or other reasons. If this happens, you will be informed by your trial doctor.

803

804

4 Changes to Subject information/informed consent for pregnant partner version 1

Trial title:

~~Safety and efficacy of once weekly liquid growth hormone (NNC0195-0092) in adults with growth hormone deficiency~~

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period

5 Changes to Subject information/informed consent for male partner version 1

Trial title:

~~Safety and efficacy of once weekly liquid growth hormone (NNC0195-0092) in adults with growth hormone deficiency~~

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period

Protocol Amendment

no 2
to Protocol, final version 2.0
dated 04 July 2014

Trial ID: NN8640-4054

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period

Trial phase: 3a

Applicable to Japan

Amendment originator:

[redacted]

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1 Introduction including rationale for the protocol amendment

This amendment is based on requests from the Pharmaceuticals and Medical Devices Agency (PMDA) after the clinical trial notification submission in Japan. All the changes listed below will be applicable to Japan only.

1.1 The changes required by the PMDA

- The criterion for confirmed diagnosis of AGHD in Japan will be corrected (sections 1 and 6.2)
- At all visits planned to perform a pregnancy test, urine pregnancy test in women of childbearing potential will be performed (sections 2 and 8.3.7, and section 1.6 of the SI/IC-JP)
- The maximum daily dose of Norditropin® FlexPro® will be changed from 1.1 mg to 1.0mg (section 5.3.4)
- The adequate contraceptive methods for Japan will be specified (section 6.3)
- The following sentence will be inserted in exclusion criterion no. 12: Subjects with suspicion of hepatitis will be excluded from the trial (section 6.3)
- If physicians definitely diagnose diabetes mellitus during the trial, the subject will be discontinued from treatment (section 6.6.1)
- The wording of eligibility requirement regarding malignancy will be corrected (section 1.5 of the SI/IC-JP)
- A volume of single blood donation will be corrected (section 1.7 of the SI/IC-JP)
- Information on findings and safety margins for reductions in foetal weigh observed in the reproductive and development toxicity study will be stated in SI/IC (section 3.4 of the SI/IC-JP)
- The following sentence will be inserted in SI/IC: The highly effective contraceptive measure should be selected based on the consultation with your primary physician (sections 3.4 and 3.5 of the SI/IC-JP)

1.2 Additional changes

- Trade name of needles provided by Novo Nordisk during the trial will be changed from NovoFine® to PenNeedle® due to a difference in the trade name (sections 9.5 and 12.4.1)

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Changes to section 1 of the protocol

Key inclusion criteria

- **FOR ALL COUNTRIES EXCEPT JAPAN:**
    - Confirmed diagnosis of adult growth hormone deficiency (if a subject satisfies at least one of the following criteria)
    a. Insulin tolerance test (ITT) or glucagon test: a peak GH response of < 3 ng/mL (3 µg/L)
    b. Growth hormone releasing hormone (GHRH) + arginine test according to body mass index (BMI)
        i. a. BMI< 25 kg/m^2, a peak GH < 11 ng/mL (µg/L)
        ii. b. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)
        iii. c. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)
    c. Three or more pituitary hormone deficiencies at screening and IGF-I SDS < -2.0

FOR JAPAN ONLY: Confirmed diagnosis of adult growth hormone deficiency ~~(subjects with adult onset AGHD need to satisfy at least one of the following criteria, subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria)~~:

I. Adult onset: subjects caused by organic disease with multiple pituitary hormones deficiency need to satisfy at least one of the following criteria. If isolated GHD subjects need to satisfy at least 2 of the following criteria.

II. Childhood onset: subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria. If subjects caused by organic disease with multiple pituitary hormones deficiency need to satisfy at least one of the following criteria.

a. ITT test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
b. glucagon test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
c. GHRP-2 tolerance test: a peak GH of ≤ 9 ng/mL (assay using recombinant GH standard)

2.2 Changes to section 2 of the protocol

The footnote number 5 under Table 2-1

To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample At V2 the test is mandatory and needs to be performed from a urine sample. If required locally this may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than V1b and V2, optional urine pregnancy testing may be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements.

FOR JAPAN ONLY: *To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample and a urine sample. At V2 the test is mandatory and needs to be performed from a urine sample. This may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than V1b and V2, urine pregnancy test should be performed according to the flow chart.*

The footnote number 4 under Table 2-2

Optional urine pregnancy testing in women of childbearing potential may be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements.

FOR JAPAN ONLY: *Urine pregnancy test in women of childbearing potential should be performed according to the flow chart.*

2.3 Changes to section 5 of the protocol

5.3.4 Titration for subjects treated with daily Norditropin® FlexPro®

The minimum daily dose of Norditropin® FlexPro® is 0.05 mg. If the algorithm returns a dose of less than 0.05mg, the weekly dose of Norditropin® FlexPro® must be 0.05 mg. The maximum daily dose of Norditropin® FlexPro® is 1.1mg *(**FOR JAPAN ONLY:** 1.0 mg)*.

2.4 Changes to section 6 of the protocol

6.2 Inclusion criteria

4. **FOR ALL COUNTRIES EXCEPT JAPAN:** Confirmed diagnosis of adult growth hormone deficiency (if a subject satisfies at least one of the following criteria)
    a. Insulin tolerance test (ITT) or glucagon test: a peak GH response of < 3 ng/mL (3 µg/L)
    b. Growth hormone releasing hormone (GHRH) + arginine test according to body mass index (BMI)
        a. BMI< 25 kg/m^2, a peak GH < 11 ng/mL (µg/L)
        b. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)
        c. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)
    c. Three or more pituitary hormone deficiencies at screening and IGF-I SDS < -2.0

FOR JAPAN ONLY: Confirmed diagnosis of adult growth hormone deficiency ~~(subjects with adult onset AGHD need to satisfy at least one of the following criteria, subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria)~~:

I. Adult onset: subjects caused by organic disease with multiple pituitary hormones deficiency need to satisfy at least one of the following criteria. If isolated GHD subjects need to satisfy at least 2 of the following criteria.

II. *Childhood onset: subjects with a history of childhood GHD need to satisfy at least 2 of the following criteria. If subjects caused by organic disease with multiple pituitary hormones deficiency need to satisfy at least one of the following criteria.*
    a. ITT test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
    b. glucagon test: a peak GH of ≤ 1.8 ng/mL (assay using recombinant GH standard)
    c. GHRP-2 tolerance test: a peak GH of ≤ 9 ng/mL (assay using recombinant GH standard)

6.3 Exclusion criteria

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)
    a. **FOR BRAZIL ONLY**: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory
    b. **FOR GERMANY ONLY**: Adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal IUD, sexual abstinence or vasectomised partner
    c. **FOR SWEDEN ONLY**: Adequate contraceptive measures are:
        i. oral (except low-dose gestagen (lynestrenol and norestisteron))
        ii. injectable, or implanted hormonal contraceptives
        iii. intrauterine device, intrauterine system (for example, progestin-releasing coil)
        iv. vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate)
    d. **FOR THE UK ONLY**: Contraception requirements as per the at any time applicable MHRA guidelines
    e. ***FOR JAPAN ONLY:*** *Adequate contraceptive measures are abstinence, diaphragm, condom [by the partner], intrauterine device, sponge, spermicide or oral contraceptives*

12. History of positive results of tests for hepatitis B and/or C
    a. ***FOR JAPAN ONLY:*** *History of positive results of tests for hepatitis B and/or C or suspicion of hepatitis*

6.6.1 Treatment discontinuation

4. Any other condition develops that is cited in exclusion criteria (except for development of diabetes mellitus during the course of the trial that can be controlled with standard therapy)

a. ***FOR JAPAN ONLY:*** *Any other condition develops that is cited in exclusion criteria. If physicians definitely diagnose diabetes mellitus during the course of the trial the subject should be discontinued from treatment*

2.5 Changes to section 8 of the protocol

8.3.7 Pregnancy test

A blood pregnancy test (beta subunit of human chorionic gonadotropin [beta-HCG]) will be performed at Screening in women of childbearing potential (refer to exclusion criterion 3). At visit 2 a urine pregnancy test will be performed before randomisation. During the trial for all other site visits, urine pregnancy testing may be performed at the investigator's discretion, such as for a missed menstrual cycle, or according to local requirements.

FOR JAPAN ONLY: *A blood pregnancy test (beta subunit of human chorionic gonadotropin [beta-HCG]) and a urine pregnancy test will be performed at Screening in women of childbearing potential (refer to exclusion criterion 3). At visit 2 a urine pregnancy test will be performed before randomisation. During the trial for all other site visits than V1b and V2, urine pregnancy test should be performed according to the flow chart (see Section 2).*

2.6 Changes to section 9 of the protocol

9.5 Auxiliary supplies

- Needles, NovoFine® *(**FOR JAPAN ONLY:** PenNeedle®)*
- ecap
- DFU for PDS290 and FlexPro®
- ecap info card

2.7 Changes to section 12 of the protocol

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- NNC0195-0092 PDS290 10mg/1.5ml
- NNC0195-0092 PDS290 Placebo
- Norditropin® FlexPro® 10 mg/1.5ml
- Needles, NovoFine® 32G Tip *(**FOR JAPAN ONLY:** PenNeedle® 32G)*
- ecap

3 Changes to subject information/informed consent form for Japan, version 2.0

1.5 Clinical trial requirements

In order to be eligible for clinical trial participation you must:

- be diagnosed with growth hormone deficiency prior to entering this clinical trial or as part of this clinical trial.
- not previously have received growth hormone treatment at all **or** at least not during the last 6 months prior to the first injection of trial drug.
- be between 23 and 79 years old.
- be willing to follow all instructions provided by the trial doctor.
- have the time and willingness to attend the clinic for all assessments required.
- handle and administer the trial drug according to the instructions given.
- practice a highly effective method of birth control (contraception) during the clinical trial.
- ~~not have a history of malignancy with the exception of intracranial tumour, carcinoma or leukaemia. If you have suffered from leukaemia or malignant intracranial tumour, disease recurrence cannot have occurred within the last 5 years.~~
- *not have active malignant disease or a history of malignancy except for the following cases:*
    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 file*
- not have evidence of intracranial tumour growth within 12 months prior to the first injection of trial drug if you previously have suffered from intracranial tumour.
- not participate in any other clinical trials during your participation in this clinical trial.

1.6 Examinations and analyses

- Pregnancy test:

Women of child bearing potential will have a blood pregnancy test *and a urine pregnancy test* performed at visit 1b and a urine pregnancy test performed at visit 2 to exclude pregnancy. At specific visits (see overview tables) a urine pregnancy test is performed to exclude pregnancy ~~if the trial doctor finds it is required (e.g. if missed period)~~.

1.7 Blood and urine samples

The lab equipment may provide standard analyses not requested for this clinical trial but produced automatically in connection with the requested analyses. Such data will not be provided to Novo Nordisk A/S but provided to and reviewed by the trial doctor.

Only results from routine blood samples and urine analyses will be available to you through your trial doctor during the trial.

During the entire trial, approximately 400 mL of blood will be collected from you (less than a single blood donation of ~~500 ml~~ *200 to 400 mL*). The blood volume collected at each visit ranges from approximately 6 to 30 mL of blood (½ - 2 tablespoons).

3.4 Pregnancy information for females

When administered in pregnant rats, increased incidences of bone variations were found in foetus at a dose of 18 mg/kg/day (these were not malformation but slight variations which spontaneously occur in this strain of rat and do not effect on function and shape of foetus). In the pregnant rabbits, reductions in foetal weights at 3 and 9 mg/kg were found. The No Observed Adverse Effect Level for embryo-foetal development in rats was 6 mg/kg/occasion and the No Observed Adverse Effect Level for foetal growth in the rabbit was 1 mg/kg/occasion.

These doses are approximately 6 fold higher in rats and 2 fold higher in rabbits than the maximal planned dose in this trial, i.e. 8 mg/subject/occasion in human, respectively.

The risks of the trial product administration to a pregnant woman or an unborn child are unknown, therefore, you cannot participate if you are pregnant or if you intend to become pregnant and/or are unwilling to obey the birth control requirements of this clinical trial. During the clinical trial you and your partner must use highly effective contraception (less than 1% failure rate). *The highly effective contraceptive measure should be selected based on the consultation with your primary physician.*

3.5 Pregnancy information for males

The risks of trial drug candidates to a pregnant woman or an unborn child are unknown, therefore, you cannot participate if your partner intends to become pregnant. During the clinical trial you and your partner must use highly effective contraception (less than 1% failure rate). *The highly effective contraceptive measure should be selected based on the consultation with your primary physician.*

Protocol Amendment

no 3
to Protocol, final version 2
dated 04 July 2014

Trial ID: NN8640-4054

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, with a 53-week extension period

Trial phase: 3a

Applicable to all countries

Amendment originator:

[redacted]

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Page

1 Introduction including rationale for the protocol amendment

The amendment is a result of feedback from Ethics Committee, a wish from Novo Nordisk to clarify relevant sections of the protocol based partly on feedback from investigators.

The focus and rationales for the amendment are:

- Based on feedback from investigators in several of the countries, it has become apparent, that availability of the ACTH stimulation drug is a challenge combined with drug shortage of the stimulating agent from manufacturer. The protocol amendment will reflect a specified process of assessing adrenal insufficiency with an alternative test procedure to ACTH stimulation test. The changes will impact inclusion criterion 9 in the protocol, the assessment section for ACTH stimulation test (section 8.5.8), and the subject informed consent form.

- Novo Nordisk wishes to clarify the process for photos of local tolerability assessment (section 8.5.12) and therefore this section has been updated with an external review step by a dermatologist. This has been added to ensure that the clinical validity of the photos support the adverse event description.

- Novo Nordisk wishes to add clarifying details regarding the process for follow up after LSLV of subjects with two consecutive positive anti-drug antibody results. Therefore, section 8.5.13 has been updated in the amendment.

- The Ethic Committee in Germany has requested Novo Nordisk to make the following changes:

    - Clarification on how trial phases are listed, i.e. clarification if the trial phase duration covers treatment only or treatment and washout period(s).

    - Protocol title has been updated to include ’open label’ to clarify that the extension period has an open-label design.

    - Two additional exclusion criteria have been added, which are applicable to Germany only. These criteria cover exclusion of subjects committed to an institution and persons employed with the sponsor/CRO/trial centre.

    - Regulatory Authority (RA) has been added to the list of abbreviations.

- Relevant sections to ensure full understanding of the protocol:

    - Novo Nordisk wishes to clarify, that information about adverse events to NNC0195-0092 or Norditropin® are only stated in the reference safety information. Therefore, section 6.5 has been updated.

    - Novo Nordisk wishes to clarify, that dosing at start of extension trial period must only take place when the quality of the DXA scan performed at visit 14 is confirmed by imaging vendor (section 8.4.1)

    - Novo Nordisk wishes to clarify when and how deviation from the titration schedule must be handled, therefore a figure has been added to visually explain this (section 5.3.5).

    - Novo Nordisk wishes to allow adrenal insufficient subjects who have received stable replacement therapy for 3 months the option of re-screening. Additionally, Novo Nordisk wishes to clarify the assessments which have to be re-performed at re-screening. Therefore, section 8.2 has been updated.

Furthermore, minor corrections and clarifications have been added.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Changes to protocol version 2.0 dated 04 Jul 2014

2.1.1 Title of protocol

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, followed by a 53-week *open-label* extension period

2.1.2 List of abbreviations

~~*CDISC – Clinical Data Interchange Standards Consortium*~~
CRO – Contract Research Organisation
ITT – insulin tolerance test
RA – Regulatory Authority

2.1.3 Section 1 Summary

Primary endpoint
Change from baseline to end of main *treatment* ~~trial~~ period (Week 34) in truncal fat percentage

Key secondary endpoints for efficacy
Changes from baseline to end of main *treatment* ~~trial~~ period (Week 34) in the following key variables will be used to address the primary objective

Key secondary endpoints for safety
The following key endpoints will be used to support the secondary objectives of evaluation of safety in both the main (up to week 35) and extension (up to week 88) trial periods *(including follow-up visits/washout periods)*:

Trial design:
This is a multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial. The trial will compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily dosing of Norditropin® FlexPro® in adults with GHD during a 35-week period (8 week dose titration, 26 week fixed dose treatment *[34 weeks treatment period]* followed by 1 week washout), *followed by* ~~with~~ a 53-week *open-label* extension period (8 week dose titration, 44 week fixed dose treatment *[52 weeks treatment period]* followed by 1 week washout). After the main trial period placebo subjects will be switched to NNC0195-0092 treatment and Norditropin® FlexPro® subjects will be randomised 1:1 to NNC0195-0092 or Norditropin® FlexPro®.

2.1.4 Section 2 Flow chart

The nomenclature for the assessments listed in the flowchart will be updated based on the Clinical Data Interchange Standards Consortium (CDISC).

Only one set of footnotes (numbered from 1 to 16) will be displayed after both the main trial and the extension trial flow charts have been displayed.

In addition, the flow chart will be updated according to the relevant changes below.

Flow chart main trial and extension trial:

- Period: ~~Titration period, fixed dose~~
- *Trial* Period*s*, visit 1a and visit 1b: *screening*
- *Trial* Period*s*, visit 2: *randomisation*
- *Trial* Period*s*, visit 3-10 and visit 16-23: *titration*
- *Trial* Period*s*, visit 11-14 and visit 24-28: *treatment*
- Visit *number*
- ~~Time (weeks + days)~~ *Timing of visit Weeks*
- Visit window ~~(d~~Days~~)~~
- ~~Screen.~~ replaced with *site*
- ~~Rand.~~ replaced with *site*
- ~~EOT 1~~ and ~~EOT 2~~ replaced with *Site*
- Visit 9 and visit 22, cortisol sample: *x*
- Visit 10 and visit 23, cortisol sample: ~~x~~
- Visit 14 and 28, visit window: ~~+/- 2~~
- Visit 14 and 28, visit window: *+2*
- ~~ecap accountability~~
- ACTH ~~stimulation test~~*/ITT*

- Extension trial: ~~Fasting serum~~ cortisol[7]
- ~~Dose adjustment~~ replaced with *New dose of trial product*
- *Reminders: Training in trial product and pen handling*

Footnotes main trial and extension trial:

- 3: ~~All IGF visit may be performed by local sampling service as directed by Novo Nordisk if permitted by the investigator and local requirements.~~ The phone visits can be site visits instead if required by local practice or regulation or at investigator's discretion.
- 3: This footnote will only relate to visit 8 and visit 21.
- 7: This footnote will be added to anti-body sampling for visit 14 and visit 28 and to PK sampling for visit 15.
- 8: The PRO questionnaires must be performed after all fasting related activities and before all other trial-related activity at each applicable visit. TSQM is not assessed at ~~screening~~ *randomisation.*
- 11: ~~If subject is not being treated with glucocorticoid replacement, perform ACTH stimulation test.~~ *If a subject has morning cortisol below normal range, ACTH stimulation test or ITT must be performed . The morning serum cortisol sample collection, which is the basis for the ACTH stimulation test or ITT, should be performed at visit 9, 14 and 22, respectively, before 9 am when the subject is already fasting.*
- 16: Add to DXA. *The quality of the DXA scan obtained at visit 14 must be confirmed by the imaging laboratory prior to conducting visit 15.*
- Footnotes will relate to assessments at specific visits instead of relating only to the assessments.

2.1.5 Section 4 Objective(s) and endpoint(s)

Primary endpoint
Change from baseline to end of main *treatment* ~~trial~~ period (Week 34) in truncal fat percentage

Supportive secondary efficacy endpoints
Changes from baseline to end of main *treatment* ~~trial~~ period (Week 34) in the following variables will be used to address the primary objective:

Supportive secondary safety endpoints
The following key endpoints will be used to support the secondary objectives of evaluation of safety in both the main (up to week 35) and extension (up to week 88) trial periods *(including follow-up visits/washout periods)*:

2.1.6 Section 5.1 Type of trial

This is a multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily dosing of Norditropin® FlexPro® in adults with GHD during a 35-week period, *followed by* ~~with~~ a 53-week *open-label* extension period.

Two hundred and eighty (280) subjects will be randomised in a 2:2:1 ratio to receive NNC0195-0092, Norditropin® FlexPro® or placebo during a 35-week period (8 weeks of titration, followed by 26 weeks of treatment *[34 week treatment period]* and 1 week of washout). The randomisation will be stratified according to two region levels (Japan and all other countries), sex (male and female) and diabetic status (diagnosed with diabetes mellitus vs. not diagnosed with diabetes mellitus). All subjects completing the 35-week *main trial* period will continue their active treatment with NNC0195-0092 weekly injection or Norditropin® FlexPro® daily injection in a non-placebo-controlled design for an additional 53-week *open-label* extension period (8 weeks of titration, followed by 44 weeks of treatment *[52 weeks treatment period]* and 1 week of washout).

2.1.7 Section 5.2 Rationale for trial design

The extension period is an outcome of *Regulatory Authority (RA)* ~~HA~~ interactions and allows for longer-term evaluation of efficacy and safety of NNC0195-0092. Subjects treated with Norditropin® FlexPro® during the main trial are re-randomised to NNC0195-0092 and Norditropin® FlexPro® at the beginning of the extension to obtain additional safety data for once weekly treatment and still compare efficacy and safety between the active treatments.

2.1.8 Section 5.3 Treatment of subjects

For the first *34*~~5~~-week treatment period, the first dose will be administered by the subject on Day 0 (randomisation), and the last dose will be administered by the subject at home during Week 33.

2.1.9 Section 5.3.2 Dose titration algorithm

The titration algorithm depends on the obtained difference in IGF-I SDS between the value at any time during the titration period and the IGF-I SDS value at ~~randomisation~~ *screening*.

2.1.10 Section 5.3.3 Titration for subjects treated with either NNC0915-0092 or Placebo

If NNC0195-0092 or placebo 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 periods*, they should contact the trial site since the *IGF visit* ~~blood sampling~~ and subsequent visit*s* will ~~potentially~~ have to be rescheduled (see section 5.3.5). Injections must remain in the body areas of thighs and/or abdomen with rotation within these body areas *for every injection*.

2.1.11 Section 5.3.4 Titration for subjects treated with daily Norditropin® FlexPro®

If Norditropin® FlexPro® subjects forget or are unable to give 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 visit *in the titration periods*, the subject should contact the trial site since the IGF visit and subsequent visits will have to be rescheduled *(see section 5.3.5)*~~, i.e. postponed two weeks~~.

2.1.12 Section 5.3.5 Deviation from titration schedule

The below figure will be added to the protocol to visually explain when and how the deviation from the schedule should be handled.

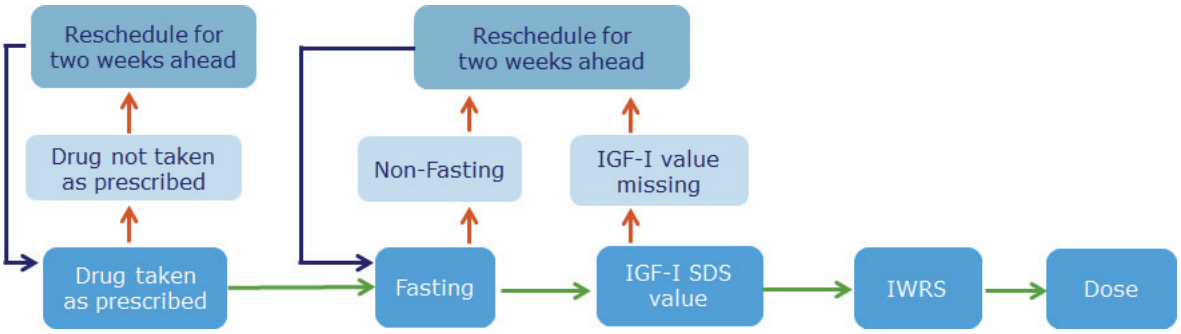

Figure 2–1 ***Flow of rescheduling visits in the titration periods***

2.1.13 Section 5.3.6 Treatment during the extension period

After database lock of the extension period the trial sites will be informed about the subject's treatment allocation during the 3~~4~~5-week treatment period in the main trial.

2.1.14 Section 6.2 Inclusion criteria

Criterion 4

FOR ALL COUNTRIES EXEPT JAPAN:

4c. Three or more pituitary hormone deficiencies at screening and IGF-I SDS < -2.0 *(screening IGF-I SDS value provided by central laboratory)*

Criterion 9

Adequate adrenal function (confirmed with ACTH stimulation test or *ITT* within the last 90 days prior to randomisation; if not result is available, ACTH stimulation test *or ITT* will be performed as part of the screening procedure after the informed consent is signed) or adequate and stable replacement therapy (as judged by the investigator) for at least 90 days prior to randomisation

2.1.15 Section 6.3 Exclusion criteria

Criterion 3 *d.*

FOR UK ONLY: Contraception requirements as per the at any time applicable MHRA guidelines. ~~*Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, sterilisation, interactive device and interactive system, or consistent use of barrier methods.*~~

Criterion 16

***APPLICABLE* FOR JAPAN ONLY:**

Criterion 24

APPLICABLE FOR GERMANY ONLY: *Subjects committed to an institution per official directive or judicial order are to be excluded from participation.*

Criterion 25

APPLICABLE FOR GERMANY ONLY: *Persons employed with the sponsor/the contract research organisation (CRO)/the trial centre or the investigator or rely on them in any other way, must be excluded from participation.*

2.1.16 Section 6.5 Dose reduction criteria

If adverse events with a probable relationship to the trial drug are persistent ~~(e.g. oedema, hypertension, arthralgia, carpal tunnel syndrome, and/or GH induced hyperglycaemia)~~ but allow continuation in the trial as judged by the investigator and subject, dose reduction in consecutive steps of 25% of the current dose can be considered at the investigator's discretion. If after consecutive dose reduction steps AEs still persist the subject's treatment may be discontinued or the subject may be withdrawn according to treatment discontinuation/withdrawal criterion number 2

2.1.17 Section 6.6.1 Treatment discontinuation

Criterion 4

Any other condition develops that is cited in exclusion criteria (*APPLICABLE FOR ALL COUNTRIES EXCEPT JAPAN* - except for development of diabetes mellitus during the course of the trial that can be controlled with standard therapy).

Criterion 5

Development of neutralising antibodies to NNC0195-0092 defined by 2 consecutive samples found positive for in vitro neutralising antibodies and influence on PK as described in section 8.5.13. ~~The investigator will be notified by the sponsor if a subject has had 2 samples positive for in vitro neutralising antibodies immediately after obtaining knowledge of the results.~~

2.1.18 Section 8.1 Visit procedures

All laboratory analyses in this trial will be performed by the central laboratory unless stated otherwise for the single parameter. *The only exceptions;*

- Urine pregnancy tests will be performed at the sites with test material supplied by the central laboratory.
- *For the ACTH stimulation tests and ITT it will be possible to either perform local analysis of cortisol or have the material (tubes, labels etc.) supplied and cortisol samples analysed by the central laboratory.*

2.1.19 Section 8.2 Handling of Screening failures, re-screening, treatment discontinuation and withdrawals

Re-screening and re-sampling
Re-screening of subjects is allowed ONLY if the screening window of 21 days between visit 1b and 2 is exceeded. *At re-screening the subject will receive a new subject ID, and all V1b assessments must be re-performed. The DXA scan is valid for 21 days from the actual scan date, hence exceeding the due date for the DXA scan, will result in a new DXA scan before randomisation can be performed.* No separate informed consent is required.

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria related to any laboratory parameters with exception of free T4, ~~and/or~~ testosterone, *or subjects who are tested to be adrenal insufficient*. Subjects *in replacement therapy for* ~~with~~ pituitary deficiencies ~~referred to specialists treating GHD~~ are not always sufficiently replaced with thyroxines, ~~and/or~~ testosterone, *or glucocorticoids* as evidenced by a low free T4*,* ~~or~~ testosterone, *or cortisol*. These subjects can be re-screened once when appropriate replacement therapy has been instituted and

stable for at least three months *(90 days)* at the discretion of the investigator. *This will include a new subject ID and all V1b assessments must be re-performed.*

Re-sampling is allowed during an unscheduled visit (section 8.6) if samples are lost or damaged before arriving at the analysing laboratory.

2.1.20 Section 8.3.3 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, dose, indication, start date and stop date or continuation. For medications containing oestrogen also the route of administration must be recorded.

Subjects should continue using adequate contraceptive measures (as defined in the exclusion criterion 3, section 6.3) until at least 16 days after last trial drug administration.

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.

2.1.21 Section 8.3.5 Subject diaries

From randomisation a diary will be dispensed to subjects at ~~every visit~~ *relevant visits (ref. section 2 Flow chart)* and it will be returned at *one of* the next site visits (~~visits marked as site visits in the flowchart, se section 2)~~.

2.1.22 Section 8.4.1 DXA body composition measurement

The quality of the baseline DXA scan obtained at Visit 1b must be confirmed by the imaging laboratory before the subject can be randomised. *The quality of the DXA scan obtained at visit 14 must be confirmed by the imaging laboratory prior to conducting visit 15.* The DXA scans will be provided to the imaging laboratory designated by Novo Nordisk for reading in a blinded manner. If a subject withdraws prematurely from the trial, an end-of trial DXA will be performed.

2.1.23 Section 8.4.8 Patient reported outcomes

PRO will be assessed at randomisation, at several occasions during trial conduct and at the two EOT visits (see section 2) using *three* ~~four~~ questionnaires: TRIM-AGHD[25], SF-36v2[26], *and* TSQM[27].

2.1.24 Section 8.5.5 *Total* Testosterone

Total t~~T~~estosterone will be assessed at the screening visit in *male* subjects receiving testosterone replacement therapy.

2.1.25 Section 8.5.7 ~~Fasting s~~*S*erum cortisol

For general monitoring of adrenal glucocorticoid function, fasting serum cortisol will be assessed at screening and every 2 to 3 months throughout the trial (see section 2). ~~Subjects must be fasting 8 hours before sample collection, with only water allowed.~~ *On specific time points the fasting serum cortisol must be taken as a morning serum cortisol sample (see section 8.5.8). The sampling of the morning serum cortisol should be performed before 9 am.* ~~If the subject comes to a fasting visit in a non-fasting state this needs to be recorded in the eCRF~~. *This will be used f*or subjects with ~~fasting~~ *morning* serum cortisol below normal range, who are not currently receiving glucocorticoid replacement therapy, *then* a confirmatory ACTH stimulation test *or ITT*, ~~additional to the ACTH stimulation testing outlined in~~ *(see* ~~S~~*s*ection 8.5.8*)*, should be performed *to characterise the adrenal insufficiency* ~~and appropriate treatment initiated~~.

2.1.26 Section 8.5.8 ~~Adrenocorticotropic hormone (ACTH) stimulation~~ *Adrenal insufficiency testing*

Cortisol levels will be assessed *according to section 8.5.7*, ~~at screening, at the end of the two titration periods and at the start of the extension period (see~~ section 2~~)~~. If a subject is not treated with glucocorticoid replacement *therapy* an ACTH stimulation test *or ITT* will be performed at screening if not performed within 3 months *(90 days)* prior to planned randomisation. *The morning serum cortisol sample collection, which is the basis for the ACTH stimulation test or ITT, should be performed at visit 9, 14 and 22 before 9 am when subjects are already fasting. Then an additional ACTH stimulation test or ITT at the corresponding visits 10, 15 and 23, must be performed in subjects who have morning serum cortisol between 3- 18µg/dL (or 80-500 nmol/L)*[31,32.] ~~*below normal range, i.e. men, and women not on oral oestrogen <80 nmol/l (3 µg/dL), women on oral oestrogen: < 128 nmmol/l (4.8 µg/dL) (morning cortisol – diagnostic cut-off values)*~~

Appropriate replacement therapy should be initiated according to local practice. Moreover it is recommended to teach the subject in which situations that may require increase in the steroid dose or in worst case scenario when to seek emergency care to limit the risk of adrenal crisis. The most common causes of adrenal crisis are but not limited to: fever, infection, pregnancy or surgery. It is the investigators responsibility to treat and instruct the subjects adequately.

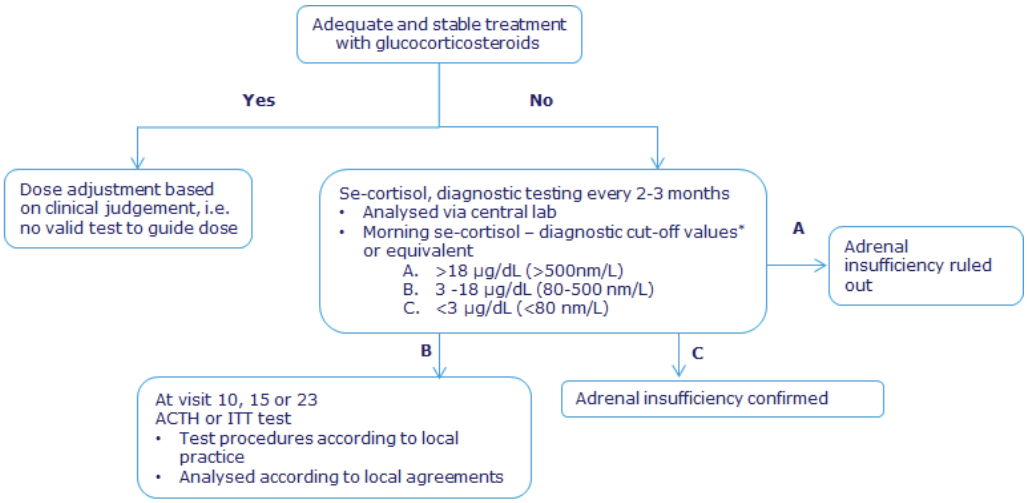

Figure 2–2 ***Requirement for adrenal insufficiency testing***

2.1.27 Section 8.5.12 Local tolerability

….
All pictures will be *evaluated by an external dermatologist and subsequently* transferred to Novo Nordisk.

2.1.28 Section 8.5.13 Anti-drug antibodies

Anti-drug antibodies will be assessed at randomisation and 2, 4, 8 and 16 weeks *plus 4 days (16+4d)* after randomisation and thereafter every two to three months throughout the trial ~~and at EOT and~~ *until the last* follow-up *visit* (see section 2). All samples must be drawn prior to trial drug administration if this is planned on a sampling day. Samples will be analysed *on a regular basis during the trial. The first analysis will occur after 6 months of recruitment, and then every 3 months for the remainder of the main and extension trial, with higher frequency* up to all three DBLs in the trial, i.e. after 50 subjects randomised to NNC0195-0092 have completed the main trial period, after all subjects have completed the main trial period and after completion of the extension period.

All subjects who have had ~~a~~ *two consecutive* positive antibody test result (high titre antibodies and/or persistent 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. *During the trial this will be covered by the regular anti-drug antibody sampling approximately every 3 months, and 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 safety committee meeting* of *any* positive antibody results in case of clinically relevant impact on efficacy and/or safety. The process for assessing the impact on efficacy and safety is ~~described in~~ *performed by the safety committee (*section 12.7.1*)*. If anti-drug antibody follow up extends beyond the LSLV of the extension period of the trial, 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 ~~may~~ *will* be reported *either* as an amendment to the Clinical Trial Report *or in a separate Clinical Trial Report*.

….

To evaluate the impact of antibody formation, results of antibody and in vitro neutralising antibody analyses will be compared to PK by collecting samples to assess serum concentrations of NNC0195-0092 at the same days as ~~for days after the last dosing and 3 days prior to~~ antibody sampling ~~takes place~~.

….

NNC0195-0092 antibodies

Determination of antibodies against NNC0195-0092 in subjects randomised to NNC0195-0092 will be performed by Novo Nordisk using a validated antibody binding assay. ~~The assay is a bridging enzyme-linked immuno-sorbent assay (ELISA) developed by Novo Nordisk to specifically determine antibody levels against NNC0195-0092.~~ Confirmed anti-NNC0195-0092 antibody positive samples will be further tested for cross-reactivity to hGH and for in vitro neutralising effect. The in vitro neutralising effect of anti-NNC0195-0092 antibodies will be evaluated in a validated cell-based neutralising antibody assay and by correlation to PK/PD.

hGH antibodies

Anti-hGH antibodies in subjects randomised to Norditropin® FlexPro® will be analysed by Novo Nordisk using a validated antibody binding assay. ~~The assay is a bridging ELISA developed by Novo Nordisk to specifically determine antibody levels against hGH.~~ Confirmed anti-hGH antibodies will be further assessed for neutralising effect of anti-hGH antibodies in a validated cell based neutralising antibody assay and by correlating to PK/PD.

2.1.29 Section 8.5.14 Assessments in case of suspicion of severe *systemic* hypersensitivity

If a severe immediate *systemic* hypersensitivity reaction to the trial product *(NNC0195-002/placebo/Norditropin®) occurs or* is suspected, a blood sample for assessment of tryptase (total and/or mature tryptase) should be taken within 3 hours of the reaction if practically feasible. *Under all circumstances* a blood sample for assessment of anti-drug antibodies including IgE isotype of these will be taken 2-4 weeks after the incident, i.e. at least 2 weeks after the trial product treatment has been discontinued. If tryptase is measured an additional baseline tryptase sample should be

taken at the same time as the *anti-drug antibodies* ~~ADA~~ and IgE sample is obtained. Tryptase concentrations (if measured) as well as results of anti-drug antibodies and IgE isotype antibodies *should* ~~will~~ be ~~collected by Novo Nordisk and~~ included in the final SAE report.

2.1.30 Section 8.5.15 Eye examination

Fundusphotography will be performed in subjects diagnosed with diabetes mellitus before inclusion into the trial (see *inclusion* ~~exclusion~~ criterion *10* ~~*16*~~).

2.1.31 Section 11 Randomisation procedure and breaking of blinded codes

Two hundred and eighty subjects will be randomised in a 2:2:1 ratio to receive NNC0195-0092, Norditropin® FlexPro® or placebo during a 3*4*~~5~~-week *treatment* period.

….

All subjects completing the *main trial period* ~~35 weeks~~ will continue on active treatment in ~~a non-placebo controlled~~ , *open-label* design for an additional 53-week extension-period.

2.1.32 Section 12.2 Reporting of adverse events

Figure 12-1 need to be replaced as a MESI form for medication error is included in NN8640-4054, also below text will be added as a result;

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

MESIs, regardless of seriousness, must be reported using both the AE form and the SIF *and a MESI form. The MESI form is a form tailored to collect specific information related to the individual MESI.*

The AE form for a non-serious AE not fulfilling the MESI criteria should be signed when the event is resolved or at the end of the trial.

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 SIF 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.

- ***SAEs fulfilling the MESI criteria:*** *In addition to above, the MESI form* ***within 14 calendar days*** *of the investigator's first knowledge of the AE.*

…..

- **Non-serious AE fulfilling the MESI criteria**: The AE form, SIF and *MESI form* within 14 calendar days of the investigator's first knowledge of the event.

…..

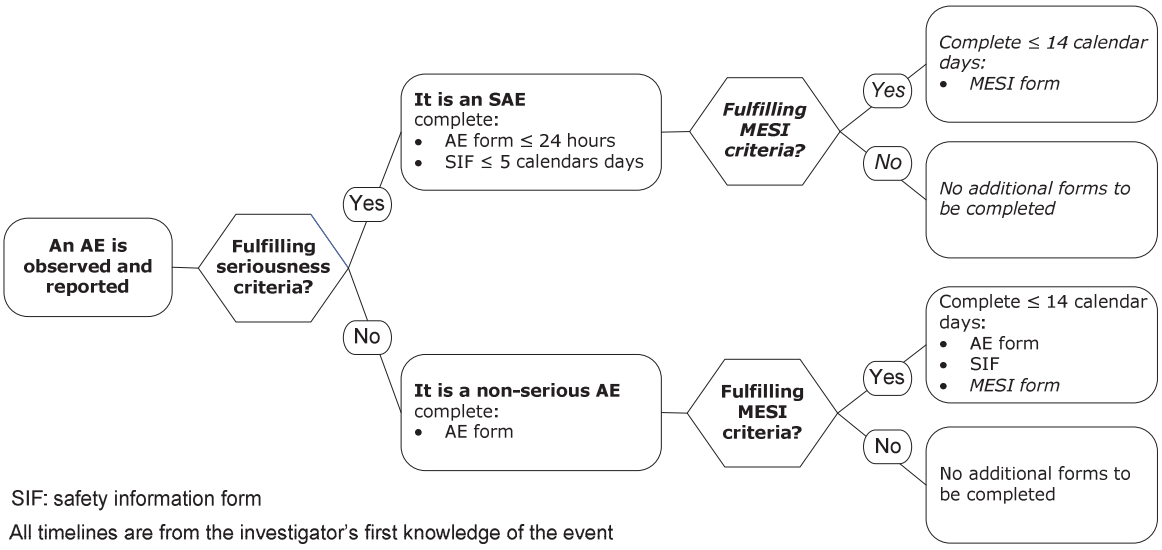

Figure 2–3 Initial reporting of AEs

~~2.1.33 Section 12.7.1 Novo Nordisk safety committee~~

~~Novo Nordisk has constituted an internal NNC0195-0092 safety committee to perform ongoing safety surveillance according to the NNC0195-0092 safety committee guideline. The NNC0195-0092 safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.~~

2.1.34 Section 17.3 Primary endpoint

The primary endpoint is change from baseline (randomisation) to end of main *treatment* ~~trial~~ period (Week 34) in the truncal fat percentage.

2.1.35 Section 17.4.1.1 Efficacy endpoints

Changes from baseline to end of main *treatment* ~~trial~~ period (Week 34) in the following variables will be used to address the primary objective:

…

2.1.36 Section 17.4.1.2 Safety endpoints

Adverse events will be analysed using descriptive statistics. All adverse events with onset after the first administration of trial product and up until Week *354* will be included in the main trial period analysis.

2.1.37 Section 27 References

17 Investigator's Brochure: NNC0195-0092, Growth hormone deficiency in children and adults, current version or updates hereof. Novo Nordisk. ~~27 June 2013~~ *01September 2014*.

31 Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003; 361(9372):1881-1893.

32 Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol 2014.

Protocol Amendment

no 4.0-IN to Protocol, final version 4 dated 02 December 2014

Trial ID:NN8640-4054

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, followed by a 53-week open-label extension period

Trial phase: 3a

Applicable to INDIA ONLY

Amendment originator:

Name: [redacted]

Department or business area: [redacted]

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

Additional Laboratory investigations have been added for India only to reflect reconfirmation of baseline evaluations in the central laboratory as required by Central Drug Standard Control Organisation (CDSCO), Office of Drugs Controller General (India)

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Changes to protocol version 4.0 dated 02 December 2014

2.1.1 Section 8.1 Visit procedures

All laboratory analyses in this trial will be performed by the central laboratory unless stated otherwise for the single parameter. The only exceptions;

- Urine pregnancy tests will be performed at the sites with test material supplied by the central laboratory.
- For the ACTH stimulation tests and ITT it will be possible to either perform local analysis of cortisol or have the material (tubes, labels etc.) supplied and cortisol samples analysed by the central laboratory.

FOR INDIA ONLY : Blood samples from GH diagnostic tests, i.e. after Insulin tolerance test (ITT) or glucagon test will be drawn at screening, and analysed by the central laboratory before randomisation if relevant to confirm subject eligibility. Additionally for female subjects, luteinising hormone (LH), follicle stimulating hormone (FSH) and Estradiol tests will be analysed by the central laboratory at the screening visit, if relevant to confirm subject eligibility.

2.1.2 Table 2–1 Trial Flow Chart for the main trial period

Trial Periods		Screening	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Treatment	Follow-up
Visit number		1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Visit type		IC	Site	Site	IGF	Site	IGF	Site	IGF	Phone [3]	IGF	Site	IGF	Site	Site	Site	Site
Timing of visit	Weeks	V1-1d minimum	-3 to -2 weeks	0	1+3d	2	3+3d	4	5+3d	6	7+3d	8	9+3d	16+4d	25+4d	33+4d	35
Visit window	Days					+1		+1		+1		+1		±7[4]	±7[4]	+2	
SUBJECT RELATED INFO / ASSESSMENTS																	
Informed consent		x															
In/exclusion criteria			x	x													
Withdrawal criteria						x						x		x	x	x	x*
Concomitant illness			x														
Concomitant medication			x	x		x		x		x		x		x	x	x	x
Demography			x														
Medical history			x														
Randomisation				x													
Body measurements			x														
Height			x														
Pregnancy test			x[5]	x[5]		x[5]						x[5]		x[5]	x[5]	x[5]	x[5]
ITT/Glucagon			*x*[17]														
Luteinizing Hormone			*x*[17]														
FSH			*x*[17]														
Estradiol			*x*[17]														
EFFICACY																	
Body measurements			x	x		x						x		x	x	x	x

Trial Periods		Screening	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Treatment	Follow-up
Visit number		1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Visit type		IC	Site	Site	IGF	Site	IGF	Site	IGF	Phone[3]	IGF	Site	IGF	Site	Site	Site	Site
Timing of visit	Weeks	V1-1d minimum	-3 to -2 weeks	0	1+3d	2	3+3d	4	5+3d	6	7+3d	8	9+3d	16+4d	25+4d	33+4d	35
Visit window	Days					+1		+1		+1		+1		±7[4]	±7[4]	+2	
Waist circumference				x												x	
Body weight			x	x		x						x		x	x	x	x*
PRO questionnaires			x[8]												x[8]	x[8]	
Biomarkers			x	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]		x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7] *
IGF-1			x	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]		x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7] *
IGFBP-3			x	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]		x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]*
Lipids			x													x	
PK Sampling				x[7]	x[7]	x[7]	x[7]	x[7]	x[7]		x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]
DXA scan			x[6]													x[16]	
Biochemistry			x									x		x	x	x	
hsCRP			x									x		x	x	x	
Protein markers																	
Interleukin 6			x									x		x	x	x	
SAFETY																	
Adverse events				x		x		x		x		x		x	x	x	x
Local tolerability				x[12]		x						x		x	x	x	x*
ECG			x									x		x	x	x	
Physical examination			x	x		x						x		x	x	x	x*
Vital signs			x	x		x						x		x	x	x	x*
Biochemistry			x									x		x	x	x	
Haematology			x									x		x	x	x	
Hormones			x									x		x	x	x	
Cortisol			x								x			x	x	x	

Trial Periods		Screening	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Treatment	Follow-up
Visit number		1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Visit type		IC	Site	Site	IGF	Site	IGF	Site	IGF	Phone[3]	IGF	Site	IGF	Site	Site	Site	Site
Timing of visit	Weeks	V1-1d minimum	-3 to -2 weeks	0	1+3d	2	3+3d	4	5+3d	6	7+3d	8	9+3d	16+4d	25+4d	33+4d	35
Visit window	Days					+1		+1		+1		+1		±7[4]	±7[4]	+2	
Free T4			x									x		x	x	x	
TSH			x									x		x	x	x	
Total T3			x									x		x	x	x	
Total T4			x									x		x	x	x	
Total testosterone			x[9]														
ACTH/ITT			x[10]									x[11]					x[11*]
Antibodies				x[7]		x[7]		x[7]				x[7]		x[7]	x[7]	x[7]	x[7]
Glucose metabolism			x									x		x	x	x	
Fasting insulin			x									x		x	x	x	
Fasting plasma glucose			x									x		x	x	x	
HbA1c			x									x		x	x	x	
Eye examination			x[13]														x[13]
Fundusphotography			x[13]														x[13]
OTHER ASSESSMENTS																	
Compliance						x						x		x	x	x	
MRI scan			x[15]														
CT scan			x[15]														
TRIAL MATERIAL																	
Administration of trial product																	
Dosing (observed trial drug administration)				x		x						x					x*
Dispensing visit				x		x		x				x		x	x		x*

Trial Periods		Screening	Screening	Randomisation	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Titration	Treatment	Treatment	Treatment	Treatment	Follow-up
Visit number		1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14[1]	15[2]
Visit type		IC	Site	Site	IGF	Site	IGF	Site	IGF	Phone [3]	IGF	Site	IGF	Site	Site	Site	Site
Timing of visit	Weeks	V1-1d minimum	-3 to -2 weeks	0	1+3d	2	3+3d	4	5+3d	6	7+3d	8	9+3d	16+4d	25+4d	33+4d	35
Visit window	Days					+1		+1		+1		+1		±7[4]	±7[4]	+2	
New dose of trial product						x[14]		x[14]		x[14]		x[14]					x[14*]
Drug accountability				x		x		x				x		x	x		x
IV/IWRS call			x	x		x		x		x		x		x	x		x
REMINDERS																	
Trial Conduct																	
Attend visit fasting			**x**	**x**	**x**	**x**	**x**	**x**	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
Handout and instruct in diary				x		x		x				x		x	x		x
Training in trial product and pen handling				x		x						x					x
Sign off Casebook																	
ecap dispensing and training																	x*
ecap returning																	
Diary returning						x		x				x		x	x		x

Footnotes main and extension trial

1. If a subject discontinues treatment prematurely during the 34-week period, procedures for treatment discontinuation described in section 8.2 must be followed
2. All assessments marked with * do not need to be performed if a subject withdraws from the trial up to and including visit 15
3. The phone visits can be site visits instead if required by local practice or regulation or at investigators discretion.
4. Visits 12 and 13 and V25, V26 and V27 can be moved either one whole week earlier or one whole week later.
5. **FOR ALL COUNTRIES EXCEPT JAPAN**: To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample At V2 the test is mandatory and needs to be performed from a urine sample. If required locally this may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than Visit 1b and V2, optional urine pregnancy testing may be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements. **FOR JAPAN ONLY**: To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample At V2 the test is mandatory and needs to be performed from a urine sample. If required locally this may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than V1b and V2, urine pregnancy test should be performed according to the flow chart.
6. Baseline DXA should be obtained at Visit 1b however if it is not possible, it should be performed within 4 calendar days from Visit 1b since the quality of the scanned image must be confirmed by the imaging laboratory before the subject can be randomised
7. Before trial drug administration (if dosing planned on visit day)
8. The PRO questionnaires must be performed after all fasting related activities and before all other trial-related activity at each applicable visit. TSQM is not assessed at randomisation.
9. Testosterone is assessed only in male subjects receiving testosterone replacement therapy
10. If subject is not being treated with glucocorticoid replacement and has not had adrenocorticotropic hormone (ACTH) stimulation test or ITT within past 3 months, perform ACTH stimulation test or ITT.
11. If a subject has morning cortisol below normal range, ACTH stimulation test or ITT must be performed. The morning serum cortisol sample collection, which is the basis for the ACTH stimulation test or ITT, should be performed at visit 9, 14 and 22, respectively, before 9 am when the subject is already fasting.
12. After trial drug administration.
13. Fundusphotography performed in subjects diagnosed with diabetes mellitus only (see inclusion criterion 10). Fundusphotography performed ≤ 90 days prior to randomisation is acceptable if results are available for evaluation at randomisation.
14. Besides the IGF-I based dose adjustment during the titration period, dose reduction can be considered during the entire study period (including the two titration periods) 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 dose reduction takes place during the titration periods or for deviations to the titration schedule see section 5.3.5.
15. Only for subjects with a history of pituitary adenoma or other benign intracranial tumour. MRI/CT if an MRI or CT scan has not been performed ≤ 9 months (defined as ≤ 270 days) prior to randomisation (results must be available for evaluation at randomisation).
16. The quality of the DXA scan obtained at visit 14 must be confirmed by the imaging laboratory prior to conducting visit 15.
17. ***APPLICABLE FOR INDIA ONLY:*** *The samples will be analysed at central laboratory.*

Protocol Amendment

no 5
to Protocol, final version 4.0
dated 02 December 2014

Trial ID: NN8640-4054

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, followed by a 53-week open-label extension period

Trial phase: 3a

Applicable to Japan

Amendment originator:

[redacted]

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1 Introduction including rationale for the protocol amendment

This amendment is a correction of error appearing in final protocol version 4.0 incorporating amendment 2-JP dated 09-Sep-2014 and amendment 3-global dated 28-Nov-2014. The text in footnote number 5 under Table 2 does not reflect the following change defined in the amendment 2-JP, therefore, this will be corrected.

- At all visits planned to perform a pregnancy test, urine pregnancy test in women of childbearing potential will be performed

This change is based on request from the Pharmaceuticals and Medical Devices Agency (PMDA) and will be applicable to Japan only.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Changes to section 2 of the protocol

The footnote number 5 under Table 2

FOR ALL COUNTRIES EXCEPT JAPAN: To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample At V2 the test is mandatory and needs to be performed from a urine sample. If required locally this may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than Visit 1b and V2, optional urine pregnancy testing may be performed at the investigator's discretion (such as for a missed menstrual cycle) or according to local requirements.
FOR JAPAN ONLY: To be performed in females only. At Visit 1b the test is mandatory and needs to be performed on a blood sample *and a urine sample.* At V2 the test is mandatory and needs to be performed from a urine sample. ~~If required locally t~~*T*his may be supplemented by a blood sample (results of the second blood sample are not required for randomisation). During the trial for all other site visits than V1b and V2, urine pregnancy test *in women of childbearing potential* should be performed according to the flow chart.

Protocol Amendment global

no 6
to Protocol, final version 4.0
dated 02 Dec 2014

Trial ID:NN8640-4054

A multicentre, multinational, randomised, parallel-group, placebo-controlled (double blind) and active-controlled (open) trial to compare the efficacy and safety of once weekly dosing of NNC0195-0092 with once weekly dosing of placebo and daily Norditropin® FlexPro® in adults with growth hormone deficiency for 35 weeks, followed by a 53-week open-label extension period

Trial phase: 3a

Applicable to all countries

Amendment originator:

[redacted]

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1 Introduction including rationale for the protocol amendment

This protocol amendment is prepared to address recruitment issues that have become evident over the last 6 months. The changes described in this protocol amendment have been endorsed by Novo Nordisk management (Development Project Committee). The protocol further addresses a request from FDA. The FDA has requested the protocol be changed to have ECGs performed at the time around mean C_{max}.

This protocol amendment addresses changes to both inclusion and exclusion criteria (some inclusion/exclusion criteria have shown to be overlapping, hence excluding relevant subjects). Below the major changes are described.

Inclusion criterion #4:
The purpose of the inclusion criterion #4c is to include subjects with panhypopituitarism. The subjects should be included based on medical record data for IGF-I SDS or new IGF-I value obtained at screening. In the current wording subjects with panhypopituitarism may have to undergo stimulation tests, as the IGF-I SDS is based on central values. As this is contradictory to the current guideline (please see the consensus guideline) the inclusion criterion #4 has been aligned (to current guideline).

We will allow patients that have been screen failed as a result of the previous criterion #4c to be re-screened according to the updated text when approved locally by HAs and IECs/IRBs.

Inclusion criterion #8:
The purpose of the testosterone inclusion criterion is to ensure that male subjects who are on testosterone replacement therapy are sufficiently treated. Changes in testosterone treatment may impact the primary outcome due to changes in body compositions. The change in inclusion criterion #8 will ensure the adequate treatment of male subjects and additionally minimise the false positive screen failures arising due to the fluctuations of serum testosterone induced by testosterone treatment.
The change in the testosterone inclusion criterion will ensure that male subjects who are on testosterone replacement therapy can be included in a differentiated manner:

- For male subjects already in replacement therapy the investigator must ensure adequate and unchanged dose for 90 days, to ensure that the subject is sufficiently treated.
- For male subjects not in replacement therapy with testosterone, the serum testosterone must be within normal range and if the value is below, testosterone replacement therapy should be initiated. Hereafter, the male subjects may be rescreened once.

Male subjects who were screening failures as a result of the previous inclusion criterion #8 can be re-screened according to the updated text when approved locally by HAs and IECs/IRBs.

Inclusion criterion #9
This criterion has been edited to reflect the separate inclusion criterion for testosterone.

Inclusion criterion #10
The text of this criterion has been simplified. No change of content.

Exclusion criterion #8
This criterion has been updated to reflect current standard practise of treatment of skin cancers. Several other accepted procedures exist, hence the wording reflects that the purpose of the criterion is to ensure that subjects are sufficiently treated.
(ref http://www.cancer.gov/cancertopics/pdq/treatment/skin/Patient/page1
and
http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/Basal_cell_carcinoma_Squamous_cell_carcinoma_Guide_Nov_2008-Final_with_Corrigendums.pdf)

Exclusion criterion #9.
The purpose of this exclusion criterion is to ensure that subjects who have undergone surgery or have a stable adenoma can be included in the trial. This has been added to reflect the current clinical guideline practice where adenomas are subject to less follow up after 3 years with no symptoms and no growth (ref. http://press.endocrine.org/doi/abs/10.1210/jc.2010-1048?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed).
It is important to emphasize, that subjects with a stable adenoma can only be included in the trial if they show absence of growth of the adenoma.

Exclusion criterion #12,
The criterion has been updated to reflect, that subjects who have undergone immunisation may be included in the trial.

Other changes
FDA requests that ECGs should be taken at time around the mean C_{max}. This requirement is implemented in the protocol by revising the schedule and procedures planned on visit 13 and visit 26.

The visit schedule has been updated with the option of performing IGF-I visits on day 3 as well as on day 4. This allows for more days to randomise, which will provide flexibility primarily in the titration period, but also in the treatment period.

Furthermore, we have revised text regarding database locks to correct inconsistent use of the term database lock. We will generate an interim immunogenicity report for anti-drug antibodies after 50 subjects receiving NNC0195-0092 have completed the main trial period (34 weeks of treatment),

and have actual database locks after all subjects have completed the main trial period (partial DBL) including all data for subjects completing V1a-V15, and the extension trial period (final DBL) including all data for subjects completing V1a-V29.

Finally, we have deleted redundant text regarding DXA scans to ensure that information is only stated in the relevant documents, i.e. Image Acquisition Guidelines and Site Operations Manual.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes to protocol

2.1 Section 1 Summary

Key inclusion criteria

…..

FOR ALL COUNTRIES EXCEPT JAPAN: Confirmed diagnosis of adult growth hormone deficiency. ~~If a subject satisfies at least~~ *Subjects must satisfy* one of the following criterion, *and documentation of test results must be available before randomisation (either from subjects' file or new test)*:

a. Insulin tolerance test (ITT) or glucagon test: a peak GH response of < 3 ng/mL (3 µg/L)
b. Growth hormone releasing hormone (GHRH) + arginine test according to body mass index (BMI)
    a. BMI< 25 kg/m^2, a peak GH < 11 ng/mL (*11* µg/L)
    b. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)
    c. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)

Three or more pituitary hormone deficiencies ~~at screening~~ and IGF-I SDS < -2.0 ~~(screening IGF-I SDS value provided by central laboratory)~~

Key exclusion criteri~~a~~*on*

Active malignant disease or history of malignancy. Exceptions to this exclusion criterion:

a. ~~Resected~~ *Resection* of in situ carcinoma of the cervix *uteri* ~~and~~
b. Complete eradication of 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 file.

2.2 Section 5.1 Type of trial

~~A blinded interim reporting of all safety parameters as described in sections 8.5 and 17.5 is planned to be done when 50 subjects randomised to NNC0195-0092 have completed the main trial. Data for all subjects up to week 35 (see Table 2–1) who have completed the main trial at this time will be included.~~

2.3 Section 5.3.1

…..

The procedure for dose reduction is described in section *6.5*~~6.~~4.

2.4 Section 5.3.5

….

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, *dose not taken as prescribed*),

- the **previous IGF-I sampling visit** will, depending on whether the visit has taken place or not,
  - be repeated two weeks later as ~~an unshceduled~~ *a re-scheduled visit* if the *IGF-I* visit has already taken place
  - or be rescheduled to two weeks later if ~~it~~ *the IGF-I visit* has not taken place

2.5 Section 6.2 Inclusion criteria

2.5.1 Inclusion criterion 4

FOR ALL COUNTRIES EXCEPT JAPAN: Confirmed diagnosis of adult growth hormone deficiency. ~~If a subject satisfies at least~~ *Subjects must satisfy* one of the following criterion, *and documentation of test results must be available before randomisation (either from subjects' file or new test)*:

c. Insulin tolerance test (ITT) or glucagon test: a peak GH response of < 3 ng/mL (3 µg/L)
d. Growth hormone releasing hormone (GHRH) + arginine test according to body mass index (BMI)
   a. BMI< 25 kg/m^2, a peak GH < 11 ng/mL (*11* µg/L)
   b. BMI 25–30 kg/m^2, a peak GH < 8 ng/mL (8 µg/L)
   c. BMI > 30 kg/m^2, a peak GH < 4 ng/mL (4 µg/L)
e. Three or more pituitary hormone deficiencies ~~at screening~~ and IGF-I SDS < -2.0 ~~(screening IGF-I SDS value provided by central laboratory)~~

2.5.2 Added inclusion criterion 8

Adequate testosterone level (males only):

a. For male subjects in testosterone replacement therapy the dose must be adequate and unchanged for at least 90 days prior to randomisation in accordance with local guidelines and practice as judged by the investigator.
b. For male subjects not in testosterone replacement therapy the serum levels for total testosterone must be within normal limits according to the central laboratory measurements

2.5.3 Inclusion criterion ~~8~~ *9*

Subjects must have serum levels of ~~total testosterone (males only) and~~ free T4 within normal limits according to the central laboratory measurements

2.5.4 Inclusion criterion ~~9~~ *10*

Adequate adrenal function *(one of the following must be fulfilled)*:

a. confirmed with ACTH stimulation test or ITT within ~~the last~~ 90 days prior to randomisation ~~if no result is available, ACTH stimulation test or ITT will be performed as part of the screening procedure after the informed consent is signed~~

or

b. *confirmed by* adequate and stable replacement therapy (as judged by the investigator) for at least 90 days prior to randomisation

2.5.5 Inclusion criterion ~~10~~ *11*

Subjects without diabetes mellitus,~~;~~ ~~or~~ *exceptions to this inclusion criterion*: subjects diagnosed with diabetes mellitus provided that ALL *of* the following criteria are met:

……..

2.6 Section 6.3 Exclusion criteria

2.6.1 Exclusion criterion 8

Active malignant disease or history of malignancy. Exceptions to this exclusion criterion:

c. ~~Resected~~ *Resection* of in situ carcinoma of the cervix *uteri* ~~and~~

d. Complete eradication of squamous cell or basal cell carcinoma of the skin ~~with complete local excision~~.

e. 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 file.

2.6.2 Exclusion criterion 9

~~For subjects~~ *Subjects* with a history of pituitary adenoma or other benign intracranial tumour, *exceptions to this exclusion criterion*:

a. Surgical removal ~~of pituitary adenoma or other benign intracranial tumour within~~ *more than* 12 months (defined as ≤ 365 days) before randomisation.

b. Stable and clinically non-functioning adenomas (stable refers to adenomas that do not meet the criterion for surgery and have documented absence of growth for at least 3 years).

~~b. Evidence of growth of pituitary adenoma or other benign intracranial tumour within the last 12 months (defined as ≤ 365 days) before randomisation~~

For both #9a and #9b: 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.

2.6.3 Exclusion criterion 12

History of positive results of tests for hepatitis B and/or C *(exceptions to this exclusion criterion: vaccination towards Hepatitis B virus and Hepatitis C virus).*

…….

2.6.4 Exclusion criterion 22

Inability to undergo DXA whole body scanning due to a body weight or size which exceeds the limit of the DXA scanner. ~~Weight and size limits differ between scanner types. Details about weight and size limits are described in the image acquisition guideline from the imaging laboratory~~

2.7 Section 5.2

The randomised, placebo-controlled~~, partly~~ *(*double-blind*)*, active controlled *(open)*, multicentre design is based on regulatory scientific advices.

….

2.8 Section 6.6 Treatment discontinuation and withdrawal criteria

~~Efforts should be made for subjects to attend and complete scheduled visit procedures.~~

…….

2.9 Section 8.1 Visit procedures

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) 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.

At screening, confirmation of GHD diagnosis should be obtained if not available in the subjects' file.

….

The investigator must assess all results outside the reference ranges as either clinically significant or not clinically significant and sign and date ~~each page of~~ each page of the lab*oratory* report. For parameters which are not blinded this review needs to be documented prior to the subject's next site visit.

….

Surveillance of laboratory safety data (with the exception of anti-drug antibody data) will be performed by a medical specialist at least every ~~2~~ 3 months based on safety surveillance reports.

~~The medical specialist will evaluate the laboratory safety data and look for potential safety signals or issues (safety surveillance).~~ If a ~~signal or alert is~~ finding is identified, the medical specialist will immediately inform the chairman of the safety committee.

2.10 Section 8.2 Handling of Screening failures, re-screening, treatment discontinuation and withdrawals

……

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria related to any laboratory parameters with exception of *the following inclusion criteria*;

1. *inclusion criterion. #8: low testosterone, for subjects not on replacement therapy*
2. *inclusion criterion #9: free T4 out of range*
3. *inclusion criterion #10: adrenal insufficiency*

~~Subjects in replacement therapy for pituitary deficiencies are not always sufficiently replaced with thyroxines, testosterone or glucocorticoids as evidenced by a low free T4, testosterone or cortisol.~~

Screen failures due to inclusion criteria #9 and #10: The ~~These~~ subjects can be re-screened once when appropriate replacement therapy has been instituted *or adjusted, to adequate and* stable *dose* for at least 3 months (90 days) *prior to re-screening* at the discretion of the investigator. This will include a new subject ID and all V1b assessments must be re-performed.

Screen failures due to inclusion criterion. 8: The subjects can be re-screened once when appropriate replacement therapy has been instituted and remained unchanged and adequate for at least 3 months (90 days) prior to re-screening. This will include a new subject ID and all v1b assessments must be repeated.

Patients that have been screen failed on protocol version 4.0 dated 02-Dec-2014 as a result of inclusion criterion #4c, inclusion criterion #8, or exclusion criterion #22 will be allowed to be re-screened according to the updated text when this protocol has been approved locally by HAs and IECs/IRBs..

……

Treatment discontinuation

All ~~Effots~~ efforts should be made for subjects to attend and complete scheduled visit procedures~~.~~ except *IGF-I sampling visit and dose adjustment visit (V3-11in the main trial, or V16-24 in the extension trial).*

Withdrawal

If ~~the~~ *a* subject ~~does not participate in all visits (withdrawal)~~is withdrawn, the investigator must aim to perform procedures similar to those for the respective end of trial (EOT) visits (V14 or V28) as soon as possible and a post-treatment follow-up visit (V15 or V29, at least two weeks after last treatment with NNC0195-0092 and at least 8 days after last treatment with Norditropin® FlexPro®).

…..

2.11 Section 8.3.4 MRI and CT

An MRI or CT scan can be performed ~~at screening~~ *before randomisation*, if required, to confirm eligibility in relation to exclusion criterion 9. The only information collected in the eCRF is whether the subject is eligible for trial participation.

2.12 Section 8.4.1 DXA body compositions measurement

……

Processes for image acquisition are outlined in an image acquisition guideline (IAG).~~: A single whole body DXA scan will be acquired with the subjects positioned supine, with their arms near their sides on the scanner table. Subjects should be normally hydrated, are not permitted to eat for at least 2 hours prior to the scan, must empty their bladder preceding the scan, and are not allowed to wear any metal or plastic (zippers, snaps, fasteners, grommets, belts, and under-wire bras etc.) or compressive clothing during the scan.~~ Besides the three scans per subject described in this protocol a limited number of repeat scans might be acquired if required due to technical reasons.

~~Each trial site DXA scanner will need to be qualified by the imaging laboratory prior to scanning subjects. DXA scanner qualification will require submitting baseline DXA instrument local spine phantom quality control (QC) scan results and a whole body DXA scan test transfer. During the trial, all sites must continue to acquire spine phantom QC scans at least three times per week and submit a copy of their QC database (once a month) to the imaging laboratory. Each subject must be scanned using the same DXA scanner for the duration of the trial. The imaging laboratory must be informed of any scanner software or hardware upgrades. If scanning on the same scanner is not possible or software or hardware upgrades occur, procedures as outlined in the IAG must be followed.~~

A cross calibration using a cross calibration phantom will be performed at least once at each site prior to the ~~second partial~~ database lock (DBL) of the main trial period.

2.13 Section 8.4.5 Cardiovascular parameters

……

The investigators will receive the results from the analysis only after LSLV of the extension period in order to avoid un-blinding.

2.14 Section 8.5.3 Biochemistry

….
eGFRcreatinine (CKD-EPI)[27] a derived variable based on s-creatinine and multiplication factors for race and sex, will be calculated by the central laboratory.

2.15 Section 8.5.5 Total testosterone

Total testosterone will be assessed at the screening *and on an ongoing basis throughout the trial* in *all* male subjects.

For males not receiving testosterone replacement therapy *the testosterone value must be within normal reference range at screening.*

2.16 Section 8.5.7 Serum cortisol

…..
If~~,~~ ~~then~~ *morning serum cortisol is below normal range* then a confirmatory ACTH stimulation test or ITT, (see ~~section 8.5.8,~~ *figure 8.1*), should be performed to characterise the adrenal insufficiency.

2.17 Section 8.5.8 Adrenal insufficiency testing

…….
Cortisol levels will be assessed according to sections 2, and 8.5.7. If a subject is not treated with glucocorticoid replacement therapy an ACTH stimulation test or ITT ~~will~~ *must* be performed ~~at screening~~ ~~if not performed~~ within 3 months (90 days) prior to planned randomisation.

2.18 Section 8.5.9 ECG

....
ECGs will also undergo central assessment. ECG recorders will be provided to all sites. For electronic central ECG recorders and ECG evaluation vendor details, see attachment I.

Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal ECG reading. If the abnormality, according to the investigator's judgement, represents an AE or SAE such findings should be reported by the investigator.

The ECG assessment must be performed using the provided ECG machine in the screening period, and results must be available before randomisation.

On visit 13 and visit 26 ECGs must be performed at the time around mean C_{max}, which is maximum 24 hours after dosing. Therefore, visit 13 (week 25) and visit 26 (week 64) must be planned within 24 hours after dosing (i.e. week 25 + 1 day and week 64 + 1 day).

For subjects randomised to NNC0195-0092/placebo with dosing on Mondays, Tuesdays, Wednesdays, Thursdays or Sundays, the dose must be taken as planned and visit 13 and visit 26 performed the day after dosing (see table 8-1).

For subjects randomised to NNC0195-0092/placebo with dosing on Fridays or Saturdays visit 13 and visit 26 and the previous dose must be scheduled according to table 8-1.

Table 8–1 ECG visit and dosing schedule for subjects on NNC0195-0092/placebo

Day of randomisation	***Visit day in trial week 25 or 64***	***New dosing day in week 25 or 64***
Sunday	*Monday (1 day later)*	*NA*
Monday	*Tuesday*	*NA*
Tuesday	*Wednesday*	*NA*
Wednesday	*Thursday*	*NA*
Thursday	*Friday*	*NA*
Friday	*Friday*	*Thursday (1 day early)*
	Monday (3 days later)	*Sunday (2 days later)*
Saturday	*Monday (2 days later)*	*Sunday (1 day later)*

For subjects randomised to Norditropin® FlexPro® the dose must be taken as planned daily and visit 13 and visit 26 scheduled according to table 8-2..

Table 8–2 ECG visit and dosing schedule for subjects on Norditropin® FlexPro®

Day of randomisation	***Visit day in trial week 25 or 64***	***Dosing***
Sunday	*Monday*	*Daily*
Monday	*Tuesday*	*Daily*
Tuesday	*Wednesday*	*Daily*
Wednesday	*Thursday*	*Daily*
Thursday	*Friday*	*Daily*
Friday	*Friday*	*Daily*
	Monday (3 days later)	*Daily*
Saturday	*Monday (2 days later)*	*Daily*

2.19 Section 8.5.13 Anti-drug antibodies

The first analysis will occur *when a total of 100 subjects have been randomised* ~~after 6 months of recruitment~~, and then every 3 months for the remainder of the main trial and extension trial, with higher frequency up to ~~all three~~ the DBLs in the trial. ~~, i.e. after 50 subjects randomised to NNC0195-0092 have completed the main trial period, after all subjects have completed the main trial period and after completion of the extension period.~~

2.20 Section 8.5.15 Eye Exam

Fundusphotography will be performed in subjects diagnosed with diabetes mellitus before inclusion into the trial (see inclusion criterion 10). It can be performed by the Investigator or a local Ophthalmologist according to local practice ~~at screening~~ before randomisation and at the end of the main and extension periods.

…..

2.21 Section 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 *(visit 1b)* after the subject has signed the informed consent until the end of the post-treatment follow-up period (i.e. Visit 29 or Visit 15 if a subject does not wish to participate in the extension part of the trial).

…..

2.22 Section 14 Monitoring procedures

…
The first monitoring visit will be performed as soon as possible after FSFV, and no later than 4 weeks after, *this will include a visit at the DXA radiology unit as well.*

The on-site monitoring visit interval to the DXA radiology unit must not exceed 6 months at sites with active subjects, for sites with no active subjects, monitoring visits to the DXA radiology unit must be performed at least every 12 months.

2.23 Section 15 Data management

The trial contains an interim immunogenicity report, and two database locks are planned during the trial. ~~Two partial database locks are planned to be done during the trial (facilitating interim safety reporting and~~ *A DBL of the* main trial period data~~, respectively)~~ as well as a database lock after the extension period of the trial is completed. For details please refer to section 17.5.

2.24 Section 17.5 Interim reporting, reporting of main and extension periods of the trial

The trial contains an interim immunogenicity report, and two ~~Two partial~~ database locks are planned during the trial. *A partial DBL of the* ~~(facilitating interim safety reporting and analysis of~~ main trial period data~~, respectively)~~ as well as a *final* database lock after the extension period of the trial is completed.~~ (facilitating the analysis of the extension trial data).~~

~~First partial DBL~~ ***Interim immunogenicity report***

A blinded interim ~~safety~~ *immunogenicity* report~~ing~~ will be ~~performed~~ generated when 50 subjects randomised to NNC0195-0092 have completed *34 weeks of treatment*. ~~the main trial.~~

The interim immunogenicity report will contain the following:

~~Data for all subjects up to and including V15 who have completed the main trial at this time will be included in a partial database lock (first partial database lock of trial data) with the following exceptions:~~

- ~~Antibody samples will be fully analysed but not be loaded in the clinical database to avoid unblinding~~
- Anti-drug antibody data for non-neutralising antibodies against NNC0195-0092 and hGH not classified as high titre antibodies (see section 8.5.13) will be reported as a tabulated summary in a blinded manner. This will include number of subjects with antibodies in the once weekly arms (NNC0195-0092 + placebo) versus number of subjects with antibodies in the once daily arm (hGH) including antibody titres and results for in vitro neutralising effect. Handling of data and report preparation is the responsibility of the analysing laboratory
    - Should any subjects develop high titre and/or persistent in vitro neutralising antibodies (see section 8.5.13) the safety committee might recommend unblinding of specific data for further analysis and an independent ad hoc safety group (see section 12.7.1) will be established. The purpose of an ad hoc safety group is to review unblinded data and based on analyses recommend further action to the safety committee. This ad hoc group will be able to report relevant data in an unblinded manner. Ad hoc safety group members must NOT be involved in daily project activities
        - Data for PK, IGF-I, IGFBP-3 will be fully analysed *for relevant subjects* to support the independent ad hoc safety group if needed but data will not be loaded in the clinical database to avoid unblinding.

~~Data will be analysed using descriptive statistics and will support the future phase 3 trial programme in children with GHD (regulatory requirement).~~ As the ~~safety~~ *immunogenicity* data will be reported in a blinded manner ~~(once weekly arms combined (NNC0195-0092 or placebo) versus Norditropin® FlexPro®)~~ no impact *on blinding* is expected on the remainder of the trial.

~~Second partial~~ ***Partial DBL*** **(main trial)**

Data for all subjects up to and including V15 who have completed or discontinued the main trial will be included in a partial database lock ~~(second partial database lock of trial data)~~. After the ~~second~~ partial DBL the sponsor will become unblinded while the subjects and site personnel will remain blinded *to the main trial treatment allocation*. ~~regarding the NNC0195-0092 versus Placebo allocation during the main period.~~

Final DBL (extension *trial*)

….

2.25 Section 17.6 Population PK analysis

….
A more technical and detailed elaboration of the population pharmacokinetic analysis will be done in the modelling analysis plan (MAP) which will be finalised before the *partial* ~~second~~ DBL. Results will be reported in a report separate from the CTR.

2.26 Section 27 References

27 Levin A, Kidney International 2013; 85, 49-61

2.27 Changes to Flow chart – section 2

+1 day visit window will be added to the IGF-I visits in the main trial and extension trial titration periods (visits 3, 5, 7, 9, 11, 16, 18, 20, 22, and 24)

ECG assessment at visits 13 and 26 will be performed at week X *+1 day after dosing* in stead of + 4 days from dosing as the ECG assessment should be performed at the time around the mean C_{max}, also the ECG assessment will be added to the two follow up visits 15 and 29. Furthermore ECG assessments will be deleted from the fixed dose period in both main trial and extension trial (visits 10, 12, 14, 23, 28).

Testosterone assessment for male subjects will be added to visits where biochemistry samples are collected (visits 10, 12, 13, 14, 23, 25, 26, 27, and 28), and footnote 9 will be added to the new assessments.

Correction of typing errors;
- PRO assessment: V1b is corrected to V2.
- Timing of visit for V1a: correct to V1*b* -1d minimum
- * added to V15 for handout of diary and training in trial drug (this should not be performed for subjects who withdraw)
- Minor typos

Footnote 9: Testosterone is assessed only in *male* subjects ~~receiving testosterone replacement therapy~~

Adding footnote:
[17] V1a and V1b may be combined if site SOPs and IEC/IRB decision allow this, i.e. that patients as standard practice attend all clinic visits in a fasting state.

[18] *Visit 13 and visit 26 and the previous dose must be scheduled according to table 8-1 or table 8-2.*

Update to abbreviation list

eGFR (Estimated Glomerular Filtration Rate)

3 Changes to the informed consents

Master informed consent, version 4.0, dated 02 December 2014.

3.1 Section 3 Clinical trial requirements

… ~~not have~~ *have no* evidence of intracranial tumour growth *since removal of the tumour* ~~within 12 months prior to the first injection of trial drug~~ if you previously have suffered from intracranial tumour.

3.2 Section 4 Examinations and analyses

It may be necessary for your trial doctor to perform some of the assessment required for the second visit (visit 1b) to the clinic on different days. If this is the case your trial doctor will inform you when you should come in to the clinic to have the remaining assessments performed.

If more than 21 days pass between your second (visit 1b) and third visit (visit 2) to the clinic you will be asked to come in for the second visit (visit 1b) again and have all required assessments at this visit performed again (a DXA scan will only have to be performed again if more than 21 days pass between the first DXA scan obtained and *the time you come in for visit 2).* ~~the second time you have to come in for visit 1b).~~ You will not be asked to sign a new informed consent form.

If the blood samples which will be taken at the second visit to the clinic (visit 1b) show that your thyroid function or adrenal function is not adequate or your testosterone level is not within the acceptable range (only for males not in testosterone treatment) your trial doctor will initiate appropriate replacement treatment, or adjust your current treatment. You will then be asked to come in to the clinic for a second visit 1b when your replacement treatment has been stable for 3 months. At the second visit 1b you will have all required assessments performed again.

3.3 Flowchart

In main and extension trial:

- x for ECG assessment at visit 10, visit 14, visit 23 and visit 28 is deleted.
- *x* for ECG assessment at visit 13, 15 and visit 29 is added.
- visit schedule is changed for visit 13 and 26 (week X +1)

3.4 Section 5.1.1 Assessments performed at the clinic visits are listed below:

Test of adrenal function:

The lack of adequate pituitary gland function in growth hormone deficient patients can lead to reduced amount of cortisol in your body. Testing of your adrenal function can be done by an ACTH test or insulin tolerance test (ITT). *Your trial doctor will determine if you need a test and also decide which* type of test. ~~is decided upon by your trial doctor.~~

3.5 Section 7 Discontinuation of trial drug

If you or your trial doctor decides to discontinue trial drug treatment but you are still willing to participate in the clinical trial, you will be asked by your trial doctor to attend ~~all~~ *some of the* remaining visits *with the exception of the dose adjustment visits in the main and extension trial period (i.e. visit 3-11 and visit 16-24).* ~~and~~ *At the remaining visits you will attend,* ~~have~~ *all* ~~the corresponding~~ *required* assessments *will be* performed except trial drug administration.

3.6 Section 12.2 Pregnancy information for males

The risks of trial drug candidates to a pregnant woman or an unborn child are unknown, therefore, you cannot participate if your partner intends to become pregnant. During the clinical trial *and at least 16 days after your last dose of trial medication,* you and your partner must use highly effective contraception (less than 1% failure rate).