Cover Page for Protocol and SAP

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02616562
Sponsor trial ID:	NN8640-4172
Official title of study:	A randomised, multinational, active-controlled, (open labelled), dose finding, (double-blinded), parallel group trial investigating efficacy and safety of once-weekly NNC0195-0092 treatment compared to daily growth hormone treatment (Norditropin® FlexPro®) in growth hormone treatment naïve pre-pubertal children with growth hormone deficiency
Document date*:	12 September 2022

*Document date refers to the date on which the document was most recently updated.

Protocol

Trial ID: NN8640-4172

A randomised, multinational, active-controlled, (open-labelled), dose finding, (double-blinded), parallel group trial investigating efficacy and safety of once-weekly NNC0195-0092 treatment compared to daily growth hormone treatment (Norditropin® FlexPro®) in growth hormone treatment naïve pre-pubertal children with growth hormone deficiency

Redacted protocol and SAP
includes redaction of company confidential information.

Including

- Protocol version 1 dated 02-Sep-2015
- Amendment 1-BR dated 07-Oct-2015
- Amendment 2-JP dated 21-Oct-2015
- Amendment 3-JP dated 25-Jan-2016
- Amendment 4-JP dated 27-Apr-2016
- Amendment 5-Global version 2.0 dated 08-Sep-2016
- Amendment 6-Global version 1.0 dated 15-Dec-2017
- Amendment 7-Global version 1.0 dated 19-Dec-2018
- Amendment 8-SE dated 03-Apr-2019
- Amendment 9-Global version 1.0 dated 11-Nov-2019
- Amendment 10-DE version 1.0 dated 18-Dec-2019
- Amendment 11 SE- version 1.0 dated 27-Apr-2020
- Amendment 12 Global version 1.0 dated 08-Feb-2021
- Amendment 13 Global version 1.0 dated 12-Sep-2022

Trial phase: 2

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List of abbreviations

ADHD	attention deficit hyperactivity disorder
AE	adverse event
AGHD	adult growth hormone deficiency
ALT	alanine aminotransferase
AME	Absorption, metabolism and excretion
AST	Aspartate Aminotransferase
BA	bone age
BMI	body mass index
CA	chronological age
CCDS	company core data sheet
CDC	Centers for Disease Control and Prevention
cm	centimeter
CPN	chronic progressive nephropathy
CRF	case report form
CTR	clinical trial report
DBL	data base lock
DMC	data monitoring committee
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
EudraCT	European drug regulatory authorities clinical trials
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
FHD	first human dose
FSFV	first subject first visit
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
GH-PPQ	growth hormone patient preference questionnaire

HbA1C	glycosylated haemoglobin
HDL	high density lipoprotein
hGH	human growth hormone
HV	height velocity
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IGF-I	insulin-like growth factor I
IGFBP-3	insulin-like growth factor binding protein 3
IRB	institutional review board
IWRS	interactive web response system
Japic CTI	Japan Pharmaceutical Information Centre Clinical Trial Information
LAR	legally acceptable representative
LDL	low density lipoprotein
LOCI	luminescent oxygen channelling immunoassay
LSFV	last subject first visit
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MESI	medical event of special interest
MMRM	mixed model for repeated measurements
NAH	near adult height
NCR	no carbon required
NOAEL	no observed adverse event level
PD	pharmacodynamic
PK	pharmacokinetic
PP	per protocol
PRO	patient reported outcome
RoW	rest of the world
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(ly)

SD	standard deviation
SDS	standard deviation score
SDV	source data verification
SGA	small for gestational age
SIF	safety information form
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TB-CGHD-O	The Treatment Burden Measure – Child Growth Hormone Deficiency - Observer
TB-CGHD-P	The Treatment Burden Measure – Child Growth Hormone Deficiency – Parent/Guardian
TMM	Trial Materials Manual
TRIM-CGHD-O	Treatment Related Impact Measure – Child Growth Hormone Deficiency- Observer
UTN	Universal Trial Number

1 Summary

This is a 368 week clinical trial in prepubertal children with growth hormone deficiency (GHD) comparing several blinded dose levels of NNC0195-0092 with an active open labelled control arm, from now on referred to as cohort I. Cohort I subjects, in countries where NNC0195-0092 is not available for prescription for children with GHD at the time when they complete the long-term safety extension (364 weeks), will be offered to continue the trial and receive treatment with NNC0195-0092, [redacted] mg/kg/week, until NNC0195-0092 is available for prescription in the subjects' respective countries or until August 2024, at the latest. The protocol has been amended to include two additional cohorts, cohort II (< 2 years and 26 weeks at screening) **FOR SWEDEN ONLY** not applicable as no subjects will be enrolled into cohort II **END OF TEXT FOR SWEDEN ONLY** and cohort III (age > 9 years (girls)/> 10 years (boys) and ≤ 17 years at screening) **FOR INDIA ONLY** not applicable as no subjects will be enrolled into cohorts II and III **END OF TEXT FOR INDIA ONLY** for the 208 week long-term safety extension trial period where all subjects are treated with NNC0195-0092.

NNC0195-0092 is a novel long-acting human growth hormone (hGH) derivative designed for once-weekly administration in children with GHD and adults with GHD (AGHD).

Objective(s) and endpoint(s):

Primary objective (cohort I):

- To evaluate the efficacy of multiple dose regimens of once-weekly NNC0195-0092 after 26 weeks of treatment in GH treatment naïve pre-pubertal children with GHD compared to once-daily hGH administration (Norditropin® FlexPro®).

Secondary objectives (cohort I):

- To evaluate the safety of multiple dose regimens of once-weekly NNC0195-0092 during 26 weeks of treatment in GH treatment naïve pre-pubertal children with GHD.
- To evaluate the efficacy and safety of multiple dose regimens of once-weekly NNC0195-0092 for up to 364 weeks of treatment in GH treatment naïve pre-pubertal children with GHD compared to Norditropin® FlexPro®.
- To investigate the impact of NNC0195-0092 relative to Norditropin® FlexPro® on wellbeing, psychosocial functioning and treatment satisfaction in GH treatment naïve pre-pubertal children with GHD.
- To monitor NNC0195-0092 and Norditropin® pharmacokinetic (PK) throughout the trial.

Primary objective (cohort II and III):

To evaluate the safety of once-weekly NNC0195-0092 during up to 208 weeks of treatment in children with GHD.

Primary endpoint (cohort I)

- Height velocity (HV) (cm/year) during first 26 week of treatment, measured as standing height with stadiometer at baseline and after 26 weeks.

Key secondary endpoints (cohort I)

- **Efficacy**
  - Changes from baseline to end of main trial period (week 26) in the following variables will be used to address the primary objective:
    - Height standard deviation score (SDS)
    - HV SDS
- **Safety**
  - The following endpoints will be used to support the secondary objectives of evaluation of safety for up to 364 weeks of treatment:
    - Incidence of adverse events, including injection site reactions
    - Occurrence of anti-NNC0195-0092 and anti-hGH antibodies

Primary endpoint (cohort II and III)

Incidence of adverse events, including injection site reactions, during up to 208 weeks of treatment in children with GHD.

Trial design:

This is a randomised, multinational, open-labelled, multiple dose, active-controlled, double-blinded, dose-finding, parallel group trial investigating efficacy and safety of once-weekly NNC0195-0092 treatment compared to daily GH treatment (Norditropin® FlexPro®) in GH treatment naïve pre-pubertal children (cohort I) diagnosed with GHD. The trial will consist of a 26 week main trial period, followed by a 26 week extension trial period, a 104 week safety extension period, a 208 week long-term safety extension trial period and a 30 day follow up period. The trial is designed as a 4 arm parallel group trial with 3 dose levels of once-weekly NNC0195-0092 treatment and 1 active control arm of once-daily Norditropin® FlexPro®. In the long-term safety extension trial period all subjects will be treated with NNC0195-0092 ([redacted] mg/kg/week). Two additional age groups; cohort II (< 2 years and 26 weeks at screening) **FOR SWEDEN ONLY** not applicable as no subjects will be enrolled into cohort II **END OF TEXT FOR SWEDEN ONLY** and cohort III (age > 9 years (girls)/> 10 years (boys) and ≤ 17 years at screening) **FOR INDIA ONLY** not applicable as no subjects will be enrolled into cohorts II and III **END OF TEXT FOR INDIA ONLY** are included in the 208 week long-term safety extension trial period only.

The randomisation of cohort I will be stratified by age (< 6 and ≥ 6 years) and by gender to minimize bias of the age and gender on primary endpoint. All cohort II and III subjects will be treated with NNC0195-0092 ([redacted] mg/kg/week).

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

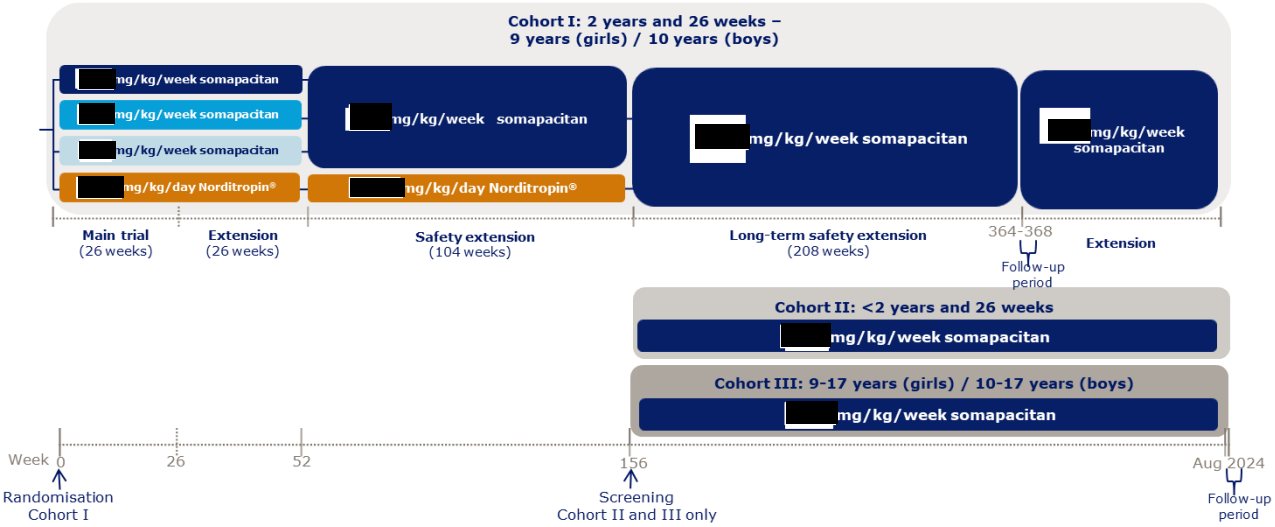

Figure 1–1 Trial design

For cohort I, the extension after the long-term safety extension is for subjects completing the long-term safety extension of the trial when NNC0195-0092 is not available for prescription in their country. The extension will end when NNC0195-0092 is available for prescription in their country or in August 2024, at the latest. The follow-up period for cohort I subjects continuing in the extension will be 30 days after last treatment with NNC0195-0092 in the trial. See Figure 1–1 for an overview of the trial design.

Trial population:

In the main trial period of the study sixty (60) subjects will be randomised in a 1:1:1:1 manner ([redacted] mg/kg/week NNC0195-0092: [redacted] mg/kg/week NNC0195-0092: [redacted] mg/kg/week NNC0195-0092: [redacted] mg/kg/day Norditropin® FlexPro®) to receive either NNC0195-0092 or Norditropin® FlexPro®. When the subjects have completed the main trial period (week 26) and extension trial period (week 52) all subjects initially randomised to NNC0195-0092 will be allocated to open-labelled NNC0195-0092 [redacted] mg/kg/week. Subjects randomised to Norditropin® FlexPro® will continue the treatment with Norditropin® FlexPro® [redacted] mg/kg/day in the safety extension trial period and be switched to open-labelled NNC0195-0092 ([redacted] mg/kg/week) in the long-term safety extension trial period. For the long-term safety extension trial period additional subjects will be enrolled (cohort II and III). All subjects in cohort II and III will be treated with [redacted] mg/kg/week NNC0195-0092.

Key inclusion criteria (cohort I)

- Pre-pubertal children
  - Boys: Tanner stage 1 for pubic hair and testis volume < 4 mL [1], age ≥ 2 years and 26 weeks and ≤ 10.0 years at screening
  - Girls: Tanner stage 1 for breast development (no palpable glandular breast tissue) and pubic hair [1], age ≥ 2 years and 26 weeks and ≤ 9.0 years at screening

- Confirmed diagnosis of GHD within 12 months prior to screening as determined by two different GH stimulation tests, defined as a peak GH level of ≤7.0 ng/ml. For children with three or more pituitary hormone deficiencies only one GH stimulation test is needed. **FOR JAPAN ONLY**: Confirmed diagnosis of GHD within 12 months prior to screening as determined by one GH stimulation tests for patients with intracranial organic disease or symptomatic hypoglycaemia and two different GH stimulation test for other patients, defined as a peak GH level of ≤ 6 ng/ml by assay using recombinant GH standard. **END OF TEXT ONLY APPLICABLE FOR JAPAN.**
- No prior exposure to GH therapy and/or IGF-I (insulin-like growth factor I) treatment.
- Height of at least 2.0 standard deviations below the mean height for chronological age (CA) and gender according to the standards of Centers for Disease Control and Prevention 2-20 years: Girls/Boys stature-for-age and weight-for-age percentiles CDC [2] at screening.
- Annualized height velocity (HV) at screening below the 25th percentile for CA and gender or below -0.7 SD score for CA and sex, according to the standards of Prader [3] calculated over a time span of minimum 6 months and maximum 18 months prior to screening.

Key inclusion criteria (cohort II) FOR SWEDEN AND INDIA ONLY not applicable as no subjects will be enrolled into cohort **II END OF TEXT FOR SWEDEN AND INDIA ONLY**

- < 2 years and 26 weeks and a minimum weight of 5 kg **at screening**.
- Confirmed diagnosis of GHD, the GHD diagnosis must be confirmed by investigator according to local practice.
- For GH treatment naïve subjects, no prior exposure to GH therapy and/or IGF-I treatment.
- For GH treatment naïve subjects, IGF-I SDS < -1.0 at screening, compared to age and sex normalized range according to central laboratory measurements.

Key inclusion criteria (cohort III) FOR INDIA ONLY not applicable as no subjects will be enrolled into cohort III END OF TEXT FOR INDIA ONLY

- Age:
  - Girls: > 9.0 years and ≤ 17.0 years at screening.
  - Boys: > 10.0 years and ≤ 17.0 years at screening.
- Confirmed diagnosis of GHD
  a) for GH treatment naïve subjects, confirmed diagnosis within 12 months prior to screening as determined by two different GH stimulation tests, defined as a peak GH level of ≤ 7.0 ng/ml. For children with three or more pituitary hormone deficiencies only one GH stimulation test is needed. **FOR JAPAN ONLY:** Confirmed diagnosis of GHD within 12 months prior to screening as determined by one GH stimulation tests for patients with intracranial organic disease or symptomatic hypoglycaemia and two different GH stimulation test for other patients, defined as a peak GH level of ≤ 6 ng/ml

by assay using recombinant GH standard. **END OF TEXT ONLY APPLICABLE FOR JAPAN.**

b) for non-GH treatment naïve subjects, confirmed GHD diagnosis by investigator according to local practice

- For GH treatment naïve subjects, no prior exposure to GH therapy and/or IGF-I treatment.

- Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.

Key exclusion criteria (cohort I, II FOR SWEDEN ONLY not applicable as no subjects will be enrolled into cohort **II END OF TEXT FOR SWEDEN ONLY and III FOR INDIA ONLY not applicable as no subjects will be enrolled into cohorts II and III END OF TEXT FOR INDIA ONLY)**

- Any clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing/length measurements:
  - Chromosomal aneuploidy and significant gene mutations causing medical "syndromes" with short stature, including but not limited to Turner syndrome, Laron syndrome, Noonan syndrome, or absence of GH receptors.
  - Congenital abnormalities (causing skeletal abnormalities), including but not limited to Russell-Silver Syndrome, skeletal dysplasias.
  - Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
- Children born small for gestational age (SGA - birth weight and/or birth length < -2 SD for gestational age).
- Concomitant administration of other treatments that may have an effect on growth, including but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).
- Prior history or presence of malignancy and/or intracranial tumour.

Assessments:

Assessments for efficacy include: height measurements, PRO (patient reported outcome) questionnaires (PRO's only applicable for cohort I).

Assessments for safety include: adverse events including local tolerability and bone age assessment (bone age assessment not applicable for cohort II).

Trial product(s):

All trial products will be administered as subcutaneous injections.

- NNC0195-0092 [redacted] mg/[redacted] mL PDS290-10 pen-injector
- NNC0195-0092 [redacted] mg/[redacted] mL PDS290-10 pen-injector

- NNC0195-0092 [redacted] mg/[redacted] mL PDS290-15 pen-injector (only trial product available in long-term safety extension)
- Norditropin® FlexPro® [redacted] mg/[redacted] mL pen-injector

Cohort I subjects, in countries where NNC0195-0092 is not available for prescription for children with GHD at the time when they complete the long-term safety extension (364 weeks), will be offered to continue the trial and receive treatment with NNC0195-0092, [redacted] mg/kg/week, until NNC0195-0092 is available for prescription in the subjects' respective countries or until August 2024 (expected last end-of-treatment visit for cohort I) at the latest. Novo Nordisk will inform the sites when NNC0195-0092 is considered available for prescription in the respective countries. However, if the health authorities in the subject's country reject the marketing application for treating children with GHD with NNC0195-0092, treatment with NNC0195-0092 will be stopped for the relevant subjects. If NNC0195-0092 is not yet approved and commercially available in the country treatment will continue until August 2024.

2 Flow chart

Table 2-1 Flowchart main and extension trial periods (cohort I)

Trial Periods	Protocol section	Information	Screening	Randomisation	Treatment	Treatment	Treatment	Treatment	Treatment
Visit number		0	1	2	3[1]	4[1]	5[2]	6[1]	7[2]
Timing of visit Weeks		V1 -1day minimum	-3 to -2	0	4	13	26+1 day	39	52+1 day
Visit window Days				0	+-7 d	+-7 d	+ 3 d	+-7 d	+3d
SUBJECT RELATED INFO/ASSESSMENTS									
Informed consent	18.2	X							
Child assent	18.3	X							
In/exclusion criteria	6.2 6.2.2		x	x					
Randomisation	11.1			x					
Withdrawal criteria	6.5.2 8.3.4				x	x	x	x	x
Concomitant illness	8.4.2		x						
Concomitant medication	8.4.3		x	x	x	x	x	x	x
Demography	8.4.1		x						
Medical history	8.4.2		x						
EFFICACY									
Body measurements									
Height	8.5.1.1		x	x		x	x	x	x
Body weight	8.5.1.2		x	x	x	x	x	x	x
PRO questionnaires									
TRIM-CGHD-O	8.8.1			x			x		x

Trial Periods	Protocol section	Information	Screening	Randomisation	Treatment	Treatment	Treatment	Treatment	Treatment
Visit number		0	1	2	3[1]	4[1]	5[2]	6[1]	7[2]
Timing of visit Weeks		V1 -1day minimum	-3 to -2	0	4	13	26+1 day	39	52+1 day
Visit window Days				0	+-7 d	+-7 d	+ 3 d	+-7 d	+3d
TB-CGHD-O	8.8.1						x		x
TB-CGHD-P	8.8.1						x		x
Biomarkers									
IGF-I	8.7.7		x	x	x	x	x	x	x
IGFBP-3	8.7.7		x	x	x	x	x	x	x
PK Sampling	8.7.8			x	x	x	x	x	x
Pubertal status	8.5.2		x				x		x
Date of menarche[4]	8.5.2				(x)	(x)	(x)	(x)	(x)
SAFETY									
Adverse events	8.4.2 8.6.1 12.2			x	x	x	x	x	x
Injection site reactions	8.6.2			x	x	x	x	x	x
ECG	8.6.4		x						x
Physical examination	8.6.6		x	x	x		x		x
Vital signs	8.6.7		x	x		x	x	x	x
X-ray									
Bone age	8.6.5		x						x
Antibodies	8.7.6			x	x	x	x	x	x
Biochemistry	8.7.1		x			x	x	x	x
Haematology	8.7.2		x			x	x	x	x
Glucose metabolism	8.7.4		x				x		x
Hormones	8.7.3		x				x		x
Lipids	8.7.5		x				x		x

Trial Periods	Protocol section	Information	Screening	Randomisation	Treatment	Treatment	Treatment	Treatment	Treatment
Visit number		0	1	2	3[1]	4[1]	5[2]	6[1]	7[2]
Timing of visit Weeks		V1 -1day minimum	-3 to -2	0	4	13	26+1 day	39	52+1 day
Visit window Days				0	+-7 d	+-7 d	+ 3 d	+-7 d	+3d
Pregnancy test[4]	8.7.9				(x)	(x)	(x)	(x)	(x)
OTHER ASSESSMENT									
Subject compliance	8.9				x	x	x	x	x
TRIAL MATERIAL									
Administration of trial product									
Dosing				x	x	x	x	x	x
Dispensing visit				x	x	x	x	x	x[3]
Drug accountability	9.4			x	x	x	x	x	x
IWRS call	10		x	x	x	x	x	x	x
REMINDERS									
End of trial									
Attend visit fasting			x				x		x
Training in trial product and pen handling	8.10			x	x				
Handout and instruct in diary	8.8.2			x					
Diary review	8.8.2				x	x	x	x	x
Diary returning	8.8.2								
End of treatment									
Sign off Casebook							x		x
Handout ID card	8.1		x						

For subjects randomised to NNC0195-0092 visit must be performed on a planned dosing day

[2] For subjects randomised to NNC0195-0092 visit should take place 1-4 days after trial drug administration

[3] Dispensing of trial product for the safety extension trial period

[4] Only for female subjects having menarche during the trial

Table 2-2 Table Flowchart safety extension trial period (cohort I)

Trial Periods	Protocol section	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Follow-up
Visit number		8[1]	9[2]	10[1]	11[2]	12[1]	13[2]	14[1]	15[2]	16[5]
Timing of visit Weeks		65	78 +1 day	91	104 +1 day	117	130 +1 day	143	156 +1 day	157
Visit window Days		+-7 d	+3 d	+-7 d	+3 d	+-7 d	+3 d	+-7 d	+3 d	+2 d
SUBJECT RELATED INFO/ASSESSMENTS										
Withdrawal criteria	6.5.2 8.3.4	x	x	x	x	x	x	x	x	
Concomitant medication	8.4.3	x	x	x	x	x	x	x	x	x
EFFICACY										
Body measurements										
Height	8.5.1.1	x	x	x	x	x	x	x	x	
Body weight	8.5.1.2	x	x	x	x	x	x	x	x	
PRO questionnaires										
TRIM-CGHD-O	8.8.1				x				x	
TB-CGHD-O	8.8.1				x				x	
TB-CGHD-P	8.8.1				x				x	
GH-PPQ[3]									x	
Biomarkers										
IGF-I	8.7.7	x	x	x	x	x	x	x	x	
IGFBP-3	8.7.7	x	x	x	x	x	x	x	x	
PK Sampling	8.7.8	x	x	x	x	x	x	x	x	x
Pubertal status	8.5.2		x		x		x		x	

Trial Periods	Protocol section	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Follow-up
Visit number		8[1]	9[2]	10[1]	11[2]	12[1]	13[2]	14[1]	15[2]	16[5]
Timing of visit Weeks		65	78 +1 day	91	104 +1 day	117	130 +1 day	143	156 +1 day	157
Visit window Days		+-7 d	+3 d	+-7 d	+3 d	+-7 d	+3 d	+-7 d	+3 d	+2 d
Date of menarche[4]	8.5.2	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
SAFETY										
Adverse events	8.4.2 8.6.1 12.2	x	x	x	x	x	x	x	x	x
Injection site reactions	8.6.2	x	x	x	x	x	x	x	x	x
ECG	8.6.4				x				x	
Physical examination	8.6.6		x		x		x		x	
Vital signs	8.6.7	x	x	x	x	x	x	x	x	
X-ray										
Bone age	8.6.5				x				x	
Antibodies	8.7.6	x		x		x		x		x
Biochemistry	8.7.1		x		x		x		x	
Haematology	8.7.2		x		x		x		x	
Glucose metabolism			x		x		x		x	
Hormones	8.7.3		x		x		x		x	
Lipids	8.7.5		x		x		x		x	
Pregnancy test[4]	8.7.9	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
Subject compliance	8.9	x	x	x	x	x	x	x	x	
TRIAL MATERIAL										

Trial Periods	Protocol section	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Follow-up
Visit number		8[1]	9[2]	10[1]	11[2]	12[1]	13[2]	14[1]	15[2]	16[5]
Timing of visit Weeks		65	78 +1 day	91	104 +1 day	117	130 +1 day	143	156 +1 day	157
Visit window Days		+-7 d	+3 d	+-7 d	+3 d	+-7 d	+3 d	+-7 d	+3 d	+2 d
Administration of trial product										
Dosing		x	x	x	x	x	x	x	x	
Dispensing visit		x	x	x	x	x	x	x	x	
Drug accountability	9.4	x	x	x	x	x	x	x	x	
IWRS call	10	x	x	x	x	x	x	x	x	
REMINDERS										
Attend visit fasting			x		x		x		x	
Training in trial product and pen handling	8.10								x	
Diary review	8.8.2	x	x	x	x	x	x	x	x	
Sign off Casebook					x				x	x

[1] For subjects randomised to NNC0195-0092 visit must be performed on a planned dosing day

[2] For subjects randomised to NNC0195-0092 visit should take place 1-4 days after trial drug administration

[3] Applicable for subjects switching from Norditropin® to NNC0195-0092. Site staff informs subjects about completion of GH-PPQ at week 160

[4] Only for female subjects having menarche during the trial

[5] Subjects that discontinue treatment early should perform the follow-up at least 7 days after treatment discontinuation.

Table 2-3 Flow chart long-term safety extension trial period (cohort I)

Trial Periods	Protocol section	Long-term safety extension trial period																Follow-up
Visit number		17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,5]	
Timing of visit Weeks		169	182	195	208+1day	221	234	247	260+1day	273	286	299	312+1day	325	338	351	364+5days	Last treatment in trial +30days[7]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+-1	+2
SUBJECT RELATED INFO/ASSESSMENTS																		
Withdrawal criteria	6.5.2 8.3.4	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	8.4.3	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medical history[1]	8.4.2	x																
EFFICACY																		
Body measurements																		
Height	8.5.1.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Body weight	8.5.1.2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PRO questionnaires																		
TRIM-CGHD-O	8.8.1				x				x				x				x	

Trial Periods	Protocol section	Long-term safety extension trial period																Follow-up
Visit number		17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,5]	
Timing of visit Weeks		169	182	195	208+1day	221	234	247	260+1day	273	286	299	312+1day	325	338	351	364+5days	Last treatment in trial +30days[7]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+-1	+2
TB-CGHD-O	8.8.1				x				x				x				x	
TB-CGHD-P	8.8.1				x				x				x				x	
Biomarkers																		
IGF-I	8.7.7		x		x		x		x		x		x		x		x	
IGFBP-3	8.7.7		x		x		x		x		x		x		x		x	
PK Sampling	8.7.8				x				x				x				x	
Pubertal status	8.5.2		x		x		x		x		x		x		x		x	
Date of menarch[3]	8.5.2	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
SAFETY																		
Adverse events	8.4.2 8.6.1 12.2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Trial Periods	Protocol section	Long-term safety extension trial period																Follow-up
Visit number		17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,5]	
Timing of visit Weeks		169	182	195	208+1day	221	234	247	260+1day	273	286	299	312+1day	325	338	351	364+5days	Last treatment in trial +30days[7]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+-1	+2
Injection site reactions	8.6.2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	8.6.4				x				x				x				x	
Physical examination	8.6.6		x		x		x		x		x		x		x		x	
Vital signs	8.6.7		x		x		x		x		x		x		x		x	
X-ray																		
Bone age					x[6]				x				x[6]				x	
Antibodies	8.7.6				x				x				x				x	
Biochemistry	8.7.1		x		x		x		x		x		x		x		x	
Haematology	8.7.2		x		x		x		x		x		x		x		x	
Glucose metabolism	8.7.4		x		x		x		x		x		x		x		x	
Hormones	8.7.3		x		x		x		x		x		x		x		x	
Lipids	8.7.5		x		x		x		x		x		x		x		x	

Trial Periods	Protocol section	Long-term safety extension trial period																Follow-up
Visit number		17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,5]	
Timing of visit Weeks		169	182	195	208+1day	221	234	247	260+1day	273	286	299	312+1day	325	338	351	364+5days	Last treatment in trial +30days[7]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+-1	+2
Pregnancy test[3]	8.7.9	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
OTHER ASSESSMENT																		
Subject compliance	8.9	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
TRIAL MATERIAL																		
Administration of trial product																		
Dosing		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)[8]	
Dispensing visit		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)[8]	
Drug accountability	9.4	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
IWRS call	10	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
REMINDERS																		
End of trial																	(x)[9]	
Attend visit fasting			x		x		x		x		x		x		x		x	

Trial Periods	Protocol section	Long-term safety extension trial period																Follow-up
Visit number		17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,5]	
Timing of visit Weeks		169	182	195	208+1day	221	234	247	260+1day	273	286	299	312+1day	325	338	351	364+5days	Last treatment in trial +30days[7]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+3	+-7	+-7	+-7	+-1	+2
Diary review	8.8.2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Diary returning	8.8.2																(x)[9]	
End of treatment																	(x)[9]	
Sign off Casebook																		X

[1] Parental height measured or recorded

[2] Visit should take place 1-4 days after trial drug administration

[3] Only for female subjects having menarche during the trial

[4] Trial drug should be administered 4-6 days prior to last site visit to ensure wash out prior to antibody test

[5] Visit 32 is the end of treatment visit for subjects who will end the trial at visit 32. Subjects who continue in the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024 at the latest, will have an end of treatment visit when they end treatment, see flowchart in Table 2-4.

[6] Collected if performed as per local practice

[7] The follow-up visit should take place 30 days after last treatment. This follow-up visit is only applicable for subjects ending the trial at visit 32. See flowchart in Table 2-4 for follow-up visit for subjects continuing in the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024.

[8] Only for subjects continuing in the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024, at the latest.

[9] Only for subjects ending the trial at visit 32.

Table 2-4 Flow chart cohort I: Extension until NNC0195-0092 is available for prescription for children with GHD or until August 2024, at the latest

Trial Periods	Protocol section	Extension until NNC0195-0092 is available for prescription for children with GHD or until August 2024, at the latest						Follow-up
Visit number		33	34	35	36	37	38[1]	
Timing of visit Weeks		377	390[2]	403	416 +1 day[2]	429	Last treatment +5 days[3] Latest Aug-2024	Last treatment + 30 days[4]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-1	+2
SUBJECT RELATED INFO/ASSESSMENTS								
Withdrawal criteria	6.5.2 8.3.4	x	x	x	x	x	x	
Concomitant medication	8.4.3	x	x	x	x	x	x	x
Medical history	8.4.2							
EFFICACY								
Body measurements								
Height	8.5.1.1	x	x	x	x	x	x	
Body weight	8.5.1.2	x	x	x	x	x	x	
Biomarkers								
IGF-I	8.7.7		x		x		x	
IGFBP-3	8.7.7		x		x		x	
PK Sampling	8.7.8				x		x	
Pubertal status	8.5.2		x		x		x	
Date of menarche[5]	8.5.2	(x)	(x)	(x)	(x)	(x)	(x)	(x)
SAFETY								
Adverse events	8.4.2 8.6.1 12.2	x	x	x	x	x	x	x
Injection site reactions	8.6.2	x	x	x	x	x	x	x
ECG	8.6.4				x		x[7]	
Physical examination	8.6.6		x		x		x	
Vital signs	8.6.7		x		x		x	

Trial Periods	Protocol section	Extension until NNC0195-0092 is available for prescription for children with GHD or until August 2024, at the latest						Follow-up
Visit number		33	34	35	36	37	38[1]	
Timing of visit Weeks		377	390[2]	403	416 +1 day[2]	429	Last treatment +5 days[3] Latest Aug-2024	Last treatment + 30 days[4]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-1	+2
X-ray								
Bone age					x[5]		x[7]	
Antibodies	8.7.6				x		x	
Biochemistry	8.7.1		x		x		x	
Haematology	8.7.2		x		x		x	
Glucose metabolism	8.7.4		x		x		x	
Hormones	8.7.3		x		x		x	
Lipids	8.7.5		x		x		x	
Pregnancy test[6]	8.7.9	(x)	(x)	(x)	(x)	(x)	(x)	(x)
OTHER ASSESSMENT								
Subject compliance	8.9	x	x	x	x	x	x	
TRIAL MATERIAL								
Administration of trial product								
Dosing		x	x	x	x	x		
Dispensing visit		x	x	x	x	x		
Drug accountability	9.4	x	x	x	x	x	x	
IWRS call	10	x	x	x	x	x	x	
REMINDERS								
End of trial							x	
Attend visit fasting			x		x		x	
Diary review	8.8.2	x	x	x	x	x	x	
Diary returning	8.8.2						x	

Trial Periods	**Protocol section**	**Extension until NNC0195-0092 is available for prescription for children with GHD or until August 2024, at the latest**						**Follow-up**
Visit number		33	34	35	36	37	38[1]	
Timing of visit Weeks		377	390[2]	403	416 +1 day[2]	429	Last treatment +5 days[3] Latest Aug-2024	Last treatment + 30 days[4]
Visit window Days		+-7	+-7	+-7	+3	+-7	+-1	+2
End of treatment							x	
Sign off Casebook								x

[1] Visit to be performed when NNC0195-0092 is available for prescription for children with GHD or August 2024, at the latest. Visit 38 will be no later than week 442.

[2] Visit should take place 1-4 days after trial drug administration.

[3] Trial drug should be administered 4-6 days prior to last site visit to ensure wash out prior to antibody test.

[4] The follow-up visit should take place 30 days after last treatment.

[5] Collected if performed as per local practice.

[6] Only for female subjects having menarche during the trial.

[7] If X-ray and ECG were performed within 6 months prior to the end of treatment visit, these should not be performed at the end of treatment visit.

Table 2-5 Flow chart long-term safety extension trial period (cohort II FOR SWEDEN ONLY not applicable as no subjects will be enrolled into cohort II END OF TEXT FOR SWEDEN ONLY and III FOR INDIA ONLY not applicable as no subjects will be enrolled into cohorts II and III END OF TEXT FOR INDIA ONLY)

Trial Periods	Protocol section	Information for cohort II & III	Screening for cohort II & III		Long-term safety extension trial period															End of treatment	Follow-up
Visit number		0	1	2	17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,12]	
Timing of visit Weeks		- 1 day minimum	-3 to -2	0	13	26	39	52+1 day	65	78	91	104+ 1 day	117	130	143	156+ 1 day	169	182	195	Last treatment + 5 days Latest Aug 2024	End of treatment + 30 days
Visit window Days					± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	± 1	+ 2
SUBJECT RELATED INFO/ASSESSMENTS																					
Informed consent	18.2	x																			
Child assent[9]	18.3	(x)																			
In/exclusion criteria	6.3 / 6.4		x	x																	
Withdrawal criteria	6.5.2 8.3.4				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant illness	8.4.2		x																		
Concomitant medication	8.4.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Trial Periods	Protocol section	Information for cohort II & III	Screening for cohort II & III		Long-term safety extension trial period															End of treatment	Follow-up
Visit number		0	1	2	17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,12]	
Timing of visit Weeks		- 1 day minimum	-3 to -2	0	13	26	39	52+1 day	65	78	91	104+ 1 day	117	130	143	156+ 1 day	169	182	195	Last treatment + 5 days Latest Aug 2024	End of treatment + 30 days
Visit window Days					± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	± 1	+ 2
Demography	8.4.1		x																		
Medical history[1]	8.4.2		x																		
EFFICACY																					
Body measurements																					
Height/Length	8.5.1.1 / 8.5.1.2		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Body weight	8.5.1.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Biomarkers																					
IGF-I	8.7.7		x			x		x		x		x		x		x		x		X	
IGFBP-3	8.7.7		x			x		x		x		x		x		x		x		X	
PK Sampling	8.7.8			x				x				x				x				X	

Trial Periods	Protocol section	Information for cohort II & III	Screening for cohort II & III		Long-term safety extension trial period															End of treatment	Follow-up
Visit number		0	1	2	17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,12]	
Timing of visit Weeks		- 1 day minimum	-3 to -2	0	13	26	39	52+1 day	65	78	91	104+ 1 day	117	130	143	156+ 1 day	169	182	195	Last treatment + 5 days Latest Aug 2024	End of treatment + 30 days
Visit window Days					± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	± 1	+ 2
Pubertal status[8]	8.5.2		(x)			(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)	
Date of menarch[3]	8.5.2		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
SAFETY																					
Adverse events	8.4.2 8.6.1 12.2			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Injection site reactions	8.6.2			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[7]	8.6.4		x[6]					x				x				x				X[13]	
Physical examination	8.6.6		x			x		x		x		x		x		x		x		x	
Vital signs	8.6.7		x			x		x		x		x		x		x		x		x	
X-ray																					

Trial Periods	Protocol section	Information for cohort II & III	Screening for cohort II & III		Long-term safety extension trial period															End of treatment	Follow-up
Visit number		0	1	2	17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,12]	
Timing of visit Weeks		- 1 day minimum	-3 to -2	0	13	26	39	52+1 day	65	78	91	104+ 1 day	117	130	143	156+ 1 day	169	182	195	Last treatment + 5 days Latest Aug 2024	End of treatment + 30 days
Visit window Days					± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	± 1	+ 2
Bone age[5]			x									x								X[13]	
Antibodies	8.7.6			x				x				x				x				X	
Biochemistry	8.7.1		x[10]	x[10]		x		x		x		x		x		x		x		X	
Haematology	8.7.2		x[10]	x[10]		x		x		x		x		x		x		x		X	
Glucose metabolism	8.7.4		x			x		x		x		x		x		x		x		X	
Hormones	8.7.3		x			x		x		x		x		x		x		x		X	
Lipids	8.7.5		x			x		x		x		x		x		x		x		X	
Pregnancy test[3]	8.7.9		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
OTHER ASSESSMENT																					
Subject compliance	8.9				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
TRIAL MATERIAL																					

Trial Periods	Protocol section	Information for cohort II & III	Screening for cohort II & III		Long-term safety extension trial period															End of treatment	Follow-up
Visit number		0	1	2	17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,12]	
Timing of visit Weeks		- 1 day minimum	-3 to -2	0	13	26	39	52+1 day	65	78	91	104+ 1 day	117	130	143	156+ 1 day	169	182	195	Last treatment + 5 days Latest Aug 2024	End of treatment + 30 days
Visit window Days					± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	± 1	+ 2
Administration of trial product																					
Dosing				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Dispensing visit				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Drug accountability	9.4			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
IWRS call	10		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
REMINDERS																					
End of trial																				x	
Attend visit fasting[11]			x			x		x		x		x		x		x		x		x	
Training in trial product and pen handling	8.10			x	x																

Trial Periods	Protocol section	Information for cohort II & III	Screening for cohort II & III		Long-term safety extension trial period														End of treatment	Follow-up
Visit number		0	1	2	17	18	19	20[2]	21	22	23	24[2]	25	26	27	28[2]	29	30	31	32[4,12]	
Timing of visit Weeks		- 1 day minimum	-3 to -2	0	13	26	39	52+1 day	65	78	91	104+ 1 day	117	130	143	156+ 1 day	169	182	195	Last treatment + 5 days Latest Aug 2024	End of treatment + 30 days
Visit window Days					± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	+ 3	± 7	± 7	± 7	± 1	+ 2
Handout and instruct in diary	8.8.2			x																	
Diary review	8.8.2				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Diary returning	8.8.2																			x	
End of treatment																				x	
Sign off Casebook																					x
Handout ID card	8.1		x																		

[1] Parental height measured or recorded
[2] Visit should take place 1-4 days after trial drug administration
[3] Only for female subjects having menarche during the trial. Date of menarche should only be recorded once, and pregnancy test should be taken if relevant.
[4] Trial drug should be administered 4-6 days prior to last site visit to ensure wash out prior to antibody test
[5] Only collected for cohort II subjects if performed as per local practice
[6] ECG results less than 3 months old at screening may be used
[7] Collected if possible for cohort II with reasonable effort
[8] Not applicable for cohort II
[9] Only applicable if required by local regulations
[10] If, due to blood volume constraints in younger children, not possible to draw blood for all analyses at V1, these can be drawn at visit 2
[11] Fasting time for children < 2½ years is approximately 4 hours. Fasting time for children ≥ 2½ years is 8 hours.
[12] The end of treatment visit should be performed August 2024 at the latest. If X-ray and ECG were performed within 6 months prior to the end of treatment visit, these should not be performed at the end of treatment visit. For further details, see Section 8.3.3.
[13] If X-ray and ECG were performed within 6 months prior to the end of treatment visit, these should not be performed at the end of treatment visit. For further details, see Section 8.3.3.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP [4] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki [5].

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

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

3.1 Background information

3.1.1 Growth Hormone Deficiency

Growth hormone (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[6]. Besides, the importance of GH and IGF-I for facilitating growth in children, both proteins are also involved in various metabolic processes in children as well as in adults[7].

Growth hormone deficiency (GHD) may occur as an isolated hormonal deficiency or in combination with multiple pituitary hormone deficiencies. It may result from congenital, genetic, acquired (by tumours in the central nervous system, cranial irradiation, head trauma or other organic causes) or idiopathic causes. The idiopathic GHD is the most common form, accounting for approximately 75% of diagnosed patients[8].

GHD in children is characterised by a diminished growth velocity and a markedly reduced final adult height compared to that predicted based on mid parental height. When given replacement therapy with hGH, normal growth can be restored[8]. The paediatric form of the GHD and its treatment is essentially the same for most patients whether the cause of the GHD congenital, genetic, acquired or idiopathic[8-10]. GHD may be present already at birth but is generally first discovered within the first years of childhood. Apart from GHD, experience gained during the last 15-20 years shows that hGH treatment is also efficacious in restoring normal growth in children with various other forms of growth retardation, including Turner and Noonan syndromes, chronic renal failure and small for gestational age (SGA)[10,11].

Rapid proteolysis and ligand-receptor internalisation result in a short half-life for hGH.

Consequently, hGH is given as daily injections. Children and adults with GHD currently require many years or lifelong treatment and persistence with a daily subcutaneous injection regimen. Studies investigating treatment adherence have shown that approximately one-fourth of children on GH treatment miss more than two injections per week[12-14].

3.1.2 NNC0195-0092

GH and therapeutic proteins in general have a short *in vivo* half-life which necessitates continuous infusion or frequent injections for their administration. This problem can be overcome by use of protraction mechanisms as for example reversible binding to serum albumin as used for NNC0195-

0092. NNC0195-0092 is a hGH derivate consisting of a modified amino acid backbone to which a non-covalent albumin binding moiety has been attached (see the Investigator's Brochure (IB)[15]. The receptor potency and pharmacokinetic (PK) profile of NNC0195-0092 is potentially suitable for once-weekly administration in humans. It is anticipated that once-weekly therapy with NNC0195-0092 will be just as safe and efficacious as daily hGH treatment with a greater convenience and potentially adherence compared to standard once-daily GH treatment.

Clinical phase 3 data published on the once-weekly hGH product LB03002 (under development by LG Life Sciences Ltd) have demonstrated clinical efficacy in both children with GHD and AGHD similar to once-daily hGH treatment[16,17].

3.1.3 Non-clinical data

The non-clinical safety documentation of NNC0195-0092 has not revealed any safety issues that would prohibit further administration of the compound to humans. The non-clinical data supports that NNC0195-0092 is suitable for once-weekly administration in humans and thereby supports the clinical trials.

The *in vivo* proof of principle (PoP) has been demonstrated in hypophysectomised Sprague Dawley rats. The pharmacodynamic (PD) effect of NNC0195-0092 was evaluated by measuring change in body weight, nose-tail length and the circulating plasma concentration levels of IGF-I after single and multiple dosing. The results showed an efficacy at least as good as daily injected hGH.

In vivo toxicity studies of NNC0195-0092 were conducted in two pharmacologically responsive species, the rat and the Cynomolgus monkey for up to 26 weeks.

The route of administration in the non-clinical studies was subcutaneous as this is the intended clinical route of administration.

All pivotal non-clinical safety studies were conducted according to Good Laboratory Practice (GLP).

Further details on the non-clinical findings are described in the IB[15].

3.1.4 Clinical Trials

Clinical trials with NNC0195-0092 have been completed in adults and in children. No safety issues have been identified during the clinical development of NNC0195-0092 and the clinical data obtained from both adults and children support the development of NNC0195-0092 in a phase 2 trial in children [15].

As of the initial approved version of this protocol, the safety profile of NNC0195-0092 had been evaluated in a trial in healthy male subjects (Trial NN8640-3915) receiving single dose or multiple s.c. doses of the drug (single dose up to [redacted] mg/kg and multiple dose up to [redacted] mg/kg/week). Overall, the drug was well tolerated. All adverse events (AE) were mild, or moderate and primarily observed at the highest dose levels. Most common AEs were: headache, peripheral oedema, joint pain, muscle pain, increase in blood sugar and insulin levels. These AEs are similar to the AEs caused by the existing GH products on the market. A significant dose-dependent IGF-I response

was induced at all dose levels. The IGF-I profiles indicate that NNC0195-0092 may be suitable for once-weekly dosing.

A multiple dose, dose-escalation trial in adults with GHD (NN8640-3947) has been completed to investigate safety, tolerability, PK and pharmacodynamics (PD) of NNC0195-0092 compared to Norditropin® NordiFlex® in AGHD. Overall, multiple weekly doses of NNC0195-0092 administered s.c. to AGHD patients were well tolerated at all doses investigated (NNC0195-0092 [redacted] and [redacted] mg/kg), with no serious safety issues or clinically significant local tolerability issues identified. The mean serum concentrations of NNC0195-0092 following MD s.c. administration to AGHD patients increased in a dose dependent manner. A similar dose-dependent increase in mean NNC0195-0092 $AUC_{(0-168)}$ and C_{max} was consistent with dose-proportionality. A dose-dependent IGF-I response was induced. The mean IGF-I profiles indicate that NNC0195-0092 is suitable for once-weekly dosing. A clinically relevant IGF-I response was induced by weekly doses up to [redacted] mg/kg. The IGF-I response following once-weekly NNC0195-0092 [redacted] and [redacted] mg/kg and once-daily Norditropin® NordiFlex® appear similar.

One clinical trial (NN8640-4042) has also been completed in children with GHD to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of a single dose of NNC0195-0092 compared to Norditropin® SimpleXx®. Overall, single doses of NNC0195-0092 administered s.c. to children with GHD were well tolerated at all doses investigated (single dose: [redacted] – [redacted] mg/kg), with no clinically significant safety or local tolerability issues identified. The NNC0195-0092 profiles in children indicate non-linear pharmacokinetics. The mean serum concentrations of NNC0195-0092 increased in a dose dependent manner following single dose administration.

A dose-dependent IGF-I response was observed for $AUC_{(0-168h)}$ and C_{max} for all NNC0195-0092 dose levels after adjustment for baseline levels. Furthermore, the IGF-I profiles indicate that NNC0195-0092 is suitable for once-weekly dosing in children with GHD.

As of the cut off for this protocol version, additional clinical trials in the NNC0195-0092 development programme have been completed: three phase 3 trials in adults with GHD investigating safety and efficacy (trials NN8640-4043, NN8640-4244 and NN8640-4054), one clinical pharmacology trial investigating absorption, metabolism and excretion (AME) in healthy subjects (trial NN8640 4237), two clinical pharmacology trials in special population including subjects with renal impairment and subjects with hepatic impairment (trials NN8640-4297 and NN8640-4298).

No safety issues have been identified during these completed clinical trials and the clinical data obtained from both adults and children continue to support the development of NNC0195-0092 in this phase 2 trial in children [15].

3.1.5 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, 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 see the current version of the investigator's brochure (IB) for Norditropin®[18].

3.1.6 Risks and benefits

The current trial will compare the efficacy and safety of weekly NNC0195-0092 versus daily treatment with Norditropin ®FlexPro®.

The benefit-risk balance of NNC0195-0092 remains favourable.

Based on the currently available safety data on NNC0195-0092, the benefit-risk profile and safety conclusions remain unchanged since the previous edition of the IB [15] and no safety issues have been identified.

Extensive clinical experience with the existing daily GH products has all shown to be efficacious with an acceptable safety profile. The safety profile of NNC0195-0092 is expected to be similar to the existing GH products on the market and no severe or life-threatening acute effects are expected. The safety documentation to support this is based on available non-clinical studies and on completed and ongoing clinical trials.

Comprehensive non-clinical studies, encompassing in vitro and in vivo animal safety studies have not identified any safety issues that precluded i.v. or s.c. administration of NNC0195-0092 to humans. Consult the IB [15] for detailed information on non-clinical data.

For clinical trials, the safety of NNC0195-0092 was evaluated by monitoring AEs, injection site reactions, physical examination, changes from baseline in vital signs, ECG, clinical laboratory safety assessments (haematology, biochemistry and urinalysis) and NNC0195-0092 antibodies.

The current safety experience on NNC0195-0092 is based on the completed FHD and AME clinical trials in healthy subjects (trials NN8640-3915 and NN8640-4237) and in five completed clinical trials in patients (trials NN8640-3947, NN8640-4043, NN8640-4054, NN8640-4244 in AGHD, and in trial NN8640-4042 in children with GHD). In total, 86 healthy subjects and 87 AGHD patients have been exposed to NNC0195-0092 in four of these completed clinical trials. A total of 24 children with GHD have been exposed to NNC0195-0092 in the completed phase 1 trial (NN8640-4042) and 45 children in the completed main period of the ongoing phase 2 trial NN8640-4172. A review of the preliminary safety data from the one ongoing clinical trial NN8640-4172, phase 2 in children with GHD, has found no safety data that significantly change the assessment of the benefit–risk profile of NNC0195-0092. In these trials no safety issues were observed that prohibit further dose administration of the compound to patients (AGHD patients and children with GHD). Consult the IB[15] for more detailed information on clinical data.

The most frequent AEs were weight increase, oedema, peripheral oedema, and transient increase in blood glucose. Overall, the safety profile of NNC0195-0092 observed so far is similar to the existing growth hormone products for daily administration, e.g. Norditropin®.

In general AEs occur less frequently in children compared to adults treated with GH replacement therapy [11]. Current available data on clinical safety and efficacy is summarised in the IB [15].

Subcutaneous administration of NNC0195-0092 can, like any other drugs for injection, occasionally lead to undesired local side effects, such as redness, swelling, itching, and tenderness of the skin at the point of injection. In the recently completed NN8640-3947 and NN8640-4042 trials these symptoms were mild and transient. No lipoatrophy has been observed.

In the completed main period of the ongoing NN8640-4172 trial, multiple doses of NNC0195-0092 administered to children with GHD were well-tolerated at all dose levels investigated ([redacted] and [redacted] mg/kg/week) and no safety concerns were identified.

Additional details on the trial product are described in the IB [15].

Furthermore, in this trial, all subjects will receive GH treatment and subjects randomised to NNC0195-0092 will get an opportunity to receive a treatment with less frequent injections than standard practice. For the individual subjects the personal health-related benefits are related to the medical examinations and treatment follow up.

Risk of COVID-19 infection in relation to participation in trial: Subjects may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing. Physical contact between subjects and site staff should be limited to the extent possible, and protective measures implemented according to local standards. The investigator should inform subjects and site staff to not come to the site in case they have symptoms of COVID-19.

3.2 Rationale for the trial

The aim of the NN8640 project is to develop a long-acting once-weekly growth hormone (GH) product, NNC0195-0092, which is as safe and efficacious but more convenient and thus potentially with better adherence and treatment persistence 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. dose levels of NNC0195-0092 in pre-pubertal children with GHD. In addition to the pre-pubertal children in cohort I two new age groups including children < 2 years and 26 weeks, cohort II **FOR SWEDEN ONLY** not applicable as no subjects will be enrolled into cohort II **END OF TEXT FOR SWEDEN ONLY**, and children > 9 years (girls) / > 10 years (boys) and ≤ 17 years, cohort III **FOR INDIA ONLY** not applicable as no subjects will be enrolled into cohorts II and III **END OF TEXT FOR INDIA ONLY** are enrolled. The aim of adding the two age groups, cohort II and III, in the long-term safety extension period of the trial, is to enrol children with GHD to whom treatment may be relevant. Safety evaluation is the aim for these cohorts and efficacy assessments will be used to support the clinical evaluation.

The primary therapeutic indications considered for the NNC0195-0092 compound is GHD in children and adults.

The trial results will contribute with relevant information for dose selection in a phase 3 confirmatory trial.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Cohort I

Primary objective:

- To evaluate the efficacy of multiple dose regimens of once-weekly NNC0195-0092 after 26 weeks of treatment in GH treatment naïve pre-pubertal children with GHD, compared to once-daily hGH administration (Norditropin® FlexPro®).

Secondary objectives:

- To evaluate the safety of multiple dose regimens of once-weekly NNC0195-0092 during 26 weeks of treatment in GH treatment naïve pre-pubertal children with GHD.
- To evaluate the efficacy and safety of multiple dose regimens of once-weekly NNC0195-0092 for up to 364 weeks of treatment in GH treatment naïve pre-pubertal children with GHD, compared to Norditropin® FlexPro®.
- To investigate the impact of NNC0195-0092 relative to Norditropin® FlexPro® on wellbeing, psychosocial functioning, treatment satisfaction and preference in GH treatment naïve pre-pubertal children with GHD by using patient reported outcome (PRO) questionnaires.
- To monitor NNC0195-0092 and Norditropin® PK throughout the trial.

4.1.2 Cohort II and III

Primary objective:

- To evaluate safety of once-weekly NNC0195-0092 during up to 208 weeks of treatment in children with GHD.

Efficacy assessments for cohort II and III will be the same as for the long-term safety trial period for cohort I (except for PRO's).

4.2 Endpoints

4.2.1 Primary endpoint

4.2.1.1 Primary endpoint cohort I

- Height velocity (HV) (cm/year) during first 26 week of treatment, measured as standing height with stadiometer at baseline and after 26 weeks.

4.2.1.2 Primary endpoint cohort II and III

- Incidence of adverse events, including injection site reactions, during up to 208 weeks of treatment with NNC0195-0092 in children with GHD.

4.2.2 Secondary endpoints (cohort I)

4.2.2.1 Supportive secondary efficacy endpoints (cohort I)

The following endpoints will be used to support the primary and secondary objective regarding evaluation of efficacy:

Changes from baseline (week 0) to end of main trial period (week 26) in the following variables will be used to address the primary objective:

- Height standard deviation score (SDS)
- HV SDS[1] (derived from standing height from baseline (week 0) to week 26)
- Insulin-like growth factor 1 (IGF-I) SDS
- Insulin-like growth factor binding protein 3 (IGFBP-3) SDS

[1] Baseline (week 0) HV SDS is derived from reported pre-trial standing height measured at minimum 6 months and maximum 18 months prior to screening visit to standing height at baseline (week 0)

Changes from baseline (week 0) and from end of main trial period (week 26) to end of extension trial period (week 52) in the following variables will be used to support the secondary objective regarding evaluation of efficacy during the extension period.

- Height standard deviation score (SDS)
- HV SDS (derived from standing height from baseline (week 0) to week 52)
- IGF-I SDS
- IGFBP-3 SDS

The following endpoints will be used to support the secondary objective regarding evaluation of efficacy at week 52:

- HV (cm/year) at weeks 52 (derived from standing height from baseline (week 0) to week 52)
- Bone age (X-Ray of left hand and wrist, central assessed according to Greulich & Pyle atlas)[19] progression vs. chronological age
- Serum NNC0195-0092 concentrations and changes throughout the trial

Additionally, scores of the following patient reported outcome (PRO) questionnaires will be used to address the secondary objective of investigating the impact of NNC0195-0092 relative to Norditropin® FlexPro® on wellbeing, psychosocial functioning and treatment satisfaction in GH treatment naïve pre-pubertal children with GHD:

- Changes in emotional well-being score, physical health score, social well-being score and total score from baseline to week 26 and 52 in TRIM-CGHD-O (Treatment Related Impact Measure – Child Growth Hormone Deficiency- Observer)
- Total score of TB-CGHD-O (The Treatment Burden Measure – Child Growth Hormone Deficiency – Observer) at week 26 and 52.

- Total score of TB-CGHD-P (The Treatment Burden Measure – Child Growth Hormone Deficiency – Parent/Guardian) at week 26 and 52

The scores of the PROs range from 0-100. A lower score indicates a better health state.

4.2.2.2 Supportive secondary safety endpoints (cohort I)

The following endpoints will be used to support the secondary objectives of evaluation of safety for up to 364 weeks of treatment:

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

5 Trial design

5.1 Type of trial

This is a randomised, multinational, open-labelled, multiple dose, active-controlled, double-blinded, dose-finding, parallel group trial investigating efficacy and safety of once-weekly NNC0195-0092 treatment compared to daily GH treatment (Norditropin® FlexPro®) in GH treatment naïve pre-pubertal children with GHD (cohort I). The main trial period will consist of 26 weeks of treatment, followed by a 26-week extension trial period, a 104 week open labelled safety extension trial period, a long-term safety extension trial period and a 30 day follow-up trial period. In addition, cohort I subjects who complete the long-term safety extension period (364 weeks) when NNC0195-0092 is not available for prescription for children with GHD in their country, can continue treatment until NNC0195-0092 is available for prescription for children with GHD in their country or until August 2024, at the latest. The trial is designed as a 4 arm parallel group trial with 3 blinded dose levels of once-weekly NNC0195-0092 treatment and 1 active open labelled control arm of once-daily Norditropin® FlexPro®. The safety extension trial period is designed as a 2 arm parallel group trial with one dose level ([redacted] mg/kg/week) of once-weekly NNC0195-0092 treatment and 1 active control arm of once-daily Norditropin® FlexPro® ([redacted] mg/kg/day). In the long-term safety extension trial period, all subjects will be treated with once-weekly NNC0195-0092 ([redacted] mg/kg/week). In addition to the pre-pubertal cohort I, additional subjects from other paediatric age groups (cohort II **FOR SWEDEN ONLY** not applicable as no subjects will be enrolled into cohort II **END OF TEXT FOR SWEDEN ONLY** and III) **FOR INDIA ONLY** not applicable as no subjects will be enrolled into cohorts II and III **END OF TEXT FOR INDIA ONLY**) are enrolled into the long-term safety extension period. See Figure 5–1 for an overview of the trial design. The randomisation in cohort I will be stratified by region (Japan and rest-of-the-world (RoW). The randomisation in cohort I will additionally be stratified by age (< 6 and ≥ 6 years) and by gender within the RoW region to minimize bias of region, age and gender on the primary endpoint.

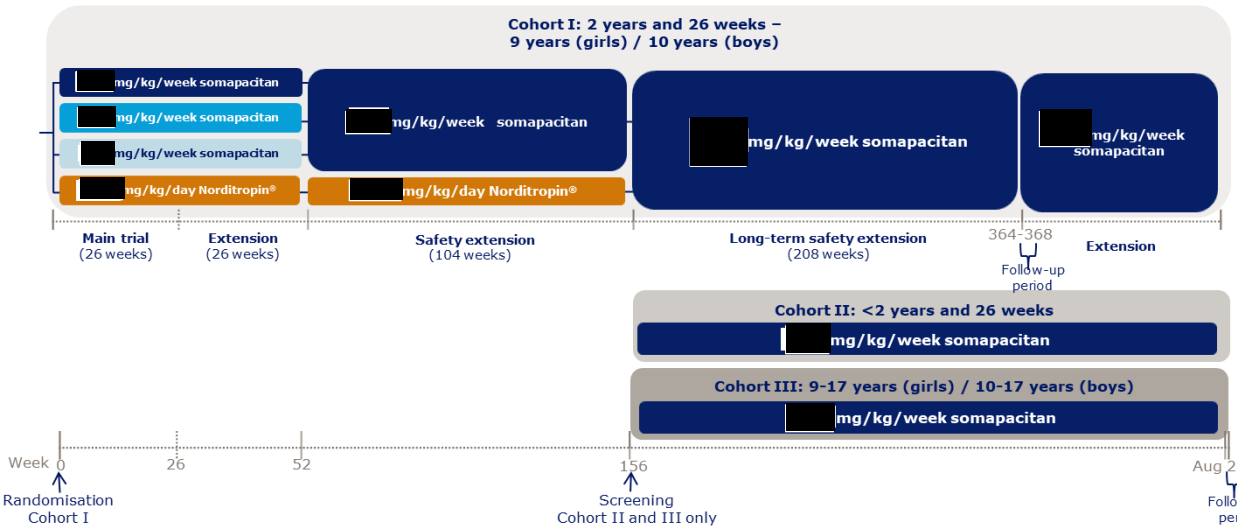

Figure 5–1 Trial design

In the main trial period of the study sixty (60) subjects will be randomised in a 1:1:1:1 ([redacted] mg/kg/week NNC0195-0092: [redacted] mg/kg/week: NNC0195-0092 [redacted] mg/kg/week NNC0195-0092: [redacted] mg/kg/day Norditropin® FlexPro®) manner to receive either NNC0195-0092 or

Norditropin® FlexPro®. After week 52 all subjects in the NNC0195-0092 arm are switched to [redacted] mg/kg/week. After week 156 all subjects on Norditropin® FlexPro® are switched to NNC0195-0092 ([redacted] mg/kg/week).

In the long-term safety extension trial period subjects from two additional age groups will be enrolled, cohort II (< 2 years and 26 weeks at screening) and cohort III (> 9 years (girls)/ >10 years (boys) and ≤ 17 years at screening) and will be treated with once-weekly NNC0195-0092 ([redacted] mg/kg/week). They will start treatment at visit 2 where after they will continue the visit schedule for the long-term safety extension (visit 17 and onwards). Subjects in cohorts II and III will be treated with NNC0195-0092, [redacted] mg/kg/week until latest August 2024 (expected last end-of-treatment visit for cohort I) (for details, see Section 8.3.3). As recruitment of subjects from these age groups may be challenging, enrolment of subjects naïve and non-naïve to GH treatment until 4 months prior to expected last end-of-treatment visit for cohort I is possible, unless recruitment has already been completed.

Data from the trial for cohort I will be analysed when all subjects have completed the 26, 52, 104 and 156 and 364 weeks of treatment. For subjects continuing treatment until NNC0195-0092 is available for prescription in their country or August 2024 at the latest, the additional data collected between week 364 (visit 32) and the end-of-treatment visit (visit 38) will be analysed additionally. Further interim reporting may be performed including cohort II and III in association with marketing authorisation application or in connection with Health Authorities e.g. FDA, EMA and PMDA requirement for/during the regulatory review. Final analysis will take place when all subjects have completed the trial.

5.2 Rationale for trial design

The trial is double-blinded with regards to different dose levels of once-weekly NNC0195-0092, but open labelled with regards to daily hGH as active-controlled arm. The open-label design is chosen in order to be able to compare local tolerability, (i.e. daily vs. weekly injections), which is not possible if a double-dummy design was applied. Furthermore, double-dummy design will not allow comparing patient satisfaction related to daily vs. weekly injections.

The safety extension trial period will be open labelled since only one dose level of NNC0195-0092 will be used. Additionally, in the long-term safety extension trial period, all subjects randomised to Norditropin® FlexPro® will be switched to NNC0195-0092 ([redacted] mg/kg/week). All subjects in cohort II and III will receive treatment with NNC0195-0092 ([redacted] mg/kg/week).

The trial will be observer blinded (applicable for cohort I only) with regards to primary endpoint (i.e. the person performing the height measurements will be blinded to treatment allocation). Observer blinding with regards to primary endpoint is not applicable for the long-term safety extension and any visits thereafter. GH treatment-naïve GHD pre-pubertal children is the trial target population for treatment as this is a sensitive and well-known model. The children need to be pre-pubertal to avoid interference of the pubertal growth spurt with the treatment effect. The trial will be multinational to ensure that the results are applicable for subjects with different demographic characteristics. Two additional age groups; cohort II (< 2 years and 26 weeks at screening) and cohort III (> 9 years (girls)/ >10 years (boys) and ≤ 17 years at screening) are included in the long-

term safety extension trial period, based on a request from the FDA, as they may benefit from GH therapy.

The 26 week main trial period is the minimum expected time needed for evaluation of cohort I's primary endpoint (annualised HV). The 26 week extension trial period and the 104 week safety extension trial period are added primarily to collect additional safety data. The 208 week long-term safety extension trial period is added to collect data on long-term safety, as well as data on subjects reaching near adult height (NAH). The entire treatment period is 364 weeks followed by a 30 day follow up period. For cohort I subjects who continue treatment until NNC0195-0092 is available for prescription, or August 2024, at the latest, the treatment period will be longer. The follow up period is included to collect information about adverse events.

5.3 Treatment of subjects

In the main trial period of the study subjects enrolled in cohort I will be randomised in a 1:1:1:1 manner to receive either NNC0195-0092 (approximately 45 subjects) or Norditropin® FlexPro® (approximately 15 subjects).

- NNC0195-0092: [redacted] mg/kg/week
- NNC0195-0092: [redacted] mg/kg/week
- NNC0195-0092: [redacted] mg/kg/week
- Norditropin® FlexPro®: [redacted] mg/kg/day

When the subjects have completed the main trial period (week 26) and extension trial period (week 52), all subjects initially randomised to NNC0195-0092 will be allocated to open labelled NNC0195-0092 ([redacted] mg/kg/week). Subjects randomised to Norditropin® FlexPro® will continue the treatment with Norditropin® FlexPro® ([redacted] mg/kg/day) until week 156, when they will be switched to NNC0195-0092 ([redacted] mg/kg/week).

After completion of the long-term safety extension (364 weeks), cohort I subjects in countries where NNC0195-0092 is not available for prescription will be offered to continue the trial and receive treatment with NNC0195-0092, [redacted] mg/kg/week until NNC0195-0092 becomes available for prescription in the subject's respective country or until August 2024 (expected last end-of-treatment visit for cohort I) at the latest. Novo Nordisk will inform the sites when NNC0195-0092 is considered available for prescription for children with GHD in the respective countries. However, if the health authorities in the subject's country reject the marketing application, treatment with NNC0195-0092 will be stopped for the relevant subjects. If NNC0195-0092 is not approved and commercially available in the country treatment will continue until August 2024.

Subjects who remain on treatment in the extension period after completion of the long-term safety extension (364 weeks) should attend site visits according to the flowchart in Table 2-4. When NNC0195-0092 becomes available for prescription in a country, the treatment for subjects in that country will be discontinued, and end-of-treatment visit (visit 38) should be performed. The follow-up visit will take place 30 days after last treatment in the trial.

For the long-term safety extension period of the trial additional subjects will be enrolled (cohort II and III) and will be treated with [redacted] mg/kg/week NNC0195-0092.

Subjects in the weekly and daily dosing arms will be trained by the site staff in the use of the pen-injector and how to inject themselves with the trial drug. The first dose will be administered by the subject (at visit 2) under supervision of the site staff (Sections 2 and 8.10). The subsequent doses will be administered by the subject at home. The subject will be instructed to inject themselves in the thighs, dorsogluteal region (upper buttocks), upper outer triceps area (back of upper arm) or in the abdomen with rotation within these body areas for each injection. Body weight will be measured at all visits during the treatment period and will be used for dosing calculation. The maximum treatment duration for a single subject is 364 weeks. No maximum calculated dose is specified.

Subjects with body weight above 50 kilograms (110 pounds) who are randomised to NNC0195-0092 will need to have two injections at dosing due to the injection pen limitations. The volume of the injections should be equal, and the injection sites should be different.

Time of injections:

- Applicable for cohort I until visit 15: NNC0195-0092 should be injected in the morning no later than 10 AM to ensure consistency of PK/PD with previous trials. The trial drug can be injected by 12 PM (noon) on the clinic visit days. Trial drug must not be administered in the morning before relevant visit procedures have been performed (Sections 8.7.6 and 8.7.8). If a subject forgets to inject the dose in the morning, the subject must take the dose as soon as possible during the same day.
- Applicable for cohort I subjects after visit 15: NNC0195-0092 can be injected anytime during the dosing day.
- Applicable for cohort II and III: NNC0195-0092 can be injected anytime during the dosing day.
- Injections with NNC0195-0092 the day before blood sampling for anti-NNC0195-0092 antibodies must occur at least 12 hours prior to planned blood sampling.
- If the dose is not administered on the planned dosing day, the dose must then be administered as soon as possible after the missed planned dosing day.
- If the dose cannot be administered within 2 days after the planned dosing day, the dose should be skipped. The next dose afterwards should be taken on the originally planned weekday compared to baseline (randomisation).
- Subjects randomised to Norditropin® FlexPro® should inject s.c. daily in the evening (to reflect standard treatment practice) throughout the trial. Injections with Norditropin® FlexPro® the night before blood sampling for anti-hGH antibodies must occur at least 12 hours prior to planned blood sampling.
- If a subject randomised to Norditropin® FlexPro® forgets or is unable to inject the dose in the evening, the dose should be skipped. The subject should continue on the next evening with the next scheduled dose.

5.4 Treatment after discontinuation of trial product

No treatment with the trial drug 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 and/or treating physician.

5.5 Rationale for treatment

All doses will be administered s.c. because this is the approved route of administration of Norditropin® and the intended route of administration of NNC0195-0092 when marketed.

The dosing regimen is once-weekly for NNC0195-0092 as the compound is developed as a once-weekly therapy for children and adults with GHD to provide improved convenience/compliance over standard hGH administration, which must be dosed daily. A trial in healthy subjects (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. Norditropin® FlexPro® will be administered in the evening, following GH standard treatment practice [18].

The dose selection for NN8640-4172 is to use the totality of evidence including data from NN8640-4042 as well as modelling and simulation of IGF-I profile to select dose levels. The proposed NNC01095-0092 dose levels, [redacted] mg/kg/week, [redacted] mg/kg/week and [redacted] mg/kg/week, were selected as follows:

- [redacted] mg/kg/week. At this dose level the maximum IGF-I level for NNC0195-0092 is expected to match the average IGF-I level of [redacted] mg/kg/day Norditropin®.
- [redacted] mg/kg/week. At this dose level the average weekly IGF-I level for NNC0195-0092 is expected to match the average IGF-I level of [redacted] mg/kg/day Norditropin®.
- [redacted] mg/kg/week. At this dose level the average weekly IGF-I level for NNC0195-0092 is expected to exceed the average IGF-I level of [redacted] mg/kg/day Norditropin® but remain below 2 SDS.

The dose selection for the safety extension periods in the trial

NNC0195-0092 ([redacted] mg/kg/week) has been chosen for the safety extension trial period as this dose would provide the highest exposure safety wise of the three doses investigated in the first year of the trial and will most likely be the dose with the lowest risk of potential being inferior efficacy wise to daily hGH.

The daily Norditropin® FlexPro® arm continues in the 2 year safety extension trial period making it possible to compare safety and efficacy to once-weekly NNC0195-0092.

NNC0195-0092 ([redacted] mg/kg/week) has been chosen for all subjects for the long-term safety extension trial period to collect long-term safety data.

The fixed body weight based regimen has been chosen for this trial as it is standard practice for GH treatment of children with GHD in most countries and the dose for the daily GH comparator in this design is within the upper dose range in the approved labelling.

After the main trial partial data base lock (pDBL) the sponsor will become unblinded while the subjects and site staff will remain blinded with regards to NNC0195-0092 dose level allocation until end of the extension period of the trial. For the safety extension period and onwards all subjects will receive open-label treatment with NNC0195-0092 [redacted] mg/kg/week.

5.6 Dose reduction criteria

If adverse events with a probable relationship to the trial drug are persistent but allow continuation in the trial, as judged by the investigator, dose reduction in consecutive steps of 25% of the current dose can be considered at the investigator's discretion. If after consecutive dose reduction steps AEs still persist, the subject's treatment may be discontinued or the subject may be withdrawn according to treatment discontinuation (6.5.1) or withdrawal criteria (6.5.2).

6 Trial population

6.1 Number of subjects

6.1.1 Number of subjects (cohort I)

Number of subjects planned to be randomised: maximum 70

Number of subjects expected to complete the trial: 56

The trial is allowing for a 7% drop out rate.

6.1.2 Number of subjects (cohort II and cohort III)

Number of subjects planned to be enrolled in cohort II and cohort III in total is: up to approximately 30 subjects or until recruitment is closed 4 months prior to last patient last visit

6.2 Inclusion criteria and exclusion criteria for cohort I

6.2.1 Inclusion criteria (cohort I)

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

1. Informed consent of parent or legally acceptable representative (LAR) of subject and child assent, as age-appropriate 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.
    a. The parent or LAR of the child must sign and date the Informed Consent Form (according to local requirements).
    b. The child must sign and date the Child Assent Form or provide oral assent (if required according to local requirements).
2. Pre-pubertal children
    - Boys: Tanner stage 1 for pubic hair and testis volume < 4 mL [1], age ≥ 2 years and 26 weeks and ≤ 10.0 years.
    - Girls: Tanner stage 1 for breast development (no palpable glandular breast tissue) and pubic hair [1], age ≥ 2 years and 26 weeks and ≤ 9.0 years.
3. Confirmed diagnosis of GHD within 12 months prior to screening as determined by two different GH stimulation tests, defined as a peak GH level of ≤ 7.0 ng/ml. For children with three or more pituitary hormone deficiencies only one GH stimulation test is needed.
   FOR JAPAN ONLY: Confirmed diagnosis of GHD within 12 months prior to screening as determined by one GH stimulation tests for patients with intracranial organic disease or symptomatic hypoglycaemia and two different GH stimulation test for other patients, defined as a peak GH level of ≤ 6 ng/ml by assay using recombinant GH standard. **END OF TEXT ONLY APPLICABLE FOR JAPAN.**
4. No prior exposure to GH therapy and/or IGF-I treatment.

5. Height of at least 2.0 standard deviations below the mean height for chronological age (CA) and gender according to the standards of Centers for Disease Control and Prevention (CDC) 2-20 years: Girls/Boys stature-for-age and weight-for-age percentiles CDC [2] at screening.
6. Annualized height velocity (HV) at screening below the 25th percentile for CA and gender or below -0.7 SD score for CA and sex, according to the standards of Prader [3] calculated over a time span of minimum 6 months and maximum 18 months prior to screening.
7. Body Mass Index (BMI) percentile >5th and <95th percentile according to Centers for Disease Control and Prevention (CDC)[2] BMI-for-age growth charts.
8. IGF-I SDS < -1.0 at screening, compared to age and sex normalized range according to central laboratory measurements.
9. Bone age (X-ray of left hand and wrist, central reviewed according to Greulich & Pyle atlas[19]) less than chronological age at screening. An X-ray taken within 13 weeks prior to screening can be used as screening data if the image is available and meets requirements for central reading.

6.2.2 Exclusion criteria (cohort I)

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

1. Previous participation in this trial. Participation is defined as randomisation.
2. Receipt of any investigational medicinal product within 3 months before screening.
   FOR BRAZIL ONLY: Participation in other trials within one year (defined as 365 days) prior to screening visit (Visit 1) unless there is a direct benefit to the research subject at the investigator´s discretion. **END OF TEXT ONLY APPLICABLE FOR BRAZIL**

3. Any clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing measurements:
   - Chromosomal aneuploidy and significant gene mutations causing medical “syndromes” with short stature, including but not limited to Turner syndrome, Laron syndrome, Noonan syndrome, or absence of GH receptors.
   - Congenital abnormalities (causing skeletal abnormalities), including but not limited to Russell-Silver Syndrome, skeletal dysplasia.
   - Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
4. Poorly controlled or uncontrolled pituitary insufficiencies or primary hormonal deficiencies of other axes (e.g., thyroid-stimulating hormone/T4, adrenocorticotropic hormone/cortisol, and vasopressin deficiency) in children who have been on stable replacement therapy for less than 6 months for thyroid replacement therapy, and less than 3 months for other hormonal deficiencies prior to screening.
5. Children born small for gestational age (SGA - birth weight and/or birth length < -2 SD for gestational age).
6. Children diagnosed with diabetes mellitus or fasting blood glucose ≥126 mg/dl (7.0 mmol/L), or HbA1c ≥ 6.5% at screening, determined by central laboratory.
7. Current inflammatory diseases (e.g. but not limited to arthritis, inflammatory bowel diseases) requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.

8. Children requiring inhaled glucocorticoid therapy (e.g. asthma) at a dose of greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks within the last 12 months prior to screening.
9. Concomitant administration of other treatments that may have an effect on growth, e.g. but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).
10. Prior history or presence of malignancy and/or intracranial tumour.
11. Prior history or presence of active Hepatitis B and/or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B and Hepatitis C).
12. Clinically significant abnormal ECG at screening, as evaluated by investigator.
13. Any clinically significant abnormal laboratory screening tests, as judged by the investigator
14. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol.
15. The subject and/or the parent/LAR are likely to be non-compliant in respect to trial conduct, as judged by the investigator.

6.3 Inclusion criteria and exclusion criteria for cohort II **FOR SWEDEN AND INDIA ONLY** not applicable as no subjects will be enrolled into cohort II **END OF TEXT FOR SWEDEN AND INDIA ONLY**

6.3.1 Inclusion criteria (cohort II)

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

10. Informed consent of parent or legally acceptable representative (LAR) of subject. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial. The parent or LAR of the child must sign and date the Informed Consent Form (according to local requirements).
11. Age < 2 years and 26 weeks and a minimum bodyweight of 5 kg **at screening**.
12. Confirmed diagnosis of GHD, the GHD diagnosis must be confirmed by investigator according to local practice.
13. For GH treatment naïve subjects, no prior exposure to GH therapy and/or IGF-I treatment.
14. For GH treatment naïve subjects, IGF-I SDS < -1.0 at screening, compared to age and sex normalized range according to central laboratory measurements.

6.3.2 Exclusion criteria (cohort II)

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

16. Previous participation in this trial. Participation is defined as randomisation.
17. Receipt of any investigational medicinal product within 3 months before screening.
18. Any clinically significant abnormality likely to affect growth:
    - Chromosomal aneuploidy and significant gene mutations causing medical "syndromes" with short stature, including but not limited to Turner syndrome, Laron syndrome, Noonan syndrome, or absence of GH receptors.
    - Congenital abnormalities (causing skeletal abnormalities), including but not limited to Russell-Silver Syndrome, skeletal dysplasias.
    - Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
19. Poorly controlled or uncontrolled pituitary insufficiencies or primary hormonal deficiencies of other axes (e.g., thyroid-stimulating hormone/T4, adrenocorticotropic hormone/cortisol, and vasopressin deficiency) as judged by to investigator.
20. Children born small for gestational age (SGA - birth weight and/or birth length < -2 SD for gestational age).
21. Children suspected of or diagnosed with diabetes mellitus.
22. Current inflammatory diseases (e.g. but not limited to arthritis, inflammatory bowel diseases) requiring systemic corticosteroid treatment as judged by investigator.
23. Children requiring inhaled glucocorticoid therapy (e.g. asthma).
24. Concomitant administration of other treatments that may have an effect on growth, e.g. but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).
25. Prior history or presence of malignancy and/or intracranial tumour.

26. Prior history or presence of active Hepatitis B and/or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B and Hepatitis C).
27. Any clinically significant abnormal laboratory screening tests, as judged by the investigator.
28. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol.
29. The subject and/or the parent/LAR are likely to be non-compliant in respect to trial conduct, as judged by the investigator.

6.4 Inclusion criteria and exclusion criteria for cohort III FOR INDIA ONLY not applicable as no subjects will be enrolled into cohort III END OF TEXT FOR INDIA ONLY

6.4.1 Inclusion criteria (cohort III)

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

15. Informed consent of parent or legally acceptable representative (LAR) of subject and child assent, as age-appropriate 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.
    a. The parent or LAR of the child must sign and date the Informed Consent Form (according to local requirements).
    b. The child must sign and date the Child Assent Form or provide oral assent (if required according to local requirements).
16. Age:
    a. Girls: > 9.0 years and ≤ 17.0 years **at screening**.
    b. Boys: > 10.0 years and ≤ 17.0 years **at screening.**
17. Confirmed diagnosis of GHD
    a) for GH treatment naïve subjects, confirmed diagnosis within 12 months prior to screening as determined by two different GH stimulation tests, defined as a peak GH level of ≤ 7.0 ng/ml. For children with three or more pituitary hormone deficiencies only one GH stimulation test is needed. **FOR JAPAN ONLY:** Confirmed diagnosis of GHD within 12 months prior to screening as determined by one GH stimulation tests for patients with intracranial organic disease or symptomatic hypoglycaemia and two different GH stimulation test for other patients, defined as a peak GH level of ≤ 6 ng/ml by assay using recombinant GH standard. **END OF TEXT ONLY APPLICABLE FOR JAPAN.**
    b) for non-naïve, confirmed GHD diagnosis by investigator according to local practice.
18. For GH treatment naïve subjects, no prior exposure to GH therapy and/or IGF-I treatment.
19. Body Mass Index (BMI) percentile >5^{th} and <95^{th} percentile according to Centers for Disease Control and Prevention (CDC)-BMI-for-age growth charts.

20. For GH treatment naïve subjects, IGF-I SDS < -1.0 at screening, compared to age and sex normalized range according to central laboratory measurements.
21. For GH treatment naïve subjects bone age (X-ray of left hand and wrist, central reviewed according to Greulich & Pyle atlas[19]) less than chronological age at screening. An X-ray taken within 13 weeks prior to screening can be used as screening data if the image is available and meets requirements for central reading.
22. Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.

6.4.2 Exclusion criteria (cohort III)

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

30. Previous participation in this trial. Participation is defined as randomisation.
31. Receipt of any investigational medicinal product within 3 months before screening.
32. Any clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing measurements:
    - Chromosomal aneuploidy and significant gene mutations causing medical “syndromes” with short stature, including but not limited to Turner syndrome, Laron syndrome, Noonan syndrome, or absence of GH receptors.
    - Congenital abnormalities (causing skeletal abnormalities), including but not limited to Russell-Silver Syndrome, skeletal dysplasias.
    - Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
33. Poorly controlled or uncontrolled pituitary insufficiencies or primary hormonal deficiencies of other axes (e.g., thyroid-stimulating hormone/T4, adrenocorticotropic hormone/cortisol, and vasopressin deficiency) as judged by investigator
34. Children born small for gestational age (SGA - birth weight and/or birth length < -2 SD for gestational age).
35. Children diagnosed with diabetes mellitus or fasting blood glucose ≥126 mg/dl (7.0 mmol/L), or HbA1c ≥ 6.5% at screening, determined by central laboratory.
36. Current inflammatory diseases (e.g. but not limited to arthritis, inflammatory bowel diseases) requiring systemic corticosteroid as judged by the investigator
37. Children requiring inhaled glucocorticoid therapy (e.g. asthma) at a dose of greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks within the last 12 months prior to screening.
38. Concomitant administration of other treatments that may have an effect on growth, e.g. but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).
39. Prior history or presence of malignancy and/or intracranial tumour.
40. Prior history or presence of active Hepatitis B and/or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B and Hepatitis C).
41. Clinically significant abnormal ECG at screening, as evaluated by investigator.
42. Any clinically significant abnormal laboratory screening tests, as judged by the investigator
43. Any disorder which, in the opinion of the investigator, might jeopardise subject’s safety or compliance with the protocol.
44. The subject and/or the parent/LAR are likely to be non-compliant in respect to trial conduct, as judged by the investigator.

45. A positive pregnancy test at screening (only applicable for female subjects that have had menarche).

6.5 Treatment discontinuation of trial product and withdrawal criteria

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

A subject who does not fulfil the eligibility criteria (inclusion/exclusion criteria) must not be enrolled. Enrolment in violation of any of the eligibility criteria is GCP non-compliance and must be reported to the sponsor without delay. This will be handled as an important protocol deviation, and the IEC/IRB and regulatory authorities must be notified according to local requirements. If there are no safety concerns, trial treatment may be continued for cohort II and III subjects or resumed at the discretion of the investigator after agreement with the sponsor's global medical expert.

If any of the below treatment discontinuation or withdrawal criteria apply, treatment may or must be discontinued or the subject may or must be withdrawn (Sections 8.3.3 and 8.3.4).

6.5.1 Treatment discontinuation criteria

1. The subject may discontinue treatment at any time at will.
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. Development of neutralising antibodies to NNC0195-0092 defined by 2 consecutive samples found positive for in vitro neutralising antibodies (or positive for high titer binding antibodies) and clinically relevant impact on efficacy and/or safety as described in section 8.7.6.
5. A subject included in violation of the inclusion/exclusion criteria must discontinue treatment (only applicable for cohort I) with trial product and will be followed as described in section 8.3.3.
6. A condition cited in the exclusion criteria develops (only applicable for cohort I until visit 15).
7. Pregnancy
8. Intention of becoming pregnant
9. Intention of fathering a child
10. Near adult height is reached (Near adult height (NAH) is defined as HV below 2 cm/year calculated over a period of at least 9 months AND for males: have reached a bone age of above or equal to 16 years; for females: have reached a bone age of above or equal to 14 years). If bone age is not available, then NAH is defined as HV below 2 cm/year calculated over a period of at least 9 months AND a chronological age of ≥17 years for males and a chronological age of ≥15 years for females.
11. Tumour development

6.5.2 Withdrawal criteria

The subject may withdraw at any time either by the will of the subject or by the parent or LAR. The subject's request to discontinue must always be respected.

1. 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 from the trial if the following applies:

2. Participation in another clinical trial.

6.6 Subject replacement

Subjects, in whom GH treatment is discontinued or withdrawn, will not be replaced.

6.7 Rationale for trial population selection

GH treatment naïve pre-pubertal children with GHD is the trial target population for treatment as this is a sensitive and well-known model for evaluating the primary endpoint; HV (cm/year) during 26-week of treatment. Paediatric patients with GHD are the target population for the primary indication of NNC0195-0092 treatment.

In the main, extension and safety extension phase of the trial only pre-pubertal children (cohort I) will be enrolled to avoid interference of the pubertal growth spurt with the treatment effect. In order to collect safety data for all GH treated paediatric age groups with open epiphyses, enrolment of children < 2 years and 26 weeks at screening (cohort II) and > 9 years (girls)/ >10 years (boys) and ≤ 17 years (cohort III) with GHD is opened for the long-term safety extension period of the trial as well as the pre-pubertal children from cohort I.

Both boys and girls with GHD will be enrolled in this trial in order to obtain information on efficacy and safety of the drug in both genders. The recruitment/randomisation will be stratified according to age group and gender (only applicable for cohort I).

7 Milestones

Planned duration of recruitment period for cohort I, first subject first visit (FSFV) - last subject first visit (LSFV) is 9 months.

Planned duration of recruitment period for cohort II and III is from HA and IEC/IRB approval of amendment 9 until 4 months prior to last subject last visit or until the sponsor has determined that an adequate number of subjects have been recruited, whatever comes first.

End of trial is defined as last subject last visit (LSLV) of the follow up period.

Recruitment (cohort I):
The screening and randomisation rate will be followed closely via the Interactive Web Response System (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

Recruitment (cohort II and III):
The screening rate will be followed closely via the IWRS in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for the trial can start treatment with NNC0195-0092.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[20], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[21], the Food and Drug Administration Amendment Act (FDAAA)[22], European Commission Requirements[23-25] and other relevant recommendations or regulations.

The trial data will also be registered at Japan Pharmaceutical Information Centre Clinical Trial Information (Japic CTI). 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.

8 Methods and assessments

In order to safeguard the subjects and to prevent discomfort to the largest extent possible, the number of assessments and blood sampling for analysis during the trial will be kept to a minimum.

8.1 Visit procedures

Procedures and assessments for the scheduled visits are described in this section. The timing of assessments is outlined in the flow chart (Section 2).

If a site visit for some reason is not performed at the scheduled time point, the investigator should arrange for the site visit to be performed as soon as possible and within the scheduled visit windows. Date of visit and visit windows are calculated in relation to randomisation visit (visit 2).

The screening assessments can be performed at any time during the screening period (between visit 1 and 2) as long as all results are available prior to randomisation at visit 2.

At visits after randomisation where it is not possible to perform blood sampling on the actual visit day (e.g. if the child does not cooperate during blood sampling) the samples can be taken within a week from the actual visit. The sampling conditions (fasting or non-fasting) and timing of sampling in relation to trial drug administration, as described in section 8.2, should always be followed.

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 the information visit (visit 0) the subject will be provided with information regarding the trial and asked to sign the informed consent and child assent form. (Section 18.2, 18.3).

At the screening visit (visit 1), 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. Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. A screening session must be performed in the IWRS.

8.2 Timing of visits and blood sampling

For the main trial period all blood samples should be collected at the randomisation visit (visit 2) prior to first study drug administration. For cohort II and III subjects who are non-GH treatment naïve, blood sampling at visit 1 and 2 should take place at least 12 hours after the last GH injection. Treatment with marketed product for GHD should discontinue no later than 12 h prior to first trial drug treatment.

In order to assure correct timing of PK and antibody sampling in relation to study drug administration, the visits after randomisation should be scheduled within the allowed visit window according to section 2 and the instructions below. Blood samples should always be collected prior to study drug administration if the visit is on a planned dosing day.

For subjects treated with NNC0195-0092

Visit	Timing of visit
3	On a planned dosing day
4	On planned dosing day
5	1-4 days after dosing
6	On a planned dosing day
7	1-4 days after dosing
8	On a planned dosing day
9	1-4 days after dosing
10	On a planned dosing day
11	1-4 days after dosing
12	On a planned dosing day
13	1-4 days after dosing
14	On a planned dosing day
15	1-4 days after dosing
16[1]	For subjects who have started treatment with a marketed GH product blood sampling should take place at least 12 hours after the last injection.
18	On a planned dosing day
20*	1-4 days after dosing
24*	1-4 days after dosing
28*	1-4 days after dosing
32*	4-6 days after dosing
34	1-4 days after dosing
36	1-4 days after dosing
38	4-6 days after last dosing of trial product

[1] Subjects that discontinue treatment early should perform the follow-up visit at least 7 days after treatment discontinuation.
*Also applicable for subjects enrolled in cohort II and III.

For subjects randomised to Norditropin® FlexPro® visits should be planned according to section 2 and 5.3.

8.3 Handling of screening failures and treatment discontinuation

8.3.1 Screening failures

If the subject is found to be not eligible to participate in the trial, the subject will be considered a screening failure.

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

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

8.3.2 Re-screening and re-sampling

Re-screening of subjects is allowed ONLY if the screening window of 21 days between visit 1 and 2 is exceeded and the subject was eligible for randomisation. No separate informed consent or child assent is required. At re-screening the subject will receive a new subject ID and all screening assessments and laboratory samples must be repeated except the X-Ray for Bone Age assessment if performed according to section 8.6.5. Re-screening is only allowed once.

Re-sampling is ONLY allowed during an unscheduled visit (Section 8.11) if samples are lost or damaged before arriving at the analysing laboratory, or the analysis failed at the laboratory. In case of re-sampling the blood volume to be drawn must be considered. (Section 8.7).

Re-sampling or Re-screening is not allowed if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters.

8.3.3 Treatment discontinuation

If a subject discontinues treatment with trial product, the investigator must aim to keep the subject in the trial following the normal visit schedule. A treatment discontinuation session must be made in the IWRS and it must be specified in the End of Trial form in the eCRF if the subject will discontinue treatment and participate in subsequent visits or withdraw from the trial.

The following assessments are not applicable for subjects that discontinue treatment with trial product but continue in the trial: Trial drug administration, pharmacokinetics assessments of NNC0195-0092 and Norditropin®, collection of technical complaints and the patient reported outcome questionnaires (only applicable for cohort I) related to treatment burden and preference: Treatment Burden Measure – TB-CGHD-O and TB-CGHD-P and GH-PPQ.

Final drug accountability must be performed. The subject can be switched to a suitable marketed product as described in section 5.4. The new medication should be recorded on the concomitant medication form in the eCRF,

Patients that are discontinued from trial product should return the electronic diary at their next contact to the site.

If a subject discontinues treatment before or at visit 5 a follow-up visit (similar to visit 16) should be performed at least 7 days after the end of treatment visit. The subject should only be followed until visit 7. At visit 7 the subject should be withdrawn and the reason for withdrawal “treatment discontinued before or at visit 5” should be entered in the eCRF.

Subjects that discontinue treatment after visit 5 should be followed until the end of the safety extension trial period (visit 15) but should not attend the follow-up visit (visit 16). A follow-up visit (similar to visit 16) should be performed at least 7 days after end of treatment. If subjects discontinue treatment at visit 15, they should perform visit 16. Subjects that continue treatment after

visit 15 (attending the long-term safety extension period) should not attend visit 16 but continue with visit 17 after visit 15. Subjects that discontinue treatment after visit 15 in the long-term safety extension trial period, should come for a last follow-up visit at least 30 days after end of treatment.

For subjects in cohort I, who continue in the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024 at the latest, the following applies:

- Subjects should be treated with NNC0195-0092, [redacted] mg/kg/week until NNC0195-0092 is available for prescription in their country or until August 2024 at the latest.
- The assessments planned for the end of treatment visit defined in the flow chart for cohort I (extension until NNC0195-0092 is available for prescription, Table 2-4) should be performed at this visit.
- If X-ray and ECG were performed within 6 months prior to the end of treatment visit, these should not be performed at the end of treatment visit. The follow-up visit will take place 30 days after last treatment in the trial, as described in the flow chart (Table 2-4).

For subjects in cohorts II and III the following applies:

- Subjects should be treated with NNC0195-0092 until August 2024, at the latest.
- The end of treatment visit should be performed August 2024, at the latest.
- The assessments planned for the end of treatment visit defined in the flow chart for cohorts II and III (Table 2-5) should be performed at this visit.
- If X-ray and ECG were performed within 6 months prior to the end of treatment visit, these should not be performed at the end of treatment visit.

- The follow-up visit will take place 30 days after last treatment in the trial as described in the flow chart (Table 2-5).

8.3.4 Withdrawals

If the subject is withdrawn, the investigator must aim to perform procedures similar to those for the respective end of trial visit as soon as possible and the follow-up visit. If a bone age assessment was performed within the past 6 months prior to the end of trial visit the assessment should not be performed again.

A treatment discontinuation session must be made in the IWRS. 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. When data has been source data verified and all queries have been resolved, the case book must be signed by the investigator in the eCRF.

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

8.4 Subject related information

8.4.1 Demography

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

8.4.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at visit 1 or found as a result of a screening procedure.

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 according to section 12.2.

Medical history is a medical event that the subject has experienced in the past. At least history of GHD and other conditions that the investigator considers relevant to this trial must be recorded.

The following should be recorded in the eCRF:

- History of GHD:
  - Idiopathic or organic GHD
  - Diagnostic method (type of GH stimulation tests) and result of peak GH values (only if applicable)
  - Only required for cohort I and III: Standing height measured minimum 6 and maximum 18 months prior to screening. For cohort I this height measurement is used to assess inclusion criterion 6.
  - Parental height: standing height for both biological parents, either measured or reported (applies to visit 17)
- Concomitant illnesses
- Relevant medical history

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

8.4.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial product(s) which is taken during the trial, from screening (visit 1) to the last visit in the trial. Details of any concomitant medication must be recorded at visit 1. 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, frequency, route of administration, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to section 12.2. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

After randomisation (visit 2 for cohort II and III) the hormone replacement therapy can be adjusted according to section 8.7.3.

8.5 Assessments for efficacy

8.5.1 Body measurements

Body measurements will be assessed according to section 2. For children above approximately 2 years standing height should be measured, for children below the age of approximately 2 years, length measurement should be performed.

8.5.1.1 Standing height

For standing height measurements, European Medicines Agency (EMA) guideline[26] should be followed.

A manual for height measurement will be provided to the sites. The use of a calibrated wall mounted stadiometer is mandatory.

Standing height should be measured

- by a trained person blinded to treatment allocation (applicable up to and including visit 16 (week 156) for cohort I) and preferably the same person throughout the trial. Starting from the long-term safety extension (week 156−364), the person performing the height measurement is not required to be blinded, as all subjects are treated with NNC0195-0092 [redacted] mg/kg/week.
- preferably by using the same stadiometer
- at the same time (± 2 hours, compare to baseline-visit 2) of the day
- without shoes
- with 3 consecutive measurements
- measured in centimetres or inches and rounded to one decimal

The following will be recorded in the eCRF

- date and time of height measurement
- result of height measurement

Confirmation that height measurements have been performed by an independent and trained person should be documented in the subjects medical records.

8.5.1.2 Length measurement

Length should be measured

- in children up to approximately 2 years by preferably the same person throughout the trial
- preferably by using the same length board
- at the same time (± 2 hours, compare to visit 2)
- without clothes (including diaper) and shoes
- with 3 consecutive measurements
- measured in centimetres or inches and rounded to one decimal

8.5.1.3 Body weight

Body weight will be measured in kilogrammes (kg) or pounds (lb) with one decimal without shoes and wearing only light clothing.

Body weight should be measured preferably at the same time of the day and by using the same scale throughout the trial, if possible.

8.5.1.4 Body Mass Index (BMI)

BMI will be calculated at the screening visit (visit 1) using the eCRF.

8.5.2 Pubertal status according to Tanner staging

Pubertal status assessed by the Tanner staging in accordance with stages 1-5 [1] will be assessed [27] according to section 2.

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

Female subjects of childbearing potential and male subjects of reproductive age should if applicable be given age appropriate sexual counselling and instructed to use adequate contraceptive methods according to local regulations throughout the trial and until the last visit.

8.6 Assessments for safety

8.6.1 Adverse events

AEs should be assessed according to section 2.

Please refer to section 12 Adverse Events for more details.

8.6.2 Injection site reactions

Injection site reactions will be evaluated according to section 2 and more frequently if deemed necessary by the investigator.

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 investigator´s discretion”.

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

If an injection site reaction fulfils the criteria for an AE, it should be reported on the AE form according to section 12. Additionally, a specific injection site reaction form must be completed in the eCRF.

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

- Burning

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

In addition to reporting the injection site reaction on the AE form and on the injection site reaction form, digital photos must be taken of the injection site at the time of identification and hereafter as often as judged by the investigator. Should injection of trial product require more than one injection, all injection sites should be evaluated.

The photos should include trial ID, subject number, date of photo, actual time of photo (24h format) and a ruler for injection site measurement. Copies of all photos will be evaluated by an external dermatologist and subsequently transferred to Novo Nordisk.

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

8.6.3 Assessment in case of suspicion of severe systemic hypersensitivity

If trial product is discontinued as a consequence of suspicion of acute hypersensitivity reaction to the trial product, blood sampling for assessments of the following should be conducted: anti-NNC0195-0092 antibodies, anti-Norditropin® antibodies, and anti-NNC0195-0092 IgE antibodies and anti-Norditropin® IgE antibodies. Blood sampling should be performed at least 2 weeks after but no later than 4 weeks after the event. GH treatment is not permitted in this period.

In the event of suspected severe systemic hypersensitivity caused by the trial product it is recommended to test for tryptase (total and/or mature tryptase) within 3 hours of the reaction at the local laboratory. Moreover, a baseline tryptase measurement is necessary 1-2 weeks after the event due to inter-individual variation in tryptase baseline concentration. The baseline tryptase sample can be obtained at the same time the antibodies samples are drawn. "Tryptase concentrations (if measured) as well as results of anti-drug antibodies and IgE isotype antibodies should be included in the final SAE report.

8.6.4 Electrocardiogram (ECG)

A standard 12 lead ECG will be taken according to section 2.

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

If the ECG is evaluated as "abnormal, clinically significant" at screening, and judged by the investigator not to be relevant for exclusion of the trial, the finding will be recorded as a concomitant illness.

The ECG results must be dated and signed by the investigator to verify that the data have been reviewed.

If ECG results taken within the last 3 months are available for cohort II and III subjects, these may be used instead. ECG should only be taken in cohort II children if possible with reasonable effort.

8.6.5 X-Ray for bone age assessment

X-Rays of left hand and wrist for bone age (BA) assessment according to the Greulich and Pyle atlas [19] will be taken according to section 2. In cohort II bone age assessment should only be performed in children if it is standard practice at the site.

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

In order to evaluate eligibility of cohort I and III, the result of the central review of the screening X-Ray image must be available in order to evaluate inclusion criterion 9 (cohort I) or inclusion criterion 21 (cohort III) (Section 6.2).

FOR GERMANY ONLY: only x-rays taken as normal routine (with regards to dose, frequency and timing of x-rays) during diagnose and thereafter yearly during treatment will be used. No extra x-ray will be performed for the study. **END OF TEXT ONLY APPLICABLE FOR GERMANY.**

The overall process for image acquisition, transfer, central analysis, reporting of results and archiving is described in the Imaging manual prepared by the central imaging laboratory.

8.6.6 Physical examination

A physical examination of the following body systems will be performed according to section 2.

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

The investigator will evaluate the findings from the physical examination and classify them as 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. At the subsequent visits, any clinically significant worsening of physical examination findings from the screening visit will be recorded as an AEs (Section 12.2).

8.6.7 Vital Signs

Vital signs should be assessed seated, if possible, according to section 2:

- systolic blood pressure (mm/Hg) seated
- diastolic blood pressure (mm/Hg) seated
- pulse (beats per minute) seated

At screening visit vital signs outside reference ranges which in the investigator judgement are "abnormal, clinically significant" should be recorded as concomitant illness.

At the subsequent visits, any clinically significant worsening or any new clinically significant findings will be recorded as AE (Section 12.2).

8.7 Laboratory assessments

All laboratory analyses in this trial will be performed by the central laboratory contracted by Novo Nordisk unless stated otherwise for a single parameter.

A detailed description of assay methods, reference ranges, procedures for obtaining samples, handling, storage and shipment of the samples (including PK and antibody samples) are specified in the trial-specific laboratory manual provided by the central laboratory.

Samples will be coded in order to keep subject's identity anonymous.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

Laboratory results except for biomarkers (IGF-I and IGFBP-3), anti-drug antibodies and PK results will be made available to the investigator by the central laboratory. All pages of the laboratory reports must be reviewed, evaluated, dated and signed by the investigator in a timely manner after receipt. It must be specified by the investigator whether out of range results are clinically significant. Any clinically significant deterioration of a pre-existing condition as well as any new clinically significant signs or symptoms occurring hereafter must be reported as an AE in accordance with section 12.2.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Surveillance of laboratory safety data (with the exception of PK and anti-drug antibody data) will be performed by a medical specialist at least every 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 identified, the medical specialist will immediately inform the chairman of the Novo Nordisk safety committee.

All laboratory samples except antibody samples will be destroyed at the latest at the completion of the clinical trial report (CTR). Antibody samples may be retained until drug approval by FDA and EMA. The retained antibody samples may be used for further characterisation for antibody response towards drug if required by health authorities or for safety reasons see section 24.2.

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

Blood sampling volume

To consider the paediatric population included in the trial the volume of blood samples will be minimised, in accordance with the EMA[28] and FDA [29] guidelines. Instructions will be provided to the trial sites regarding blood sampling volume and prioritisation of samples. If trial sites as part of routine assessments perform additional blood draws, they must ensure that the blood sampling volume will not exceed the above requirements.

Especially for cohort II, it is recommended not to attempt venepuncture more than 3 times for the purpose of obtaining sufficient blood sampling.

Table 8-1 lists the blood volume required to be collected for the scheduled trial blood samples.

Table 8-1 Approximate blood volumes collected during the trial

Visit (cohort I)	mL (cohort I)	Visit (cohort II and III)	mL (cohort II and III)
Visit 1(-3- 2weeks)	11.0	Screening visit	11.0
Visit 2	5.0	Visit 2	5.0
Visit 3	5.0	NA	NA
Visit 4	8.0	NA	NA
Visit 5	11.6	NA	NA
Visit 6	8.0	NA	NA
Visit 7	11.6	NA	NA
Visit 8	5.0	NA	NA
Visit 9	12.0	NA	NA
Visit 10	5.0	NA	NA
Visit 11	12.0	NA	NA
Visit 12	5.0	NA	NA
Visit 13	12.0	NA	NA
Visit 14	5.0	NA	NA
Visit 15	12.0	NA	NA
Visit 16[(1)]	3.0	NA	NA
Visit 18	11.0	Visit 18	11.0
Visit 20	11.6	Visit 20	11.6
Visit 22	11.0	Visit 22	11.0
Visit 24	11.6	Visit 24	11.6
Visit 26	11.0	Visit 26	11.0
Visit 28	11.6	Visit 28	11.6
Visit 30	11.0	Visit 30	11.0
Visit 32	11.6	Visit 32	11.6
Visit 34	11.0		
Visit 36	11.6		
Visit 38	11.6		
Total volume collected during the trial	**221.6[2]** **Up to 255.8[3]**	**Total maximum volume collected during the trial**	**106.4**

[1] Subjects that discontinue early should perform the follow-up visit at least 7 days after discontinuation.
[2]Only applicable for subjects completing the trial after 364 weeks.
[3]Only applicable for subjects continuing until NNC0195-0092 is available for prescription for children with GHD, or until August 2024, at the latest.

If available, local guidelines on blood sampling volumes for children should be followed otherwise the blood volume to be collected at each blood sampling visit should not exceed 1% of the subject's total blood volume. The blood volume to be collected over a period of 4 weeks should not exceed 3% of the subject's total blood volume Table 8-2.

For children weighing less than 15 kg blood sampling at visits requiring higher blood volumes than allowed, the blood sampling can be split into two different occasions with maximum one week apart. The sampling conditions (fasting or non-fasting) and timing of sampling in relation to study drug administration should always be followed.

Table 8-2 Estimated total blood volumes and maximum blood sampling volumes according to EMA guidelines.

Body weight kilogrammes (kg)	Total blood volume 80 mL/kg	Maximum blood sampling volume at any single occasion (mL)1%	Maximum blood sampling volume within 28 days (mL) 3 %
5	400	4	12
10	800	8	24
15	1200	12	36
20	1600	16	48
25	2000	20	60
30	2400	24	72
35	2800	28	84
40	3200	32	96
45	3600	36	108
50	4000	40	120

Investigator must ensure that the collected blood volume is appropriate in relation to weight of the subject. In case of re-sampling only the affected blood sample(s) should be collected and the investigator must ensure that the blood volume limit is not exceeded.

8.7.1 Biochemistry

The following will be assessed according to section 2.

- Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Bilirubin (total)

- Calcium (total)
- Creatinine
- Phosphate
- Potassium
- Sodium
- Chloride
- Uric acid
- Total protein
- Albumin
- Creatine Kinase
- Alkaline Phosphatase (AP)

GFR (glomerular filtration rate) estimated a derived variable based on s-creatinine and multiplication factors for race and sex, will be calculated by the central laboratory.

8.7.2 Haematology

The following will be assessed according to section 2.

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Mean corpuscular volume (MCV)
- Thrombocytes
- Mean corpuscular haemoglobin concentration (MCHC)
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

8.7.3 Hormones

The following will be assessed according to section 2.

- Cortisol
- Free T3
- Free T4
- Thyroid Stimulating Hormone (TSH)

After enrolment if one or more of these parameters are out of normal range, subjects should either receive replacement therapy and/or be adjusted as per investigator discretion.

8.7.4 Glucose Metabolism

The following will be assessed according to section 2.

- Fasting insulin
- Fasting plasma glucose
- HbA1c (glycosylated haemoglobin)

Subjects in cohort I and III must be fasting for at least 8 hours before sample collection, only water is allowed. Subjects in cohort II (age ≤ 2½ years) must be fasting for approximately 4 hours before sample collection, only water is allowed. If the samples are taken in a non-fasting state this needs to be recorded in the eCRF.

8.7.5 Lipids

The following will be assessed according to section 2.

- Cholesterol (total)
- HDL cholesterol
- LDL cholesterol
- Triglycerides

Subjects in cohort I and III must be fasting for at least 8 hours before sample collection, only water is allowed. Subjects in cohort II (age ≤ 2½ years) must be fasting for approximately 4 hours before sample collection, only water is allowed. If the samples are taken in a non-fasting state this needs to be recorded in the eCRF.

8.7.6 Anti-drug antibodies

Anti-drug antibodies samples will be collected according to section 2. All samples must be drawn prior to trial drug administration if trial drug administration is planned on the sampling day. Antibody sampling for subjects who have started treatment with a marketed GH product should take place at least 12 hours after the last injection.

The analysis of NNC0195-0092 and Norditropin® antidrug antibody samples will be performed by special laboratories (see Attachment I and the laboratory manual for details).

All subjects who have had 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 no further follow-up is warranted. During the trial this will be covered by regular anti-drug antibody sampling and analyses, and after LSLV, the subjects will be requested to have blood samples drawn every 3 months for follow-up analyses.

The investigator will be informed, after a Novo Nordisk safety committee meeting of any positive antibody results in case of clinically relevant impact on efficacy and/or safety. The assessment of the impact on efficacy and safety is performed by Novo Nordisk safety committee (Section 12.7.1).

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

To evaluate the impact of antibody formation, results of antibody analyses will be compared to PK by collecting samples to assess serum concentrations of NNC0195-0092 after last dosing according to section 2.

8.7.6.1 Anti NNC0195-0092 antibodies

Determination of antibodies against NNC0195-0092 in subjects randomised to NNC0195-0092 will be performed by a special laboratory using a validated antibody binding assay. Confirmed anti-NNC0195-0092 antibody positive samples will be further tested for cross-reactivity to hGH and for in vitro neutralising effect and correlation to PK/PD.

8.7.6.2 Anti hGH antibodies

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

8.7.7 Biomarkers – IGF-I and IGFBP-3

The following will be assessed according to section 2.

- IGF-I
- IGFBP-3

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

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

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

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

8.7.8 Pharmacokinetics assessments of NNC0195-0092 and hGH

Blood samples for determination of PK assessments of NNC0195-0092/hGH will be taken according to section 2. All samples must be drawn prior to trial drug administration if this is planned on a sampling day. The bioanalysis of NNC0195-0092 and Norditropin® PK samples will be performed by special laboratories (see Attachment I and the laboratory manual for details).

8.7.8.1 NNC0195-0092 assay

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

8.7.8.2 hGH assay

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

8.7.9 Pregnancy test

For female subjects a urine pregnancy test will be performed locally at site if menarche occurs, if a menstrual period is missed or if deemed necessary by the investigator or required by local law. A positive urine pregnancy test should be followed by a confirmatory serum-hCG test at the central laboratory.

For female subjects enrolled into cohort III, that have had menarche, a urine pregnancy test must be performed at screening to evaluate eligibility.

8.8 Patient reported outcomes

8.8.1 Questionnaires (applicable for cohort I only)

To assess the full spectrum of impacts and burden of GHD treatment as well as overall improvements in these aspects different questionnaires have been included. The questionnaires will be supplied in a linguistically validated version in all languages relevant to this trial. The following questionnaires will be used and assessed according to section 2.

Two observer-reported outcome (ObsRO) versions to be completed by a parent/LAR:

- Treatment Related Impact Measure – Child-Growth Hormone Deficiency – Observer (TRIM-CGHD-O)
- Treatment Burden Measure – Child-Growth Hormone Deficiency – Observer (TB-CGHD-O)

One parent/LAR PRO version assessing the treatment burden on the parent/LAR. This questionnaire should be completed by a parent/LAR:

- Treatment Burden Measure – Child-Growth Hormone Deficiency – Parent/Guardian (TB-CGHD-P)

One questionnaire will be completed by parent/LAR for subjects who have been switched from Norditropin® to NNC0195-0092 when they entered the long-term safety extension trial period. They will complete the following questionnaire in the e-diary 4 weeks after the switch of trial product:

- Growth Hormone Patient Questionnaire-Parent/Guardian (GH-PPQ)

The questionnaires assessing treatment burden (TB-CGHD-O and TB-CGHD-P) will not be assessed at visit 2 since they are not applicable for treatment naïve subjects.

The PRO questionnaires will be self-administered questionnaires, to be completed by all participating parents or LAR, irrespective of subject's treatment arm without assistance of the site

personnel. The investigator or delegated staff is only allowed to fill in the headings of the questionnaires. Written instructions on how to complete the questionnaires will be provided. Parents or LARs who cannot complete the questionnaires themselves due to physical limitations may receive assistance with completion of the questionnaires from someone other than the site staff.

After completion the PROs must be reviewed by the site staff on the same day for potential AEs, including any overall change in health and concomitant medication. When reviewing questionnaires for AEs the investigator should not influence nor question on the content of the response. The review of the completed PRO questionnaires should be performed by the investigator or delegated staff and documented either on the front page of the documents and/or in the subject's medical records. If clarification of entries in the questionnaires is needed, the parent or LAR should be questioned and a conclusion made in the subject's medical record. Only the parent or LAR can make changes in the questionnaire.

Care should be taken not to bias the patient or LAR. Data from the questionnaires will be transferred into the eCRF by the investigator or delegated staff.

TRIM-CGHD-O

The Treatment Related Impact Measure – Child Growth Hormone Deficiency – Observer is a disease specific questionnaire which measures the impact of GH treatment on symptoms, physical health and social and emotional wellbeing of children (< 10 year for boys and < 9 years for girls) with GHD ref. TRIM-CGHD-O has 33 items and a total score as well as domain specific scores can be derived.

TB-CGHD-O

The Treatment Burden Measure – Child Growth Hormone Deficiency – Observer is a disease specific questionnaire which measures the physical burden of GH treatment as well as the burden of growth hormone treatment on emotional wellbeing and interference in daily life activities of children (< 10 years for boys and < 9 years for girls) with GHD.TB-CGHD-O has 17 items and a total score as well as domain specific scores can be derived.

TB-CGHD-P

The Treatment Burden Measure – Child Growth Hormone Deficiency – Parent/Guardian is a disease specific questionnaire which measures the burden of GH treatment on the emotional wellbeing of the parent/guardian as well as the interference in daily life activities of the parent/guardian. The TB-CGHD-P has 15 items and a total score as well as domain specific scores can be derived.

GH-PPQ
The Growth Hormone Patient Preference Questionnaire (GH-PPQ) is a disease specific questionnaire which measures the patient's growth hormone treatment preference.

8.8.2 Diaries

At visit 2 the subjects will be provided with a diary device for electronic recording of data. The site staff will train the subject in the use of the diary device according to provided instructions.

The following information will be recorded in the diary.

- date, time and dose of injections of trial drug including any missed doses

Reminders will be available in the e-diary to remind the subject to record any medical problems and changes in medications and to discuss them with the investigator during site visits.

The investigator will assess whether the medical problem is to be considered an AE. If the medical problem is considered an AE, data should be recorded in the subject´s medical records and reported in the eCRF according to section 12.2. The investigator or delegated staff must report changes in concomitant medication changes into the subject's medical records and into the eCRF.

Review of diaries must be documented in the subject's medical records. If clarifications of entries are needed or discrepancies in the diary are discovered, the parent or LAR must be questioned, and a conclusion must be made in the subject's medical record. Care must be taken not to bias the subject.

The e-diary device will be returned by the subject at the end of treatment visit.

The overall process for handling diaries is described in a manual.

8.9 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 according to investigators judgement, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance:

Throughout the trial, the investigator will remind the subjects in a non-judgemental manner to follow the trial procedures and requirements to ensure subject compliance.
When subjects self-administer trial product at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit. If any suspicion of non-compliance arises the site must enter into a dialogue with the patient, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented.
Compliance will be assessed by cross checking the following sources and comparing these to the expected use:
Drug accountability information; counting returned trial product, visual inspection of pens, Review of dosing diaries and Questioning of subjects.

8.10 Training in trial product and pen handling

During visit 2 all subjects will be trained in the use of the pen-injector. After instruction the subject will administer the first injection under observation by the site staff. This can be preceded by injection with a training pen which can be administered by the subject into a pad or cushion (using a test pen is optional).

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

The following will be recorded in the eCRF:

- The subject has received training in use of the pen-injector and a step-by step instruction in administering a s.c. injection
- The subject has performed an injection on his/her own with corrective feedback provided by site staff

At visit 3 (visit 17 for cohort II and III) the site staff will follow up with the subject on the use of the pen-injector and injections administered at home.

8.11 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. Furthermore, unscheduled visits for re-sampling can take place if laboratory samples are lost or damaged before arriving at the analysing laboratory.

Visits/contacts to the site not related to the trial should not need to be reported as an unscheduled visit. Contacts for additional dispensing visits of trial drug as replacement for lost or damaged trial drug should not be recorded as unscheduled visits but need to be recorded in the IWRS.

8.12 Missing data

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

If an entire visit is missed and it is not possible to re-schedule the visit within the allowed time window, every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to visit schedule. In order to ensure subject has sufficient trial product until the next scheduled dispensing the subject must come in for an additional dispensing as soon as possible.

If a subject is unable/unwilling to attend the subsequent visit(s), procedures described in section 8.3.4 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.

9.1 Trial products

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

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
NNC0195-0092	[redacted] mg/[redacted] ml [redacted] mg/[redacted] ml [redacted] mg/[redacted] ml*	PDS290-10/ PDS290-15*	s.c.	Pen-injector
Norditropin® FlexPro®	[redacted] mg/[redacted] ml	FlexPro®	s.c.	Pen-injector

*: (only trial strength/dosage form available for the long-term safety extension)

NNC0195-0092 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. Trial product should not be shaken vigorously at any time.

Supply of trial product
Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Dispensing unit numbers (DUNs) will be distributed to the trial sites according to enrolment and randomisation.

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (Visit 2).

9.2 Labelling

Blinded labelled (main and extension trial period)

NNC0195-0092 PDS290 [redacted] mg/[redacted] ml PDS290-10/15 pen-injector will be visually identical

Open labelled (safety and long-term safety extension trial period)

Norditropin® FlexPro® [redacted] mg/[redacted] ml

NNC0195-0092 [redacted] mg/[redacted] ml PDS290-15 (for all subjects receiving NNC0195-0092 in safety extension and long-term safety extension trial period).

9.3 Storage

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
NNC0195-0092 [redacted] **mg/[redacted] ml**	Store in a refrigerator (2-8°C) Do not freeze Protect from light.	2-8°C in between Injections Do not freeze. Protect from light	Use within 6 weeks
NNC0195-0092 [redacted] **mg/[redacted] ml**			
NNC0195-0092 [redacted] **mg/[redacted] ml**			
Norditropin® FlexPro®	Store in a refrigerator (2-8°C) 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, and also 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 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. **END OF TEXT ONLY APPLICABLE FOR JAPAN.**

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.

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at randomisation and at each dispensing visit. The correct DUN(s) must be dispensed to the subject. The investigator or delegated staff personnel are responsible for ensuring that:

- Drug accountability for NNC0195-0092 or Norditropin® FlexPro® is performed on a DUN level using the IWRS drug accountability module to account for the status of each pen for each DUN.
- Subjects must return all used, partly used and unused trial product as instructed by the investigator.
- The DUNs will be recorded in a drug accountability log. The monitor will check the drug accountability.
- Destruction will be done according to local procedures after accountability is finalised and verified by the monitor.

Destruction of products must be documented in the IWRS.

9.5 Auxiliary supplies

Needles, NovoFine® (maximum 6 mm) provided by Novo Nordisk.

DFU:

NNC0195-0092 PDS290, for blinded and open-labelled trial drug

Norditropin® FlexPro®, for open-labelled trial drug

10 Interactive web response system

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation (only applicable for cohort I)
- Medication arrival
- Dispensing
- Treatment discontinuation
- Completion
- Code break (only applicable for cohort 1- main and extension phase)
- Drug accountability
- Documentation of destruction
- Data change

IWRS user manual will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes (only applicable for cohort I)

11.1 Randomisation

Sixty (60) subjects will be randomised in a 1:1:1:1 [redacted] mg/kg NNC0195-0092: [redacted] mg/kg: NNC0195-0092: [redacted] mg/kg NNC0195-0092: [redacted] mg/kg Norditropin®FlexPro®) manner to receive either NNC0195-0092 or Norditropin®FlexPro®.

The randomisation will be stratified by region (Japan versus RoW).

The randomisation within the RoW region will additionally be stratified according to

- sex (boys versus girls)
- age (< 6 years versus ≥ 6 years)

The randomisation, stratification and allocation to treatment arm will be handled by the IWRS (Section 10).

11.2 Breaking of blinded codes

In the 26 weeks main trail period and 26 weeks extension trial period the dose-levels of NNC0195-0092 will be double-blinded. The IWRS 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 IWRS, 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 IWRS is not accessible at the time of code break the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

Even if the code has been broken the subject can continue on trial product at the discretion of the investigator.

12 Adverse events and technical complaints and pregnancies

12.1 Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered 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.
- Abuse and misuse of trial product: Abuse is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm). Misuse is defined as: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol or the terms of the marketing authorisation.

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

- **Causality**

  Relationship between an AE and the relevant trial product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

    There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is important that the investigator always makes an assessment of causality for every event before the initial transmission of

the SAE data. The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Final outcome**
  - **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 serious adverse event (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] Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered

serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Note:

- Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.

- Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

[c] The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

[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.

Medication errors concerning trial products:

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

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 at screening (visit 1) until the end of the post-treatment follow-up period. 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:

- NNC0195-0092 IB current version or any updates hereof [15].
- Norditropin® FlexPro® IB current version or any updates hereof [18].

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 safety information form can be used to describe all the SAEs.

MESIs (medication errors) regardless of seriousness must be reported using both the AE form, the safety information form and a MESI form (medication error 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 safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.
  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

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

- **Non-serious AE fulfilling the MESI criteria (medication error):** The AE form, safety information form and MESI form (medication error form) **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 enter the information on the appropriate forms in the eCRF.

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

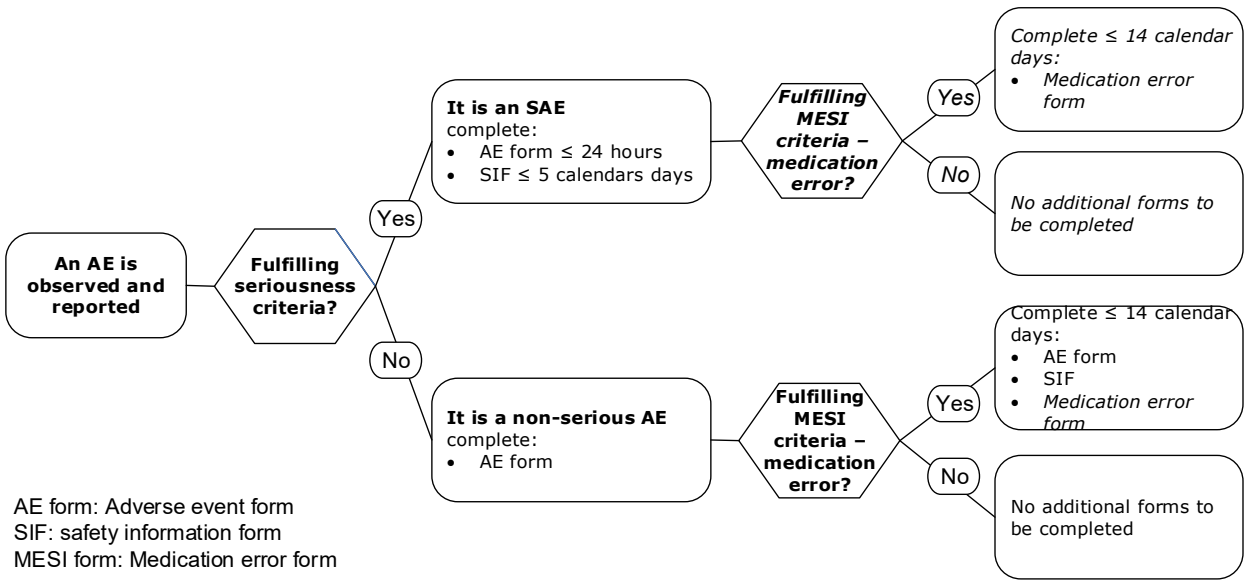

Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by Novo Nordisk:
Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP[4]. 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[4], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:

If a SAE and/or MESI is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow up information must be reported to Novo Nordisk according to the following:

- **SAEs**: All SAEs must be followed until the outcome of the event is “recovered/resolved”, “recovered/resolved with sequelae” or “fatal”, and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow-up period and is expected by the investigator to recover .The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

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

- **Non-serious AE fulfilling the MESI criteria:** Non-serious AE fulfilling the MESI criteria must be followed as specified for non-serious AEs. 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 and PDS290-10/PDS290-15 pen-injector
- Norditropin® FlexPro® [redacted] mg/[redacted] mL pen-injector
- Novo Nordisk Needles, Novo Fine®

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 Centre, 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. A technical complaint form for each batch, code or lot 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. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A 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, code or lot 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 (Section 9).

12.5 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).

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 newborn infant. If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and safety information form.

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

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.". At the last scheduled visit, male subjects must be asked if their female partner has become pregnant.

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

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

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

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

2. Reporting of AE information

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

Forms and timelines for reporting AEs:
Please see section 12.5, point 2, "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 newborn 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.

12.6 Precautions and/or overdose

At present, there is no experience of overdose with NNC0195-0092 in humans. In healthy male volunteers most common adverse events were: headache, peripheral oedema, joint pain, muscle pain and increase in blood sugar and insulin levels. In a trial in adults with GHD, the same safety profile of adverse events were registered.

These adverse events are similar to those observed for existing GH products on the market.

For further details please refer to IB[15].

Any accidental administration of a higher dose than intended meeting the defined criteria for an overdose described in section 12.1 should be reported as an AE.

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. 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.

12.7.2 Data monitoring committee

The Data Monitoring Committee (DMC) is established to review and evaluate accumulating data from an ongoing clinical trial in order to protect the safety of the subjects and to evaluate the evolving risk-benefit if required.

The DMC reviews independently blinded and unblinded safety information and provide recommendations to the safety committee according to a DMC Charter. The DMC is active during the 1-year main part (26 weeks main trial and 26 weeks extension trial period) and the 2-year safety extension trial period in agreement with the DMC Charter. After this safety extension trial period, the DMC activities cease and the safety of the trial subjects is followed by routine pharmacovigilance for clinical trial patients.

13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be provided by an external supplier.

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

The following will be provided as paper CRFs on no carbon required (NCR) paper:

- PRO questionnaires (TRIM-CGHD-O, TB-CGHD-O and TB-CGHD-P)
- Pregnancy forms (Maternal Form 1A, 1B, Maternal Form 2 and Paternal Form)

In addition NCR paper AE forms, safety information forms and technical complaints forms will be provided. These must be used if or 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

13.1.1 eCRF

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator's delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.1.2 PRO questionnaires

The site staff should not perform any entries on or corrections to the data recorded by the parents or LARs on the PRO questionnaires.

13.2 Case report form flow

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

Queries will be generated in the eCRF on an ongoing basis, and the investigator should resolve these queries on an ongoing basis. AE and technical complaint related queries and follow up requests from Novo Nordisk should be responded to within the timelines specified in section 12.

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 business days after the last subject´s last visit to the site. This is done in order to ensure the planned DBL is achieved.

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 (SDV) and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks. Starting from the long-term safety extension period, a monitoring interval up to 16 weeks can be accepted if no issues that need attention sooner have been identified. However, if no subject visit has taken place within these 12 weeks, the monitoring site visit may be postponed. If a site has no enrolled subjects, or only screen failed subjects and all subject data has been monitored and source data verified, the monitoring visit interval should be planned as relevant.

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 eCRF. The only exceptions are race and ethnicity which can be recorded directly in the eCRFs and will be considered source data.

Data recorded in the subject diary are considered source data with respect to:

- date, time and dose of injections including any missed doses

The data for medical problems and concomitant medication from the diary will only be considered as a reminder for both the subject and the investigator to discuss any medical problems or new medications during the site visits.

Historical growth data (e.g. growth charts), history of GHD including diagnosis and diagnostic method must be source data verifiable and reasonable efforts must be taken to acquire medical records from primary physicians or other hospitals and 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.

The monitor will ensure that the eCRFs are completed.

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 following data will be SDVd for screening failures:

- Date for obtaining informed consent
- Screen failure reason
- AE

Monitors must review the subject's medical records and other source data (e.g. the e-diary data uploaded to the trial database and PRO questionnaires) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

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

15 Data management

Data management is the responsibility of Novo Nordisk.

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

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

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

DBLs are planned during the trial, facilitating analysis of the 26 weeks main trial period, 52 weeks extension trial period and 104 and 156 weeks safety extension trial period the 364 weeks long-term safety extension period and the 'extension until NNC0195-0092 is available for prescription for children with GHD period' data. Further interim reporting may be performed in association with marketing authorisation application or in connection with Health Authorities e.g. FDA, EMA and PDMA requirement for/during the regulatory review. The final DBL will occur after the 208 week long-term safety extension trial period (368 weeks) is completed.

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 the first pDBL.

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

The one-sided test used for the primary endpoint is based on an alpha level of 2.5%. All other statistical tests conducted will be two sided on the 5% significance level. Age group is defined as a factor with 2 levels: <6 years ≥ 6years. No adjustment for multiple testing will be applied.

17.1 Sample size calculation

Sample size calculations (for cohort I) are based on an assumption of a standard deviation of 3.1 cm/year for HV after 26 weeks of treatment and the use of a delta value of -3.8 cm/year (where delta corresponds to the non-inferiority margin in a non-inferiority trial) and a one-sided significance level of 2.5%. This results in 15 subjects per treatment arm. Expecting at most 7% dropout during the trial, 15 subjects randomised per treatment arm should assure 87% power for getting a 95% confidence interval for the estimated treatment difference that lies completely above the chosen delta value when comparing a NNC0195-0092 treatment arm to the Norditropin® FlexPro® treatment arm, given that the two treatments are equal.

The addition of cohort II and III is based on a regulatory request from FDA and no formal sample size calculation was performed for these cohorts. The statistical considerations for cohort II and III can be found in section 17.3.2 and 17.4.3.

17.2 Definition of analysis sets

Three analysis sets are defined.

The Full analysis set (FAS) is defined as 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 treated”.

The Safety analysis set (SAS) is defined as all randomised subjects that received at least one dose of randomised treatment. Subjects will be analysed “as treated”.

The Per Protocol (PP) analysis set is defined as subjects from the FAS who have not violated any inclusion/exclusion criteria and have used the randomised treatment for at least 22 weeks (for subjects receiving NNC0195-0092) or 154 days (for subjects receiving Norditropin® FlexPro®) during the main trial period. Subjects will be analysed “as treated”.

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

17.3 Primary endpoint

17.3.1 Primary endpoint (cohort I)

Height velocity (HV) (cm/year) during 26 weeks of treatment.

Height is measured at baseline, 13 weeks and 26 weeks, and the primary endpoint is derived as:

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

For the intermediate visit, annualized HV at 13 weeks is derived similarly: (height at 13 weeks visit-height at baseline) / (time from baseline to 13 weeks visit in years).

The primary objective is to evaluate the efficacy of multiple dose levels of once-weekly NNC0195-0092 after 26 weeks of treatment in GH treatment naïve pre-pubertal children with GHD, compared to Norditropin® FlexPro® (once-daily hGH administration), and the primary analysis of the primary endpoint will be the primary tool for achieving this.

Primary analysis of the primary endpoint is based on the FAS.

Annualized HV at 13 and 26 weeks will be analysed using a mixed model for repeated measurements (MMRM), with treatment, age group, sex, region and sex by age group interaction term as factors and height at baseline as a covariate, all nested within week as a factor. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From the MMRM the treatment differences at week 26 between NNC0195-0092 treatment arms and Norditropin® FlexPro® will be estimated with the corresponding 95% CI. Subjects without post-randomisation HV data will not be included in the primary analysis.

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

17.3.2 Primary endpoint (cohort II and III)

The primary endpoint will be used to support the primary objective of evaluating safety of once-weekly NNC0195-0092 during up to 208 weeks of treatment in children with GHD:

• Incidence of adverse events, including injection site reactions

The primary endpoint will be analysed by cohort using descriptive statistics. All adverse events with onset after the first administration of trial product and up until end of trial visit or 14 days after last trial drug administration, whichever comes first, will be included in the analysis. Adverse events with onset 14 days or more after last trial drug administration will be reported in a separate listing.

17.4 Secondary endpoints

17.4.1 Supportive secondary efficacy endpoints (cohort I)

Changes from baseline to end of main trial period (week 26) in the following variables will be used to address the primary objective:

- Height standard deviation score (SDS)
- HV SDS
- IGF-I SDS
- IGFBP-3 SDS

Additionally, scores of the following PRO questionnaires will be used to address the secondary objective of investigating impact of NNC0195-0092 relative to Norditropin® FlexPro® on wellbeing, psychosocial functioning and treatment satisfaction in GH treatment naïve pre-pubertal children with GHD:

- Change from baseline to week 26 in TRIM-CGHD-O: Treatment Related Impact Measure – Child Growth Hormone Deficiency- Observer
- TB-CGHD-O: The Treatment Burden Measure – Child Growth Hormone Deficiency – Observer at week 26
- TB-CGHD-P: The Treatment Burden Measure – Child Growth Hormone Deficiency – Parent/Guardian at week 26

The secondary efficacy endpoints: change in height SDS, HV SDS, IGF-I SDS and IGFBP-3 SDS from baseline will be analysed using an MMRM similar to the MMRM used for the primary analysis of the primary endpoint with baseline assessment as covariate and treatment, age group, sex, region and sex by age group interaction term as factors, all nested within week as a factor. For the PRO based endpoints, this model corresponds to an analysis of variance with treatment, age group, sex, region and sex by age group interaction as factors. For change from baseline in TRIM-CGHD-O, the baseline score value is added to the model as a covariate.

Annualized HV at 39 weeks and at 52 weeks are derived analogous to the HV in the main trial period: (height at d weeks visit-height at baseline) / (time from baseline to d weeks visit in years), where d=39, 52.

Changes from baseline to end of extension trial period (week 52) in the above listed variables (except the two TB-CGHD PROs) will be used to support the secondary objective regarding evaluation of efficacy for up to 364 weeks of treatment and analysed analogously as above using an MMRM based on assessments 13, 26, 39 and 52 weeks (26 and 52 weeks for the PRO based endpoints). From the MMRM the treatment differences at Week 52 between NNC0195-0092 treatment arms and Norditropin® FlexPro® will be estimated with the corresponding 95% CI.

- HV (cm/year) at week 52

HV and the two TB-CGHD PROs at week 52 will be analysed using an MMRM based on assessments 13, 26, 39 and 52 weeks (26 and 52 weeks for the 2 PRO based endpoints) with treatment, age group, sex, region and sex by age group interaction term as factors, all nested within week as a factor. For the analysis of HV, height at baseline will be included in the model as a covariate, also nested within week as a factor. From the MMRM the treatment differences at Week 52 between NNC0195-0092 treatment arms and Norditropin® FlexPro® will be estimated with the corresponding 95% CI.

Changes from end of main trial period (week 26) to end of extension period (week 52) in all of the above mentioned efficacy variables will also be used to support the secondary objective regarding evaluation of efficacy for up to 364 weeks of treatment and will be analysed using descriptive statistics.

- Bone age (X-Ray of left hand and wrist, central assessed according to Greulich & Pyle atlas)[19] progression vs. chronological age
- Serum NNC0195-0092 concentrations and changes throughout the trial

In addition, NNC0195-0092 serum concentrations and changes during the trial and bone age progression vs. chronological age at visit (week 52) will be analysed using descriptive statistics.

17.4.2 Supportive secondary safety endpoints (cohort I)

The following endpoints will be used to support the secondary objectives of evaluation of safety for up to 364 weeks of treatment:

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

Adverse events will be analysed using descriptive statistics. All adverse events with onset after the first administration of trial product and up until week 26 or 14 days after last trial drug administration, whichever comes first, 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, the number of events and rate. Adverse events will be listed by treatment and subject with information on severity, relationship to trial product and demographics. Similar tables will be done for adverse events with onset after the first administration of trial product and up until week 52 for the extension trial period and for adverse events with onset after the first administration of trial product and up until week 104 and 156 , respectively, for the safety extension, and for adverse events with onset after the first administration of trial product and up until week 260 and 364 for the long-term safety extension trial period and follow-up period analysis.

Adverse events with onset 14 days or more after last trial drug administration will be reported in a separate listing. Adverse events with onset before first dosing will be reported in a separate listing.

All other safety endpoints will be analysed using descriptive statistics.

17.4.3 Other analyses

Efficacy

For cohort I, in the first year of the safety extension trial period the derivation formula for HV is: (height at 104 weeks visit-height at 52 weeks visit) / (time from 52 weeks visit to 104 weeks visit in years).

For HV in the second year of the safety extension trial period the derivation formula is: (height at 156 weeks visit - height at 104 weeks visit) / (time from 104 weeks visit to 156 weeks visit in years).

For HV in the first year of long-term safety extension trial period the derivation formula is: (height at 208 weeks visit-height at 156 weeks visit) / (time from 156 weeks visit to 208 weeks visit in years).

For HV in the third year of the long-term safety extension trial period the derivation formula is: (height at 312 weeks visit-height at 208 weeks visit) / (time from 260 weeks visit to 312 weeks visit in years).

For HV in the fourth year of the long-term safety extension trial period the derivation formula is: (height at 364 weeks visit-height at 312 weeks visit) / (time from 312 weeks visit to 364 weeks visit in years).

HV will be calculated for each year in the extension until NNC0195-0092 is available for prescription, in the same way as for the previous years.

For cohort II and III, HV at week 52 the derivation formula is: (height at 52 weeks visit-height at baseline (0 week visit 2) / (time from baseline (0 week visit 2) to 52 weeks visit in years).

For HV in the second year of the long-term safety extension trial period the derivation formula is: (height at 104 weeks visit-height at 52 weeks visit) / (time from 104 weeks visit to 52 weeks visit in years).

For HV in the third year of the long-term safety extension trial period the derivation formula is: (height at 156 weeks visit - height at 104 weeks visit) / (time from 104 weeks visit to 156 weeks visit in years).

For HV in the fourth year of the long-term safety extension trial period the derivation formula is: (height at 208 weeks visit-height at 156 weeks visit) / (time from 156 weeks visit to 208 weeks visit in years).

HV will be calculated for each year in the extension until NNC0195-0092 is available for prescription in the same way as for the previous years.

HV at week 52 (cohort II and III), 104, 156, 208, 260, 312, 364 (the latter for cohort I) and every year until the end of the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024 at the latest will be analysed using descriptive statistics.

Changes from baseline (week 0) in HV SDS, height SDS, IGF-I SDS and IGFBP-3 SDS to week *52* (cohort II and III), 104, 156, 208, 260, 312, 364 (the latter for cohort I) and every year until the end of the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024 at the latest will be analysed using descriptive statistics.

Near adult height (NAH) is defined as HV < 2 cm/year calculated over a period of at least 9 months AND for males: have reached a bone age of ≥16 years; for females: have reached a bone age of ≥14 years. If bone age is not available, then NAH is defined as HV < 2 cm/year calculated over a period of at least 9 months AND a chronological age of ≥17 years for males and a chronological age of ≥15 years for females. For subjects who have reached NAH in the long-term safety extension trial period the following variables will also be analysed using descriptive statistics: NAH SDS, change from baseline (week 0) to the year NAH is reached in height SDS, midparental target height SDS and index of genetic height potential (derived from midparental target height SDS and NAH SDS).

Bone age (X-Ray of left hand and wrist, centrally assessed according to Greulich & Pyle atlas)[19] progression vs. chronological age at week 104 and 156, 208, 260, 364 (the latter for cohort I) and every year until the end of the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024 at the latest will be analysed using descriptive statistics.

PRO data (cohort I):
Changes from baseline (week 0) in emotional well-being score, physical health score, social well-being core and total score from baseline to week 104, and 156, 208, 260, 312 and 364 in TRIM-CGHD-O (Treatment Related Impact Measure – Child Growth Hormone Deficiency- Observer) will be analysed using descriptive statistics.

Total score of TB-CGHD-O (The Treatment Burden Measure – Child Growth Hormone Deficiency – Observer) and total score of TB-CGHD-P (The Treatment Burden Measure – Child Growth Hormone Deficiency – Parent/Guardian) at week, 104 and 156, 208, 260, 312 and 364 will be analysed using descriptive statistics.

The scores of the PROs ranges from 0-100. A lower score indicates a better health state.

For subjects switching from Norditropin® to NNC0195-0092 GH-PPQ (The Growth Hormone Patient Preference Questionnaire-Parent/Guardian) at week 160 will be analysed using descriptive statistics. Answers are scored on a 5 levels scale from 'Not at all' to 'Extremely' or from 'Never' to 'All of the time'.

Safety

The following will be described using descriptive statistics for up to the end of the extension until NNC0195-0092 is available for prescription or August 2024 at the latest:

Incidence of technical complaints, including injection site reactions

Changes from baseline to week 26, 52, 104, 156, 260, 364 (the latter for cohort I) and every year until the end of the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024 at the latest in physical signs and vital signs

Changes from baseline to week 26, 52, 104, 156, 260, 364 (the latter for cohort I) and every year until the end of the extension until NNC0195-0092 is available for prescription for children with GHD or August 2024 at the latest in clinical safety laboratory parameters, including haematology,

biochemistry, hormones (e.g. fasting serum cortisol, thyroid function test), lipids, fasting glucose, fasting insulin, and HbA1c levels

17.5 Pharmacokinetics and/or pharmacodynamics modelling

If relevant, population PK and PK/PD modelling of IGF-I will be used to evaluate NNC0195-0092 exposure and exposure-response relationship to inform dose selection in future trials.

The objectives of these exploratory analyses are to:

- assess the dose-dependence of NNC0195-0092 exposure in serum
- explore the effects of covariates on NNC0195-0092 exposure
- explore the relationship between NNC0195-0092 exposure and response variables of interest, e.g. IGF-I and height velocity

The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and

will be reported separately from the CTR.

18 Ethics

In order to safeguard the subjects and to prevent discomfort to the largest extent possible, the number of assessments and blood sampling for analysis during the trial will be kept to a minimum. The visit intervals and assessments selected are similar to standard practice for GHD subjects.

All subjects included in the trial will receive active treatment with either NNC0195-0092 or Norditropin® FlexPro®.

The dose levels, [redacted] mg/kg, [redacted] mg/kg and [redacted] mg/kg, were selected as follows:

- [redacted] mg/kg. At this dose level the maximum IGF-I for NNC0195-0092 is expected to match the average IGF-I level of [redacted] mg/kg/day Norditropin®.
- [redacted] mg/kg. At this dose level the average weekly IGF-I for NNC0195-0092 is expected to match the average IGF-I level of [redacted] mg/kg/day Norditropin®.
- [redacted] mg/kg. At this dose level the average weekly IGF-I for NNC0195-0092 is expected to exceed the average IGF-I level of [redacted] mg/kg/day Norditropin® but remain below 2 SDS.

After the main trial pDBL Novo Nordisk will become unblinded to NNC0195-0092 dose levels. The results could indicate that the HV after 6 months NNC0195-0092 treatment is less when compared to HV after daily GH treatment, however, this might not be the case after 12 months NNC0195-0092 treatment (end of trial).

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

Within this trial, subjects in cohort I will be offered to continue treatment with NNC0195-0092, [redacted] mg/kg/week until NNC0195-0092 is available for prescription for children with GHD in the subject's respective country or until August 2024 (expected last end-of-treatment visit for cohort I) at the latest. However, if the health authorities in the subject's country reject the marketing application, treatment with NNC0195-0092 will be stopped for the relevant subjects. If the commercialisation of NNC0195-0092 is not possible in the country treatment with NNC0195-0092 will continue until August 2024. After a subject has finalised the trial, the subject will consult with the investigator to decide on the best available treatment.

18.1 Benefit-risk assessment of the trial

Please refer to section 3.1.6 for a description of the risks and benefits.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[4] and the requirements in the Declaration of Helsinki[5].

Before any trial-related activity, the investigator must give the subject and/or the subject's LAR verbal and written information about the trial and the procedures involved in a form that the subject or the subject's LAR can read and understand. This includes the use of an impartial witness where required according to local requirements.

The subjects or the subject's LAR 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 and/or the subject's LAR before any trial-related activity.

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

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

18.3 Child assent form

A minor´s choice to participate in a clinical trial is called "assent" as a child is not legally capable of giving consent. An assent means a child´s affirmative agreement to participate in research. The form that documents this agreement is called an "assent form".

In addition to parental consent/consent from LAR(s) assent from the child should be obtained if the child is old enough. A child assent form must be used to document the child´s affirmative agreement if applicable.
If the minor reaches legal age while participating in the trial and has only signed an age specific assent form, the subject has to re-consent to an informed consent form for subjects reaching legal age.

18.4 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 visit 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.

18.5 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 the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject may receive letters during the trial.

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

18.6 Premature termination of the trial and/or trial site

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

If 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 regulatory authorities and IRBs/IECs and provide a detailed written explanation.

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

19 Protocol compliance

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 master file and sponsor 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 (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- Local SmPC for Norditropin® FlexPro®
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- 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 the investigator at each site

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[4], applicable regulatory requirements and the Declaration of Helsinki[5].

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

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate 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 trial master file. The documents including the subject identification code list should be kept in a secure locked facility, so no unauthorized persons can get access to the data.

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

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

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

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

23 Reports and publications

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

One Principal Investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[18].

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[4].

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any

disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

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).

The investigator(s) offered authorship will be asked to comment on and approve the publication.

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

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

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

23.2 Investigator access to data and review of results

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

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 and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

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

24.2 Retention of human bio specimens

Antibody samples will be stored by Novo Nordisk or a designated laboratory until the trial has been evaluated by appropriate regulatory authorities (in EU or US) but no longer than maximum 15 years from 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 from subjects enrolled in Brazil will not be stored after the end of 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 Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the 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 trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

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

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

FOR AUSTRIA ONLY: Arzneimittelgesetz (BGBI. Nr 185/1983) last amended with BGBI Nr 59/2018

FOR GERMANY ONLY: 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 Mitigations to ensure participant safety and data integrity during an emergency situation

27.1 Definition and scope of section

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives.

In case local restrictions due to a major emergency (e.g., health outbreak, hurricanes, floods) lead to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this section based on mutual agreement.

According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency section are activated.

This section indicates the minimum requirements for assessments that should be performed during a lock-down, but sites should always try to follow the assessments outlined in the original flow chart (Section 2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines if they are issued.

27.2 Visits

Screening (Visit 1) and randomisation/baseline (Visit 2) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new participants at that site should be on hold until on-site visits are possible.

On-site visits can be converted to remote visits (video, phone or similar) or home or off-site visits.

27.3 Assessments

Assessments used for safety or the confirmatory endpoints (i.e., Height measurements, x-ray, IGF-I and PRO questionnaires) should be prioritised.

Height measurements are only to be performed during on-site visits.

Specifications regarding how to perform assessments using remote visits or as home visits will be provided by Novo Nordisk or the vendor engaged by Novo Nordisk, if relevant. Specifications will include training for staff performing remote assessments.

Local laboratories or diagnostic facilities can be used for blood sampling, x-ray and ECG at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Findings for these assessments should only be reported in the CRF if they meet the definition of an AE (refer to Section 12).

Home measurements of weight for dosing calculations cannot be performed if on-site visits are not possible and mitigation measures should be mutually agreed between Novo Nordisk and the investigator if two consecutive weight measures are missed.

If the assessments for safety and supportive endpoints cannot be performed as outlined above, they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

27.4 Trial drug

Alternative dispensing methods of trial drug may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

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