Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02527200
Sponsor trial ID:	NN8022-4179
Official title of study:	Effect of liraglutide for weight management in paediatric subjects with Prader-Willi Syndrome
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*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol – amended edition

Trial ID: NN8022-4179

Effect of liraglutide for weight management in paediatric subjects with Prader-Willi Syndrome

A randomised, placebo controlled, parallel group, multi-centre, multi-national trial with a 16-week double-blind period and 36-week open-label period

Trial phase: 3a

Applicable to all countries

Protocol originator

[redacted], Senior Trial Manager

1569, TrialOps Obesity & Metabolism 1

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	*Date*	*Applicable in country(-ies) and/or site(s)*
Protocol version 5.0	16 July 2020	All countries
Protocol version 4.0	16 March 2020	All countries
Protocol version 3.0	22 December 2017	All countries
Protocol version 2.0	28 August 2015	All countries
Original protocol version 1.0	30 April 2015	All countries

1. Protocol version 5 (16 July 2020)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[65].

2. Overall rationale for preparing protocol, version 5.0:

The protocol is amended to align the number of subjects among protocol sections 1 (Summary), 6.1 (Number of subjects), 6.6 (Subject replacement) and 17.1 (Sample size calculation).

Section # and name	*Description of change*	*Brief rationale*
1 – Summary	The number of subjects is updated as following: • Approximately 57 subjects to be randomised, 33 in part A and 24 in part B • Evaluable subjects part A: at least 28 • Evaluable subjects part B: at least 17	To update protocol section 1 with the Paediatric Investigational Plan modification approved in 04-Dec-2019 and to provide a consistent accurate estimate of the number of randomised and evaluable subjects, across all protocol sections, as required by the Italian Health Authority
6.1 – Number of subjects	The number of subjects planned to be randomised is updated to 57 in total, divided into 33 for part A and 24 for part B. The number of maximum subjects to be randomised is removed.	To align the protocol section 6.1 – the number of planned randomised subjects – with the statistical calculation for sample size described in protocol section 17.1
6.6 – Subject replacement	The split of the number of evaluable subjects per age group is updated as following: • Part A: evaluable number of subjects is increased • Part B: evaluable number of subjects is reduced	To update protocol section 6.6 with the Paediatric Investigational Plan modification approved in 04-Dec-2019 and to provide a consistent accurate estimate of the number of evaluable subjects across all protocol sections, as required by the Italian Health Authority
17.1 – Sample size calculation	The planned number of randomised subjects is updated, as well as the respective treatment difference. Table 17-2 (Overview of randomised subjects) is also updated with more accurate numbers.	To update the protocol section 17.1 with the Paediatric Investigational Plan modification approved in 04-Dec-2019 and to provide a consistent accurate estimate of the number of randomised and evaluable subjects across all protocol sections, as required by the Italian Health Authority

Table of Contents

Table of Figures

Page

Table of Tables

Page

List of abbreviations

ACTH	adrenocorticotropic hormone
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
BMI	body mass index
BOCF	baseline observation carried forward
CEA	carcinoembryonic antigen
CLAE	clinical laboratory adverse event
CL/F	apparent clearance
CPK	creatine kinase
CRF	case report form
C-SSRS	columbia suicidality severity rating scale
DHEAS	dehydroepiandrosterone sulfate
DMC	data monitoring committee
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose

FSH	follicle stimulating hormone
FU	follow up
GCP	Good Clinical Practice
GH	Growth
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high density lipoprotein
IB	Investigator's Brochure
hsCRP	high sensitivity C reactive protein
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IGF-1	insulin-like growth factor-1
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intention-to-treat
IV/WRS	interactive voice/web response system
LAR	legally acceptable representative
LDL	low density lipoprotein
LH	luteinizing hormone
LOCF	last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
MAP	modelling analysis plan
MedDRA	Medical Dictionary for Regulatory Activities
MHP	mental health professional
MESI	medical event of special interest
MI	multiple imputation
MMRM	mixed model for repeated measurements

MTD	maximum tolerated dose
NRS	numerical rating scale
PD	pharmacodynamic
PDCO	paediatric committee
PHQ-9	patient health questionnaire 9
PG	plasma glucose
PK	pharmacokinetics
PRO	patient reported outcome
PWS	Prader-Willi Syndrome
SAE	serious adverse event
s.c.	subcutaneous(ly)
SDS	standard deviation score
SDV	source data verification
SIF	safety information form
SMBG	self-measured blood glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TMM	trial materials manual
TPD	trial product discontinuation
TSH	thyroid stimulating hormone
UTN	universal trial number
V	visit
V/F	apparent distribution volume
WD	withdrawal

1 Summary

Objectives and endpoints:

Primary objective

To compare the efficacy of liraglutide versus placebo on weight loss in paediatric subjects with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.

Secondary objectives

- To compare the efficacy of liraglutide versus placebo on glycaemic control in children and adolescents with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.
- To estimate the liraglutide steady state exposure in children and adolescents with obesity and PWS after 16 weeks of treatment.
- To compare the safety of liraglutide versus placebo in children and adolescents with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.

Primary endpoints

There are two co-primary endpoints:
- Change in body mass index (BMI) standard deviation score (SDS) from baseline to 16 weeks
- Change in body mass index (BMI) standard deviation score (SDS) from baseline to 52 weeks

Key supportive secondary efficacy endpoints

- Percent of subjects achieving ≥ 5% reduction in baseline BMI at weeks 16 and 52
- Percent of subjects achieving ≥ 10% reduction in baseline BMI at weeks 16 and 52

Change from baseline to 16 and 52 weeks in:
- BMI
- Body weight (kilogram (kg), pounds (lb) and percent (%))
- Hyperphagia score:
  - total score and
  - hyperphagic behaviour, drive and severity score
- Systolic and diastolic blood pressure
- Glucose metabolism: glycosylated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG)

Trial design:

This is a multi-centre, multi-national randomised, parallel group, placebo-controlled trial with a 16-week double-blind period and a 36-week open-label period. This trial consists of a part A and a part B. Part A of the trial is conducted in adolescents (≥ 12 and < 18 years, Tanner stage 2−5) with obesity and PWS. Part B of the trial is conducted in children (≥ 6 and < 12 years, Tanner stage

below 2 (defined as Tanner stage 1 with or without premature adrenarche)) with obesity and PWS. Entry into part A and part B of the trial will be sequential. The randomisation will be stratified according to pubertal status (part A) and by presence/absence of dysglycaemia (Parts A and B). After all subjects in part A have completed the 16 week double-blind period, an independent external Data Monitoring Committee (DMC) will review the PK data and safety data from part A. The DMC will recommend to the Novo Nordisk safety committee whether children in part B should be randomised, and exposed to liraglutide/liraglutide placebo. In addition, the tolerability/safety and PK data from trial NN8022-4181 in children with obesity 7-11 years (both inclusive) will be reviewed to allow adjustments in part B.

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to that in the European Union (EU).

Trial population:

Approximately 57 subjects will be randomised 2:1 to receive liraglutide or liraglutide placebo. Approximately 33 subjects will be randomised in part A and 24 in part B.

The trial will continue until at least 45 evaluable subjects are included in total, divided as:

- Part A, at least 28 evaluable subjects
- Part B, at least 17 evaluable subjects
  - and of these subjects at least 5 need to be below 9 years of age.

Key inclusion criteria:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Confirmed diagnosis of PWS (by genetic testing)
- Male or female, age at the time of signing informed consent:
  - Part A: ≥ 12 and < 18 years
  - Part B: ≥ 6 and < 12 years
- Tanner stage 2−5 pubertal development for part A, and Tanner stage below 2 (defined as Tanner stage 1 with or without premature adrenarche) for part B
- BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points[1] and ≥ the 95th percentile for age and sex (for diagnosis of obesity)
- Stable body weight during the previous 90 days before screening (< 10 kg self-reported weight change)
- Testing has been performed to evaluate for adrenal insufficiency and documented in medical record

Key exclusion criteria

- Type 1 diabetes mellitus (T1DM)[2]
- Type 2 diabetes mellitus (T2DM)[2]
- Calcitonin ≥ 50 ng/L
- No change in treatment plan with growth hormone (GH) from randomisation to the end of the open-label period patients on growth hormone to stay on, patients off GH to stay off during this period. Adjustments in doses of growth hormone will be permitted)
- Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN2) or Medullary Thyroids Carcinoma (MTC)
- History of pancreatitis (acute or chronic)
- Treatment with any medication prescribed for weight loss within 90 days before screening (e.g. orlistat, zonisamide, topiramate/phentermine, lorcaserin, phentermine, bupropion/naltrexone, liraglutide, metformin)
- Untreated adrenal insufficiency
- Suggestive history of, or significant risk of gastroparesis (e.g. marked abdominal bloating post meal, history of vomiting, severe constipation), as judged by the Investigator

Assessments:

Efficacy

- Height
- Body weight
- Hyperphagia questionnaire
- Systolic and diastolic blood pressure
- HbA_{1c} and FPG

Pharmacokinetic

Area under the liraglutide plasma concentration - time curve (AUC)

Safety

- Adverse events
- Hypoglycaemia
- Anti-liraglutide antibodies

Trial product(s):

Liraglutide and liraglutide placebo are investigational trial products:

- Liraglutide 6.0 mg/ml, 3.0 ml, for s.c. injection with FlexPen®.
- Liraglutide placebo, 3.0 ml, for s.c. injection with FlexPen®.

2 Flow chart

Trial Periods	Screening	Screening	Randomisation	Dose escalation				Double blind treatment			Open-label treatment								End of treatment	Follow-up	TPD 16 week FU	TPD 52 week FU
Visit number	1[1]	2[1]	3	4	5	6	7	8	9	10[2]	11	12[3]	13	14[3]	15[3]	16	17[3]	18[3]	19	20	10x	19x
Timing of visit (weeks)	-2		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	54	16	52
Visit window (days)				±2	±2	±2	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-5	±5	±5
SUBJECT RELATED INFO/ASSESSMENTS																						
Informed consent and assents 18.2	x																					
In/exclusion criteria 6.2 6.3	x[12]	x	x																			
Discontinuation of trial product 6.4 8.1.8				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Withdrawal criteria 6.5 8.1.9				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Demography 8.3.1	x																					
Medical history and Concomitant illness[4] 8.3.2		x																				
History of psychiatric disorders 8.3.2.1		x																				
Concomitant medication 8.3.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Tobacco use 8.3.4		x																				

Trial Periods	Screening	Screening	Randomisation	Dose escalation				Double blind treatment			Open-label treatment								End of treatment	Follow-up	TPD 16 week FU	TPD 52 week FU
Visit number	1[1]	2[1]	3	4	5	6	7	8	9	10[2]	11	12[3]	13	14[3]	15[3]	16	17[3]	18[3]	19	20	10x	19x
Timing of visit (weeks)	-2		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	54	16	52
Visit window (days)				±2	±2	±2	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-5	±5	±5
Physical activity counselling 8.7.2.2			x	x	x	x	x	x[5]	x[5]	x	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x	x	x	x
Dietary counselling 8.7.2.1			x	x	x	x	x	x[5]	x[5]	x	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x	x	x	x
Dietary compliance 8.7.2.1				x	x	x	x	x[5]	x[5]	x	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x	x		
EFFICACY																						
Body weight 8.4.1.1		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Waist and hip circumference 8.4.1.2			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Hyperphagia questionnaire 8.4.2			x							x									x			
Systolic and diastolic blood pressure 8.4.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Lipids 8.4.4			x							x			x			x			x			
hsCRP 8.4.4			x							x			x			x			x			
Glucose metabolism 8.4.4		x	x							x			x			x			x			
SAFETY																						
Height 8.5.1		x	x							x			x			x			x		x	x
Adverse events 12		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes8.5.2 and SMBG 8.5.2.1			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			

Trial Periods	Screening	Screening	Randomisation	Dose escalation				Double blind treatment			Open-label treatment								End of treatment	Follow-up	TPD 16 week FU	TPD 52 week FU
Visit number	1[1]	2[1]	3	4	5	6	7	8	9	10[2]	11	12[3]	13	14[3]	15[3]	16	17[3]	18[3]	19	20	10x	19x
Timing of visit (weeks)	-2		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	54	16	52
Visit window (days)				±2	±2	±2	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-5	±5	±5
Pulse 8.5.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
ECG 8.5.4		x								x									x			
Pregnancy test[6] 8.5.5		x[6]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[6]			
First day of menstrual period 8.5.5.3			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Physical examination 8.5.6		x								x			x			x			x			
Biochemistry 8.5.7		x								x			x			x			x			
Haematology 8.5.7		x								x			x			x			x			
Hormones[7] 8.5.7			x							x			x			x			x			
Calcitonin 8.5.7		x								x			x			x			x			
Anti-liraglutide antibodies 8.5.8			x							x[8]									x[8,9]	x[9,11]		
Tanner staging 8.5.9		x								x[10]									x[10]			
PHQ-9 and C-SSRS (part A only) 8.5.10		x								x									x			
OTHER ASSESSMENTS																						
Liraglutide plasma concentration 8.7.1				x[8]	x[8]	x[8]		x[8]	x[8]	x[8]										X[9]		
TRIAL MATERIAL																						
Dispensing visit 9			x				x	x	x	x	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]				
Drug accountability 9.4							x	x	x	x	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]			

Trial Periods	Screening	Screening	Randomisation	Dose escalation				Double blind treatment			Open-label treatment								End of treatment	Follow-up	TPD 16 week FU	TPD 52 week FU
Visit number	1[1]	2[1]	3	4	5	6	7	8	9	10[2]	11	12[3]	13	14[3]	15[3]	16	17[3]	18[3]	19	20	10x	19x
Timing of visit (weeks)	-2		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	54	16	52
Visit window (days)				±2	±2	±2	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-5	±5	±5
IV/IWRS session 10	x		x				x	x	x	x	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]			
New dose of trial product 8.1.7				x	x	x	x															
REMINDERS																						
Training in trial product & pen handling (including injection technique) 8.1.6			x	x	x	x	x	x	x	x	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]				
Hand-out and instruct in BG meter 8.5.2.1			x																			
BG meter finger prick test 8.5.2.1			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Dispense dosing diary 8.7.3.1			x																			
Collect dosing diary				x	x	x		x	x	x												
Dispense hypoglycaemic episode diary 8.7.3.2			x																			
Collect hypoglycaemic episode diary				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Dispense menstrual period diary 8.7.3.3			x																			

Trial Periods	Screening	Screening	Randomisation	Dose escalation				Double blind treatment			Open-label treatment								End of treatment	Follow-up	TPD 16 week FU	TPD 52 week FU
Visit number	1[1]	2[1]	3	4	5	6	7	8	9	10[2]	11	12[3]	13	14[3]	15[3]	16	17[3]	18[3]	19	20	10x	19x
Timing of visit (weeks)	-2		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	54	16	52
Visit window (days)				±2	±2	±2	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-5	±5	±5
Collect menstrual period diary				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Attend visit fasting 8.1.3		x	x							x			x			x			x	x[11]		

Abbreviation list: TPD = trial product discontinuation, FU = follow up, SMBG = self-measured blood glucose, PHQ-9 = Patient Health Questionnaire 9, C-SSRS = Columbia Suicidality Severity Rating Scale, V = visit, BG = blood glucose, IV/WRS = interactive voice/web response system, ECG = electrocardiogram, hsCRP = high sensitivity C reactive protein.

Footer	Description
1	Maximum two weeks between V1 and V3. V2 must be at least 1 day after V1, and V2 must be at least 5 days before V3, to ensure blood samples are available for randomisation.
2	All assessments at V10 should be performed prior to trial medication dispensing, as the trial medication dispensing session in IV/WRS as V10 will un-blind subject's treatment.
3	Home visits possible for subjects treated with liraglutide placebo only.
4	At V2 all pre-existing conditions should be reported as medical history or concomitant illness.
5	Visit can be performed as phone/video conference visit.
6	Only for females of childbearing potential. At V2 and V19 performed as serum pregnancy test and from V3-V18 urine-stick pregnancy test, if applicable 8.5.5.
7	Estradiol for female subjects only and testosterone for male subjects only.
8	Subjects must be instructed to withhold their trial product dose until blood sampling is performed.
9	Only for subjects on open-label liraglutide treatment.
10	Tanner staging can be performed up to 2 weeks before V10 and V19.
11	No 8 hour fasting needed before V20. Minimum 2 hours after the last meal, the anti-liraglutide antibody sample at V20 is to be taken.
12	Please review inclusion criterion 7 and exclusion criterion 27 and evaluate whether a local testing for adrenal insufficiency is needed at V1

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[3] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[4].

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

3.1 Background information

Prader Willi syndrome

Prader-Willi syndrome (PWS) is a genetic disorder characterised by hypotonia with poor sucking reflex, feeding difficulties, and poor weight gain during infancy, hypogonadism, growth hormone insufficiency causing short stature, mild to moderate mental retardation, early childhood-onset hyperphagia and obesity[5]. Birth incidence has been estimated at around 1: 30,000 and population prevalence at about 1: 50,000[6].

Obesity typically manifests in early childhood and is a major cause of morbidity and mortality and is strongly associated with multiple comorbid conditions, including cardiopulmonary compromise, type 2 diabetes mellitus (T2DM), hypertension, thrombophlebitis, chronic leg oedema, and sleep apnoea[7]. Food-seeking behaviour is common in patients with PWS. Left unchecked and untreated, lack of appetite control can lead to morbid obesity[8], typically manifesting in early childhood. Therefore improvement in weight control remains the most important goal of any PWS treatment programme.

A study by Brambilla et al. investigated metabolic syndrome in 109 children with PWS aged 2−18 years (50 with obesity and 59 without obesity) and 96 controls with obesity without PWS. 16% of the subjects with obesity and PWS had metabolic syndrome (very close to that observed in the controls with obesity), whereas none of the subjects with PWS without obesity had metabolic syndrome, suggesting that obesity status play a key role in the development of metabolic syndrome.[9]

For treatment and prevention of obesity in PWS, low calorie and well-balanced diets with rigorous supervision and restriction of food access combined with regularly scheduled meals and physical activities are recommended.[10,11] The treatment of obesity in PWS is difficult and requires a comprehensive multidisciplinary approach with establishment of rigid structures to limit food intake and promote supervised physical activity.[12] Bariatric surgery is not recommended for children with PWS.[13]

The role of pharmacotherapy in PWS is uncertain. No medication has shown long-term effectiveness in controlling appetite.[14] In one study, adult patients with PWS were found to have elevated ghrelin concentrations compared to the reference population, raising the possibility that

ghrelin may contribute to the food-seeking behaviour observed in these subjects.[15] A 56-week study by de Waele et al. found that octreotide (long-acting somatostatin analogue) significantly decreased fasting ghrelin concentrations, but did not significantly affect weight, behaviour, or appetite in 9 adolescents (10.8−18.9 years) with PWS.[12] Another study found that topiramate (anticonvulsant, one of the two components of the obesity medication Qsymia®) had no significant effect on appetite and body mass index (BMI).[16] In a pilot study in adult patients with PWS and obesity and control patients with obesity, a single dose of 10 µg of the GLP-1 receptor agonist (GLP1-RA) exenatide increased satiety independently of measured appetite hormones, lowered glucose before and during a control meal and, increased insulin secretion rate in both groups. Side effects were absent in PWS.[17] In a recent case report of 6 patients by Fintini et al., the effect of long-term treatment with liraglutide (4 patients, 1.2−1.8 mg/day) or exenatide (2 patients, 20 µg/day) was evaluated in adult PWS patients with T2DM. During the 24 months of treatment, a tendency towards decreased BMI, HbA_{1c}, and waist circumference and a significantly decreased mean glycaemia during continuous glycaemic monitoring was detected, especially during the first 12 months.[18]

As children with PWS often suffer from short stature and excessive body fat, growth hormone (GH) has been used to improve linear growth and body composition.[19,20] In one study reported by Bakker et al., 8 years of GH treatment of 60 children with PWS completely normalised height standard deviation score (SDS). BMI SDS was significantly lower compared to baseline. Although percent fat SDS improved significantly during the first year of GH treatment, it had returned to baseline level after 8 years of GH treatment. One explanation for this could be, that the gradual increase in percent fat SDS seen over the years during the clinical course of PWS, cannot be fully restrained by GH treatment.[21]

Liraglutide

Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) analogue classified as a 'GLP-1 receptor agonist', with 97% homology to human GLP-1. Liraglutide has unique therapeutic potential for the treatment of obesity, due to its combined effects not only on body weight but also on glycaemic control and other weight-related comorbidities. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption.[22,23] Liraglutide is a once-daily GLP-1 analogue, obtained by derivatising GLP-1 with a fatty acid, providing a compound with protracted pharmacokinetic properties suitable for once-daily injection.

Liraglutide at once-daily doses up to 1.8 mg has been approved in approximately 90 countries for the treatment of adults with type 2 diabetes mellitus (T2DM) (under the trade name Victoza®). The moderate dose-dependent weight loss observed in clinical trials with liraglutide in T2DM, together with the reductions in glycosylated haemoglobin A1c (HbA_{1c}) and improvements in beta-cell function and cardiometabolic risk factors such as systolic blood pressure led to investigations into

its potential therapeutic use for weight management.[24] The liraglutide 3.0 mg daily dose was recently approved in the US as an adjunct to diet and exercise for weight management in adults, under the trade name Saxenda® (approval granted 23 December 2014), followed by Health Canada approval end of February 2015, and in Europe by 23 March 2015.

Four phase 3 clinical trials assessing the effect of liraglutide 3.0 mg on body weight reduction have been completed in adult subjects with obesity or overweight with or without T2DM. In general, a 5−10% mean body weight reduction was observed in subjects treated with liraglutide 3.0 mg in these trials, Detailed results from these trials can be found in the Investigator Brochure or the latest version thereof[25].

To date, two short-term (5 to 6-week) randomised, controlled trials with liraglutide in paediatric subjects have been completed. In the first trial (NN2211-1800), liraglutide at doses up to 1.8 mg was generally well tolerated in paediatric subjects with T2DM aged 10−17 years.[26] Liraglutide's safety/tolerability and pharmacokinetic profiles in adolescents were similar to those observed in adults with T2DM. In the second trial (NN8022-3967), liraglutide at doses up to 3.0 mg was well tolerated in adolescents with obesity without T2DM (aged 12−17 years); no unexpected safety or tolerability issues were detected. As in adults, liraglutide exposure increased with increasing drug dose. Since no safety/tolerability concerns were raised in the NN8022-3967 trial, a large, long-term trial (NN8022-4180) will investigate the efficacy and safety of liraglutide (doses up to 3.0 mg) for chronic weight management in adolescents with obesity (≥ 12 and < 18 years) and without diabetes type 1.

For an assessment of benefits and risks of the trial, see section 18.1, in which a description of preclinical findings includes a dose-dependent delay in sexual maturation in juvenile rats, which was more pronounced in females.

3.2 Rationale for the trial

Currently, there are no approved weight management pharmacotherapies for children and adolescents within Europe, and in the US the only medication approved by the FDA for children ≥ 12 years of age is orlistat. Obesity is a major cause of morbidity and mortality in PWS. It is challenging to achieve weight loss with diet and physical activity alone due to food-seeking behaviour and lack of appetite control in patients with PWS. Therefore there is an unmet medical need for anti-obesity medication as an adjunct to lifestyle interventions in this patient population.

4 Objectives and endpoints

4.1 Objectives

Primary objective

To compare the efficacy of liraglutide versus placebo on weight loss in paediatric subjects with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.

Secondary objectives

- To compare the efficacy of liraglutide versus placebo on glycaemic control in children and adolescents with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.
- To estimate the liraglutide steady state exposure in children and adolescents with obesity and PWS after 16 weeks of treatment.
- To compare the safety of liraglutide versus placebo in children and adolescents with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.

4.2 Endpoints

4.2.1 Primary endpoints

There are two co-primary endpoints:
- Change in body mass index (BMI) standard deviation score (SDS) from baseline to 16 weeks
- Change in body mass index (BMI) standard deviation score (SDS) from baseline to 52 weeks

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary efficacy endpoints

- Percent of subjects achieving ≥ 5% reduction in baseline BMI at weeks 16 and 52*
- Percent of subjects achieving ≥ 10% reduction in baseline BMI at weeks 16 and 52*
- Percent of subjects with no increase in BMI SDS at weeks 16 and 52

Change from baseline to 16 and 52 weeks in:
- BMI*
- Body weight (kilogram (kg), pounds (lb) and percent (%))*
- Waist circumference
- Waist to hip circumference ratio
- Hyperphagia score:
  - total score and*
  - hyperphagic behaviour, drive and severity score*
- Cardiovascular risk factors:

- High sensitivity C reactive protein (hsCRP)
- Fasting lipids: total cholesterol (TC), low density lipoprotein cholesterol (LDL-cholesterol), high density lipoprotein cholesterol (HDL-cholesterol), non-HDL cholesterol, very low density lipoprotein cholesterol (VLDL-cholesterol), triglycerides (TG), and free fatty acids (FFA)

- Systolic and diastolic blood pressure*
- Glucose metabolism: glycosylated haemoglobin (HbA_{1c})*, fasting plasma glucose (FPG)*, fasting insulin, fasting C-peptide, glycaemic category, homeostasis model assessment of beta-cell function and insulin resistance parameters (HOMA-B and HOMA-IR)

4.2.2.2 Supportive secondary PK endpoint

Model-derived area under the curve (AUC) over the dosing interval in steady state.

4.2.2.3 Supportive secondary safety endpoints

- Number of treatment-emergent adverse events during the trial
- Number of severe treatment emergent episodes of hypoglycaemia
- Number of blood glucose confirmed symptomatic episodes of hypoglycaemia
- Occurrence of anti-liraglutide antibodies

Change from baseline to 16 and 52 weeks in:

- Electrocardiogram (ECG)
- Pulse
- Laboratory parameters:
  - Haematology: haemoglobin, haematocrit, thrombocytes, erythrocytes, leukocytes, differential count (eosinophils, neutrophils, basophils, lymphocytes, monocytes)
  - Biochemistry: creatinine, creatine kinase (CPK), urea, albumin, bilirubin (total), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium total, calcium albumin corrected, amylase, lipase, and carcinoembryonic antigen (CEA)
  - Hormone levels including: calcitonin, insulin-like growth factor-1 (IGF-1), thyroid stimulating hormone (TSH), free thyroxine (free T4), prolactin, adrenocorticotropic

hormone (ACTH), cortisol, dehydroepiandrosterone sulfate (DHEAS), luteinising hormone (LH), follicle stimulating hormone (FSH), estradiol (females), testosterone (males)

- Pubertal status
- Physical examination including height
- Part A only: Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Reported Health Questionnaire-9 (PHQ-9)

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov and EudraCT)

5 Trial design

5.1 Type of trial

This is a multi-centre, multi-national, randomised, parallel group, placebo-controlled trial with a 16-week double-blind period and a 36-week open-label period. This trial consists of a part A and a part B. Part A of the trial is conducted in adolescents (≥ 12 and < 18 years, Tanner stage 2−5) with obesity and PWS. Part B of the trial is conducted in children (≥ 6 and < 12 years, Tanner stage below 2 (defined as Tanner stage 1 with or without premature adrenarche)) with obesity and PWS. Both part A and part B (for children with body weight ≥ 45 kg) will follow the trial diagram (Figure 5–1). Part B for children with body weight < 45 kg will follow the trial diagram (Figure 5–2). Entry into part A and part B of the trial will be sequential. After all subjects in part A have completed the 16-week double-blind period, an independent external Data Monitoring Committee (DMC) will review the PK data and safety data from part A. The DMC will recommend to the Novo Nordisk safety committee whether children in part B should be randomised, and exposed to liraglutide/liraglutide placebo. In addition, the tolerability/safety and PK data from trial NN8022-4181 in children with obesity 7-11 years (both inclusive) will be reviewed to allow adjustments in part B, as needed (conclusion after part A; see above).

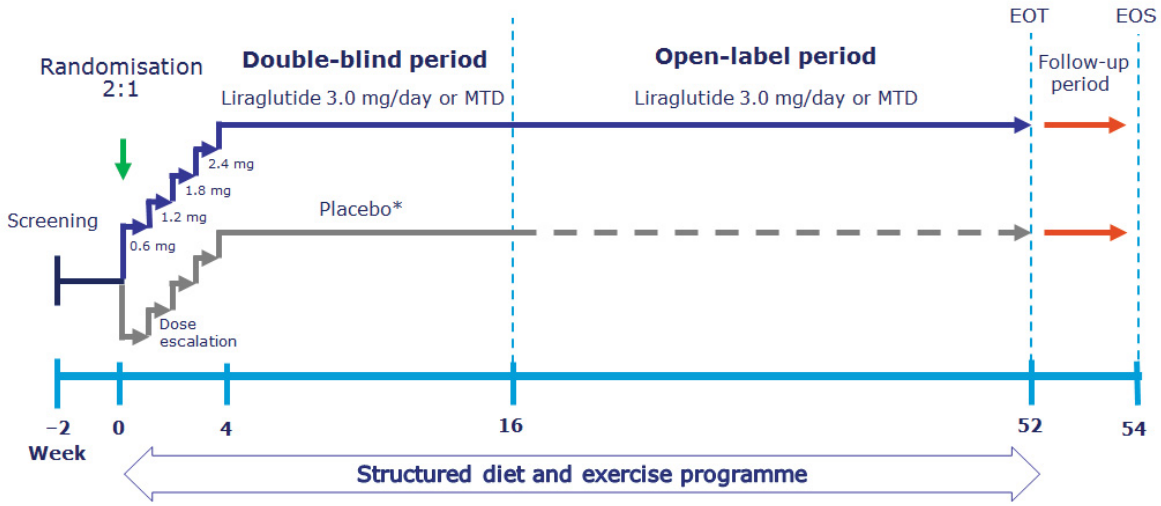


Figure 5–1 Trial diagram (Part A and part B (for children with body weight ≥ 45 kg))
Dose escalation can be prolonged to 8 weeks. **Abbreviations:** EOT = end-of-treatment; EOS = end-of-study; MTD = maximum tolerated dose.
* Placebo injections will end at week 16 for subjects allocated to the placebo arm.

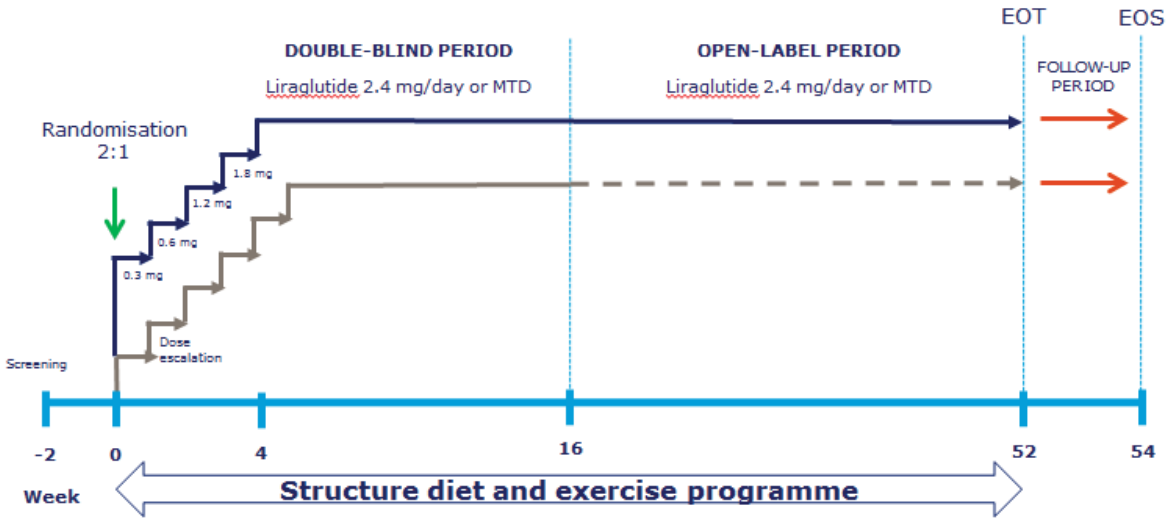


Figure 5–2 Trial diagram (Part B for children with body weight < 45 kg)
Dose escalation can be prolonged to 8 weeks. **Abbreviations:** EOT = end-of-treatment; EOS = end-of-study; MTD = maximum tolerated dose.
* Placebo injections will end at week 16 for subjects allocated to the placebo arm.

Subjects will be randomised 2:1 to receive liraglutide or liraglutide placebo. Part A has four strata as subjects are stratified according to Tanner stage 2−3 and 4−5 and by presence/absence of dysglycaemia. Part B includes subjects with Tanner below 2 (defined as Tanner stage 1 with or without premature adrenarche) and has two strata for presence/absence of dysglycaemia, see section 11.

Dysglycaemia is defined as pre-diabetes with FPG 5.6 – 6.9 mmol/L (both inclusive) (100-125 mg/dL) (both inclusive) and/or HbA_{1c} 5.7 – 6.4 % (both inclusive). The HbA_{1c} and FPG results from V2 must be used.

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to that in the European Union (EU). All subjects and/or their legally acceptable representative (LAR) will undergo counselling for weight loss and must be prescribed a structured programme for diet and physical activity throughout the trial (from randomisation to the end of the trial). Placebo injections will be stopped at week 16, at the end of the double-blind period.

Subjects treated with growth hormone therapy may enter the trial and will have no change in treatment plan with growth hormone from randomisation to the end of the open-label period (subjects on growth hormone will stay on, and subjects off growth hormone will stay off during this period. Adjustments to doses of growth hormone are permitted).

5.2 Rationale for trial design

This trial is designed in accordance with regulatory requirements (FDA 21 CFR 314.126)[27] and recommendations from the literature.[2,28]

The design has been chosen in accordance with the trial objectives and with input from the Paediatric Committee (PDCO) of the European Medicines Agency's (EMA).

The co-primary efficacy endpoints are change in BMI SDS from baseline to 16 weeks and 52 weeks. Change in BMI SDS is selected based on the EMA recommendation regarding the assessment of efficacy of new medicinal products for the treatment of obesity in children.[29] The first 16 weeks will be placebo-controlled and double-blinded to evaluate the effect of liraglutide versus placebo, as an adjunct to a structured program for diet and physical activity. The 36-week open-label period will provide supportive evidence to evaluate the continued efficacy and safety of liraglutide. Placebo injections will be stopped at the end of the double-blind period to avoid inconvenience to the subjects.

The rationale for choosing a treatment duration of 16 weeks for the primary efficacy endpoint is that this time period is considered adequate to show effect of liraglutide treatments on the endpoint, and to minimise the duration of placebo injections. The 36-week open-label period will allow additional time to evaluate the full effect of liraglutide on other efficacy endpoints including BMI, body weight, waist to hip circumference, cardiovascular risk factors (hsCRP and lipid profile), blood pressure and glucose metabolism and safety assessments. Furthermore, a 52-week total trial period is regarded to be sufficient to characterise the safety and tolerability profiles of liraglutide.

A 2:1 randomisation was chosen to ensure more subjects will receive active treatment with limited number of subjects enrolled in the trial, and therefore more safety data on liraglutide treatment is obtained.

The PK properties of liraglutide (i.e. exposure) in children and adolescents with PWS will be evaluated by population PK modelling, allowing for sparse PK sampling. The sparse sampling is implemented to reduce the burden on trial subjects and their LAR. The number of samples per subject has been chosen to allow for an adequate precision on the individual estimate for apparent clearance, CL/F. This parameter is used to derive exposure (AUC), thus allowing for a comparison with other relevant populations (such as adults with obesity, children with obesity and adolescents with obesity without PWS). Although sampling during the whole dosing interval will give adequate information on CL/F, the timing of sampling in the dosing interval has been optimized (mostly through samples) to improve precision of the CL/F estimate.

5.3 Treatment of subjects

Liraglutide or liraglutide placebo will be administered by once-daily subcutaneous (s.c.) injections either in the abdomen, thigh, or upper arm; injection site consistency is not required throughout the trial. During the 16-week double-blind period, subjects randomised to receive liraglutide placebo will receive placebo s.c. injections with injection volumes equivalent to the corresponding liraglutide dose. Liraglutide placebo contains the same excipients as liraglutide, but no active trial product. Injections can be administered at any time of day irrespective of meals. It is recommended that the time of injection is consistent throughout the trial. Subjects will be instructed to perform an air shot before the use of a new pre-filled pen. At the end-of the double-blind period, subjects randomised to receive placebo will stop injections once the investigator and subject are un-blinded to treatment allocation. During the 36-week open-label period, subjects in the liraglutide group will continue to receive liraglutide treatment. The maximum duration of treatment of a single subject, from first trial product administration to last trial product administration will be 52 weeks, and the maximum dose will be 3.0 mg/day in part A and for children in part B with a body weight ≥ 45 kg. For children in part B with a body weight of < 45 kg the maximum dose will be 2.4 mg/day.

At the first visit subjects and their LAR will be instructed in symptoms and treatment of hypoglycaemia, and in blood glucose measurements. The liraglutide dose will not be escalated if the subject experiences SMBG < 3.1 mmol/L (56 mg/dL) or < 3.9 mmol/L (70 mg/dL) in the presence of symptoms of hypoglycaemia, during the week prior to the dose escalation visit.

The following medications should not be used: orlistat, zonisamide, topiramate/phentermine, lorcaserin, phentermine and bupropion/naltrexone. Except for liraglutide as trial medication, GLP-1 receptor agonists cannot be prescribed during the trial. Metformin can only be used if the subject develops T2DM requiring an anti-diabetic agent as described in section 5.3.3.

Dosing in part B will be determined based on the results (including model-estimated steady state exposure) of the NN8022-4181 trial, a PK trial in children with obesity (Tanner stage below 2 (defined as Tanner stage 1 with or without premature adrenarche)), 7-11 years of age (both inclusive), and on the DMC review of PK data and safety data from the 16-week double-blind period from part A of this trial. If the dosing is different than for part A an amendment will be prepared.

Subjects in part A must have Tanner stage 2-5 pubertal development according to inclusion criterion 4. Pubertal development may have been hormonally induced with medical treatment.

5.3.1 Dose escalation

5.3.1.1 Dose escalation part A

Dose escalation will be based on tolerability as assessed by the investigator.

Based on the results of the NN8022-3967 PK trial in pubertal adolescents with obesity (aged 12 to < 18 years) including model-estimated steady state exposure, treatment is planned to be initiated in part A with liraglutide/placebo 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until a maximum tolerated dose (MTD) (as judged by the investigator) or a dose of 3.0 mg liraglutide/placebo is reached.

The trial product dose will be escalated only if the current dose is tolerated. If a subject has tolerability issues with the higher dose level (as judged by the investigator), it is allowed to lower to the previous dose level.

If a trial product dose is poorly tolerated, subjects are allowed to remain at a dose level for a maximum of 2 weeks. This extended time of one additional week is allowed at each dose level, i.e. the dose escalation process may take up to 8 weeks in total. It is at the discretion of the investigator to judge when the subject has reached MTD.

Escalation of the liraglutide/placebo dose is not allowed if the subject has a SMBG < 3.1 mmol/L (56 mg/dL) or < 3.9 mmol/L (70 mg/dL) in the presence of symptoms of hypoglycaemia during the week prior to the dose escalation visits. Hypoglycaemic episodes must be reported according to section 8.5.2.

Visits to the clinic occur weekly during the 4 weeks of dose escalation at V4-V7. Ideally, subjects will reach maximum dose of 3.0 mg at V7.

In those cases where more than one week is needed at any dose escalation step, the subject must still follow the visit schedule (V4-V7). For the remaining dose escalation step(s) after V7 it is at the discretion of the investigator to be in frequent contact (e.g. by phone/video conference) with the subject to ensure correct dose settings. The dose-escalation process must be completed no later than V8. Contacts regarding dose escalation must be documented in the subject's medical record and information about all dose levels must be recorded in the electronic case report form (eCRF).

5.3.1.2 Dose escalation part B

Based on result of the safety and PK data of NN8022-4181 and part A of NN8022-4179, the recommendation for part B - PWS children (aged 6 to < 12 years) with obesity is to initiate treatment with liraglutide/placebo based on weight.

For children with a body weight ≥ 45 kg, dosing will be initiated with liraglutide/placebo 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until a maximum tolerated dose (MTD) (as judged by the investigator) or a dose of 3.0 mg liraglutide/placebo is reached.

For children with a body weight < 45 kg, dosing will be initiated with liraglutide/placebo 0.3 mg daily for one week and increased to 0.6 mg after the first week, thereafter the dose is increased in weekly steps of 0.6 mg until a MTD (as judged by the investigator) or a dose of 2.4 mg liraglutide/placebo is reached.

Escalation of the liraglutide/placebo dose is not allowed if the subject has a SMBG < 3.1 mmol/L (56 mg/dL) or < 3.9 mmol/L (70 mg/dL) in the presence of symptoms of hypoglycaemia during the week prior to the dose escalation visits.

Hypoglycaemic episodes must be reported according to Section 8.5.2.

Dose escalation will be based on tolerability as assessed by the investigator. The trial product dose will be escalated only if the current dose is tolerated. If a subject has tolerability issues with the higher dose level (as judged by the investigator), it is allowed to lower to the previous dose level.

If a trial product dose is poorly tolerated during the dose escalation period, subjects are allowed to remain at a dose level for an additional week, i.e. four times in total, thus the dose escalation will last for eight weeks in total as a maximum.

Visits and phone contacts to the clinic occur weekly during dose escalation.

Trial Product dose at V8 will be defined as MTD.

5.3.2 Maintenance

In the event that a subject experiences unacceptable intolerance as judged by the investigator, the liraglutide dose may be lowered to the next, lower dose level as needed:

- Part A and part B (children with a body weight ≥ 45 kg) (from 3.0 mg to 2.4 mg, from 2.4 mg to 1.8 mg, from 1.8 mg to 1.2 mg, and from 1.2 mg to 0.6 mg).
- Part B (children with a body weight < 45 kg) (from 2.4 mg to 1.8 mg, from 1.8 mg to 1.2 mg, and from 1.2 mg to 0.6 mg and from 0.6 mg to 0.3 mg).

The reason for de-escalation of the liraglutide dose must be documented in the subject's medical record and transferred to the eCRF.

If the intolerance is due to intermittent illness or otherwise transient as judged by the investigator, the subject is allowed to return to the previous dose.

If a subject treated with the individual weight-based starting dose experiences unacceptable intolerance as judged by the investigator the subject must be discontinued from trial product (Section 8.1.8).

5.3.3 Treatment of subjects who develop type 2 diabetes mellitus during the trial

If a subject develops T2DM during the course of the trial, he/she will be allowed to remain in the trial if glycaemic control can be achieved through diet and physical activity according to local standard of care. Furthermore, additional treatment with metformin is allowed at the discretion of the investigator.

If anti-diabetes treatment other than diet, physical activity and metformin is required for glycaemic control the trial product must be discontinued (sections 6.4 and 8.1.8)

5.4 Treatment after discontinuation of trial product

As liraglutide is not currently approved for treatment of obesity in the paediatric population, it will not be available to the subjects once the trial period ends. When subjects withdraw from or complete the trial, they should continue present or be switched to other suitable dietary and physical activity program at the discretion of the investigator.

5.5 Rationale for treatment

The rationale for the dose-escalating design is to mitigate gastrointestinal adverse events. A corresponding tolerability/PK/PD trial (NN2211-1800) in paediatric subjects with T2DM, age 10−17 years, with maximum dose of 1.8 mg liraglutide has been conducted as part of the Paediatric Investigation Plan (PIP) for Victoza® T2DM. In addition, a PK/PD trial NN8022-3967 in pubertal adolescents with obesity (aged 12 to < 18 years) has been completed as part of the PIP for liraglutide 3.0 mg for treatment of obesity. In trial (NN8022-4181), liraglutide, at doses up to 3.0 mg, was generally well tolerated in children with obesity without T2DM (aged 7-11 years); no unexpected safety or tolerability issues were detected. As in adults, liraglutide exposure increased with increasing drug dose.

The starting dose of 0.6 mg applied for part A of the current trial in adolescents with obesity and PWS is based on the tolerability results in trial NN2211-1800 and NN8022-3967. The maximum dose of 3.0 mg is the approved dose for the adult population with obesity, based on efficacy and safety evaluation from the phase 2 dose finding trial (NN8022-1807) and the phase 3a programme in adults.

The weight-based starting dose of 0.6 mg for children with body weight ≥ 45 kg and 0.3 mg for children with body weight < 45 kg applied for part B is based on the limited data in patients below 45 kg with liraglutide treatment. As a precautionary measure and to ensure comparable exposure at

the start of treatment the 0.3 mg starting dose with a cap of 2.4 mg/day as a maximum dose for subjects < 45 kg is introduced.

The treatment duration of 16 weeks is considered adequate for evaluation of the effect of liraglutide on the primary efficacy endpoint during the double-blind period. The 36-week open-label period will provide supportive information on the effect of liraglutide on other efficacy endpoints and establish the safety profile of liraglutide in this patient population. A placebo group is included in the trial to compare safety between placebo and liraglutide treatment. The s.c. injection is the route of administration intended for clinical use of liraglutide.

For more information, see the latest edition of the Investigator's Brochure for: Liraglutide (NN8022) in Weight Management or any updates hereof[25].

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 64 (part A: 38; part B: 26)

Number of subjects planned to be randomised: 57 (part A: 33; part B: 24)

Number of subjects expected to complete the trial: 45 (part A: 28; part B: 17)

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Confirmed diagnosis of Prader-Willi Syndrome (by genetic testing)
3. Male or female, age at the time of signing informed consent:
   - Part A: ≥ 12 and < 18 years
   - Part B: ≥ 6 and < 12 years
4. Tanner stage 2−5 pubertal development for part A, and Tanner stage below 2 (defined as Tanner stage 1 with or without premature adrenarche) for part B
5. BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points [30] and ≥ the 95th percentile for age and sex (for diagnosis of obesity) (please refer to Appendix A)
6. Stable body weight during the previous 90 days before screening (< 10 kg self-reported weight change)
7. Testing has been performed to evaluate for adrenal insufficiency and documented in medical record

6.3 Exclusion criteria

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

1. Type 1 diabetes mellitus (T1DM)[2]
2. Type 2 diabetes mellitus (T2DM)[2]
3. No change in treatment plan with growth hormone (GH) from randomisation to the end of the open-label period (patients on growth hormone to stay on, patients off GH to stay off during this period. Adjustments in doses of growth hormone will be permitted)
4. Calcitonin ≥ 50 ng/L (please refer to Appendix C)
5. Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN2) or Medullary Thyroid Carcinoma (MTC)
6. History of pancreatitis (acute or chronic)

7. Treatment with any medication prescribed for weight loss within 90 days before screening (e.g. Orlistat, zonisamide, topiramate/phentermine, lorcaserin, phentermine, bupropion/naltrexone, liraglutide, metformin)
8. Diet attempts using herbal supplements or over-the-counter medications within 90 days before screening
9. Participation in an organised weight reduction programme (e.g. Weight Watchers®) within 90 days before screening
10. Previous surgical treatment for obesity (excluding liposuction if performed > 1 year before screening)
11. History of major depressive disorder within 2 years before randomisation
12. History of other severe psychiatric disorder (e.g. schizophrenia, bipolar disorder)
13. Part A only: PHQ-9 score of ≥ 15 at screening
14. Part A only: Any suicidal ideation of type 4 or 5 in the last 30 days prior to screening based on the C-SSRS questionnaire
15. Any lifetime history of suicidal attempt
16. Any suicidal behaviour within 30 days before randomisation
17. Surgery scheduled for the trial duration period except for minor surgical procedures, at the discretion of the investigator
18. Subjects with confirmed bulimia nervosa disorder
19. Uncontrolled treated or untreated hypertension >99th percentile for age and gender in children (please refer to Appendix B). If white-coat hypertension is suspected at the screening V2 a repeated measurement at V3 prior to other trial related activities is allowed (last measurement being conclusive)
20. Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps and in-situ carcinomas)
21. Known or suspected abuse of alcohol or narcotics
22. Known or suspected hypersensitivity to trial product(s) or related products
23. Previous participation in this trial. Participation is defined as being randomised
24. Receipt of any investigational medicinal product within 30 days before screening or participation in another trial within 30 days before screening
25. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
26. Any condition which, in the opinion of the investigator might jeopardise subject's safety or compliance with the protocol
27. Untreated adrenal insufficiency (please refer to Section 8.1.1.1)
28. Suggestive history of, or significant risk of gastroparesis (e.g. marked abdominal bloating post meal, history of vomiting, severe constipation), as judged by the Investigator

The inclusion and exclusion criteria will be checked prior to subject randomisation.

6.4 Discontinuation of trial product criteria

The subject must discontinue trial product if the following applies:

1. Due to a safety concern at the discretion of the investigator
2. Non-compliant with trial procedures at the discretion of the investigator.
3. Pregnancy
4. Intention of becoming pregnant
5. Participation in another clinical trial throughout the trial
6. Included in the trial in violation of the inclusion and/or exclusion criteria
7. Diagnosis of acute pancreatitis (section 8.6.3.3 and 8.6.2)
8. Diagnosis of medullary thyroid carcinoma
9. Weight loss attempts other than what is agreed with the dietitian as part of the trial intervention
10. If diabetes treatment other than diet, physical activity and metformin addition is initiated.
11. Initiation of treatment that based on the investigator's judgement may cause significant weight change. This should also include treatment with any of the following medications: orlistat, zonisamide, topiramate, lorcaserin, phenteremine, bupropion, naltrexone or GLP-1 receptor agonists
12. Inadequate psycho- and/or pharmaco therapeutic treatment of a subject's psychiatric disorder (section 8.5.10.3)
13. The subject and/or the subject's LAR refuse referral to a mental health professional (MHP) and it in investigator's opinion, it is unsafe for the subject to continue in the trial (section 8.5.10.3)
14. Due to safety reasons if at the recommendation of the external DMC and endorsed by the safety committee.
15. If a subject treated with the individual weight-based starting dose experiences unacceptable intolerance as judged by the investigator, the subject must be discontinued from trial product (Section 8.1.8)

See section 8.1.8 for how to handle discontinuation of trial product.

6.5 Withdrawal criteria

1. The subject may withdraw at will at any time either by the subject or by the subject's parent or the subject's legally acceptable representative. The subject's request to discontinue must always be respected

See section 8.1.9 for how to handle withdrawals.

6.6 Subject replacement

Subject replacement will be initiated if the actual withdrawal rate is higher than assumed (10% at week 16 and 20% at week 52) to ensure the number of evaluable subjects required by PDCO will be met.

The trial will continue until at least 45 evaluable subjects are included in total, divided as:

- Part A, at least 28 evaluable subjects
- Part B, at least 17 evaluable subjects
  - and of these subjects at least 5 need to be below 9 years of age.

6.7 Rationale for trial population

PWS is a rare genetic disease with an estimated incidence of 1:15,000 to 1:25,000 live births[10], therefore the number of subjects planned for this trial is relatively small.

Obesity is the major cause of morbidity and mortality in patients with PWS. The diagnosis of obesity in adolescents and children is based on BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points[1] and ≥ 95th percentile for age and sex for children.

Subjects are required to have had testing performed to evaluate for adrenal insufficiency. This must be documented in their medical records to confirm adrenal sufficiency, see section 8.1.1.1. Hypogonadism and growth hormone insufficiency (causing short stature) are commonly seen in patients with PWS[31], suggesting that pituitary hormones are affected by the disease. The secretion of cortisol, the main adrenal glucocorticoid in humans is under the control of pituitary adrenocorticotropic hormone (ACTH). Adrenal insufficiency has been reported, and although uncommon in patients with PWS, the clinical manifestations are serious.[10] Therefore it is important to ensure patients enrolled in the trial have had testing performed to evaluate for adrenal insufficiency, and that those who have this condition are under treatment.

As previously mentioned, subjects may enter the trial on GH therapy as short stature associated with PWS is an approved indication for GH therapy. It has been reported that in children with PWS, 8 years of GH treatment resulted in completely normalised height and head circumference, and a significant increase in lean body mass during the first year, and remained stable for 7 years at a level above baseline.[21] It is well known that growth hormone may affect glucose metabolism, and may increase fasting plasma glucose.[32,33] Therefore, no change in GH treatment plan should be made during the trial, and subjects not using GH therapy will stay off during the trial. Adjustments in doses of growth hormone are permitted.

As mentioned previously in section 3.1, there is limited information on the safety and effectiveness of pharmacotherapy in controlling appetite and obesity in PWS patients, especially in children and adolescents with PWS. There is a knowledge gap and lack of treatment options for weight loss/improvement in the weight-related symptoms and risk factors in PWS population. Therefore the current trial has been mandated by PDCO and will provide useful information on using liraglutide as a therapeutic option for weight management in this patient population.

7 Milestones

7.1 Part A

Planned duration of recruitment period (FPFV– LPFV): 72 weeks

Planned date for first patient first visit (FPFV): 09-Nov-2015

Planned date for first patient first treatment: (FPFT) 23-Nov-2015

Planned date for last patient first visit (LPFV): 27-Mar-2017

Planned date for last patient first treatment (LPFT): 10-Apr-2017

Planned date for last patient last visit (LPLV): 07-May-2018

7.2 Part B

Planned duration of recruitment period (FPFV– LPFV): 64 weeks

Planned date for first patient first visit (FPFV): 09-Apr-2018

Planned date for first patient first treatment: (FPFT) 23-Apr-2018

Planned date for last patient first visit (LPFV): 01-Jul-2019

Planned date for last patient first treatment (LPFT): 15-Jul-2019

Planned date for last patient last visit (LPLV): 10-Aug-2020

End of trial is defined as LPLV for part B.

7.3 Recruitment

A global recruitment strategy will be developed in cooperation with the participating countries to ensure that a sufficient number of subjects are randomised. Prior to FPFV, all sites should have a site-specific recruitment strategy in place detailing how many subjects they can recruit within a certain period.

The screening and randomisation rate will be followed closely via the interactive voice/web response system (IV/WRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no additional subjects may be screened and the IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

7.4 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[34], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[35], the Food and Drug Administration Amendment Act (FDAAA)[8], European Commission Requirements[36-38] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

The following sections describe the assessments and procedures. These are also included in the flow chart (section 2).

8.1 Visit procedures

It is the responsibility of the investigator to ensure that all site visits and phone/video conference contacts occur according to the flowchart. In order to secure consistency in data over time it is encouraged that assessments are performed consistently (e.g. using the same equipment and site staff with alike qualifications) throughout the trial.

All trial procedures must be performed as described in the protocol. Any discrepancies will result in protocol deviations and appropriate actions must be taken to avoid recurrence of the detected discrepancies.

8.1.1 Screening, visit 1

Prior to any other trial related procedures, the investigator must obtain informed assent from each subject if applicable (based on age and local regulations) and informed consent from the subject's LAR(s) (section 2). For information on informed assent and consent procedure see section 18.2.

All subjects and subject's LAR(s) must be provided with a copy of their own signed and dated informed assent form and informed consent form.

A screening session must be made in the IW/VRS. During the session each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

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

At screening, subjects will be provided with a card stating that they are participating in a trial and given 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.

All subjects should be reminded to attend V2 in a fasting state. V2 must take place at least 1 day after V1.

8.1.1.1 Adrenal insufficiency test at screening, visit 1

If the testing for adrenal insufficiency has not been performed prior to screening V1 (inclusion criterion 7), the investigator may perform a test (of their choosing) locally to evaluate for adrenal insufficiency after screening and before randomisation. The results must be available and reviewed and the subject must have initiated treatment before the randomisation visit, if applicable.

8.1.2 Visits attended fasting

Fasting visits are specified in section 2. Fasting is defined as having consumed no food and drink except for water for the last 8 hours.

Any medication which should be taken with or after a meal should be withheld on the day of the visit until blood sampling and body weight measurements have been performed. Trial product can be taken as usual in relation to fasting visits.

In case a subject attends a fasting visit in a non-fasting state, all non-fasting measurements should be performed. The subject should return to the site in a fasting state to have fasting measurements done within the visit window for the relevant visit.

8.1.3 Screening, visit 2

All screening assessments as described in section 2 must be performed. V2 must be at least 1 day after V1, and V2 must be at least 5 days before V3.

8.1.4 Screening failures

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

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

8.1.5 Re-screening

Re-screening of screening failures is allowed however there must be at least 90 days from screen failure date to re-screening. In case of re-screening, a new informed consent and assent must be obtained, a new screening number must be allocated and samples and assessments must be performed once more according to the screening procedures. For more information see section 10.

8.1.6 Randomisation, visit 3

Subject eligibility must be evaluated according to the inclusion and exclusion criteria. To randomise a subject a randomisation session must be performed in IV/WRS. The Tanner stage, HbA_{1c} and FPG result from V2 must be entered in IV/WRS (section 11).

The subject must be instructed in handling of the pen and the trial product (section 9) including training in injection site (section 5.3) and injection technique. The subject should be instructed to perform an air shot before the use of a new pre-filled pen. At all subsequent visits, subjects should be trained at the investigators discretion.

The first dose of trial product must be injected by the subject or their LAR at the site.

For training in recognition of hypoglycaemia, see section 8.5.2 and for instruction in handling of the blood glucose (BG) meter including auxiliaries and self-measured blood glucose (SMBG), see sections 8.5.2.1.

8.1.7 Dose escalation, visit 4-7

At each visit during the dose escalation period, a measurement of the subject's plasma glucose level by self-monitored blood glucose (section 8.5.2.1) must be performed before instructing the subject in dose escalation. For dose escalation see section 5.3.1.

8.1.8 Discontinuation of trial product

See section 6.4 for discontinuation of trial product criteria. For subjects with discontinuation of trial product, the investigator must at a minimum aim to:

- undertake procedures for the end of treatment visit (V19) as soon as possible and
- schedule a follow up visit (V20) two weeks later.

Depending on when the discontinuation of trial product takes place during the trial:

- If trial product is discontinued between V3 and V9, the subject should attend V10x (16 weeks after V3) and V19x (52 weeks (± 5 days) after V3)
- If trial product is discontinued between V11 and V19, the subject should attend V19x (52 weeks (± 5 days) after V3)

The end-of-trial form must be completed, and final drug accountability must be performed. A treatment discontinuation session must be made in the IV/WRS. The case book must be signed.

8.1.9 Withdrawal of informed consent/assent

See section 6.5 for withdrawal criteria. If a subject and/or their LAR withdraw informed consent/assent the investigator must aim to undertake procedures similar to those for the end of treatment (V19) as soon as possible and the follow up visit (V20) two weeks later.

The end-of-trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IV/WRS. The case book must be signed.

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 CRF.

8.1.10 Home visits

Selected site visits as indicated in the flow chart (section 2) can be converted to home visits during the open-label period for subjects in the liraglutide placebo group. The selected visits have no scheduled drug dispensing, blood sampling, ECG measurement, or physical examination.

Site staff must bring the following equipment during the home visit:

- Calibrated transportable scale
- Calibrated blood pressure monitor
- Measuring tape for measurement of waist and hips
- Urine sticks (applicable when females of childbearing potential are visited only)
- Equipment for pulse measurement
- BG meter for finger prick test (in case subject's own BG meter is not available)
- PHQ-9 questionnaire (self-completed by subjects)
- C-SSRS questionnaire:
  - questionnaire to be completed at home (if home visit is conducted by site staff certified as C-SSRS interviewer) or
  - set-up of telephone/video conference interview (if home visit is not conducted by site staff certified as C-SSRS interviewer)

Documentation for remaining assessments as per the flowchart (concomitant medication, adverse event, review and collection of menstrual information diary information etc.) must be obtained during the home visit. The site dietitian must be informed that the site visit is converted to a home visit so a telephone/video conference contact to the subject can be established.

8.2 Laboratory assessments

Laboratory assessments are performed by a central laboratory except for assessments for liraglutide plasma concentration and anti-liraglutide antibodies that are analysed by special laboratories.

Descriptions of laboratory supplies and procedures for obtaining samples, handling and storage of samples including reporting of results and information regarding who will perform the assessments are described in a trial-specific laboratory manual provided by the central laboratory.

For a list of blood samples for efficacy assessment, see section 8.4.4 and for a list of blood samples for safety assessments, see section 8.5.7. For description of samples for liraglutide plasma concentration samples, see section 8.7.1 and for anti-liraglutide antibodies, see section 8.5.8.

No additional central laboratory assessments than those described in the protocol (section 2) are allowed.

All laboratory samples except for the liraglutide plasma concentration samples and the anti-liraglutide antibody samples are sent to the central laboratory, analysed and reported to the investigator on an ongoing basis.

Blood samples for liraglutide plasma concentration and anti-liraglutide antibodies are sent for storage only at the central laboratory and later sent to the special laboratory for analysis at specific time intervals. Furthermore, selected blood samples for anti-liraglutide antibodies are sent from the special laboratory to Novo Nordisk A/S for further characterisation, see section 8.5.8

The antibody samples are analysed before LPLV but results will not be reported to the investigator as these results will not be used for any clinical evaluation during the course of the trial. The results of the antibody samples will only be reported to the investigator upon request at the end of trial.

Laboratory samples are destroyed on an ongoing basis or at the latest at the completion of the clinical trial report, except for antibody samples.

Antibody samples may be retained until approval of the paediatric indication by FDA and/or EMA or up to a period of 15 years. The retained antibody samples may be used for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons, see section 24.2.

8.2.1 Total blood volume for laboratory assessments

Approximately 150 mL blood in total is collected from each subject during the entire trial period. Blood collection is performed in accordance with the guidelines in the EU Directive 2001/20/EC[39].

Table 8–1 Volume of blood during the trial

	Visit number												All visits
	V2	**V3**	**V4**	**V5**	**V6**	**V8**	**V9**	**V10**	**V13**	**V16**	**V19**	**V20**	
Total volume*	**7.5**	**23.0**	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**	**29.0**	**22.0**	**22.0**	**27.0**	**7.0**	**147.5 ml**

**Precise volume at time of protocol preparation, minor variations may occur*

8.2.2 Laboratory reports

The central 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.

Review of laboratory reports must be documented by the investigator (signed and dated) on the document. The evaluation of screening results must be dated and signed prior to randomisation (V3) and for the subsequent visits on the day of evaluation. For any laboratory result outside the reference range, it must be specified whether the value is clinically significant or not.

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

The laboratory reports and evaluations must be retained as source documentation.

8.3 Subject related information

8.3.1 Demography

The following information must be collected (according to local regulation):

- Date of birth
- Sex
- Race
- Ethnicity

8.3.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (V1) or found as a result of a screening procedure. All concomitant illnesses should be reported.

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.

Medical history is a medical event that the subject has experienced in the past. Only relevant and significant medical history as judged by the investigator should be reported. The following medical history should be reported as a minimum if applicable: cardiovascular diseases, gallstone diseases (e.g. cholecystitis), pancreatitis and psychiatric disorders.

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

8.3.2.1 History of psychiatric disorders

Information related to psychiatric disorders (specifically history of depression, suicidal behaviour, anxiety, mood disorders, insomnia, or sleep disorders) must in addition to the medical history form also be recorded in the eCRF on a separate form.

8.3.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at V2. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation. In addition, dose and route of administration for concomitant medication treatment for weight-related co-morbidities (diabetes mellitus, hypertension and dyslipidaemia) must be recorded.

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

8.3.4 Tobacco use

Details of tobacco use must be recorded at V2.

Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

If the subject smokes or has smoked, record approximately when the subject started smoking and, if applicable, when the subject stopped smoking.

8.4 Assessments for efficacy

The timing of the assessments are outlined in the flow chart (section 2).

8.4.1 Body measurements

8.4.1.1 Body weight

Body weight must be measured to the nearest 0.1 kg or 0.1 pounds. Fasting body weight must be measured at the fasting visits (section 8.1.2). If the weight is not measured fasting at fasting visits, the subject must be called in for a new visit within the visit window to have the fasting weight measured. At the remaining visits the measurement is performed in a non-fasting state.

The same scale should be used throughout the trial. The scale must be calibrated according to the directions for use and as a minimum once a year.

Body weight should be measured without shoes and only wearing light clothing and the subject should have an empty bladder.

Body weight measured at V2 is used for the calculation of BMI to evaluate inclusion criteria. Body weight measured at V3 is used as baseline for assessment of change in body weight.

BMI is calculated in the eCRF.

8.4.1.2 Hip and waist circumference

The hip circumference is defined as the widest circumference around the buttocks.

The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest.

Three consecutive measurements each of hip and waist circumference must be performed. They should be measured in the horizontal plane and rounded up or down to the nearest 0.5 cm or 0.2 inches using a non-stretchable measuring tape.

The circumference should be measured when the subject is in a standing position wearing light clothing. At fasting visits the subject should be measured with an empty bladder. The subject should be standing, feet together with arms down their side and waist and hip accessible. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

The measurements should be performed in the following order: waist, hip, waist, hip, waist and hip. All three measurements must be recorded in the eCRF.

8.4.2 Hyperphagia questionnaire

Hyperphagia, a characteristic of patients with PWS, will be assessed using the hyperphagia questionnaire. The hyperphagia questionnaire has been developed for use in adults and children as young as 4 years of age with PWS, and has been recommended for use in this population by the 2014 2nd International Conference on Hyperphagia.

Hyperphagia is a significant source of stress for patients with PWS and their families, and can lead to complications including choking, and in extreme cases gastric rupture.

Liraglutide may influence hyperphagia through regulation of appetite. Liraglutide is known to increase feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption[40,41].

The subject's LAR must fill out the PWS hyperphagia questionnaire according to flow chart (2).

8.4.3 Systolic and diastolic blood pressure

For blood pressure at V2, three measurements must be performed. The mean value is calculated by the eCRF and must be used to evaluate eligibility of the subject (exclusion criterion 19 and Appendix B). For the subsequent visits, only one measurement needs to be performed.

The method for measuring systolic and diastolic blood pressure should follow the standard clinical practice at site, but as a minimum, the following guideline must be adhered to:

- Caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure should be avoided
- Blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- The subject should be sitting for at least 5 minutes before the first measurement is taken
- The subject should not talk during the measurement
- The same arm and cuff size should be used for blood pressure measurements at subsequent visits

Any "abnormal, clinically significant" findings at screening must be recorded as medical history/concomitant illness in the eCRF and in the subject's medical record.

Any clinically significant worsening or new clinically significant findings after V2 must be reported as an AE in accordance with section 12.

If the investigator suspects white coat hypertension at V2, a re-assessment (three measurements) of the systolic and diastolic blood pressure is allowed, as described in exclusion criterion 19.

8.4.4 Blood samples for efficacy assessments

Any "abnormal, clinically significant" findings at V2 must be recorded as medical history/concomitant illness in the eCRF. The following blood samples must be drawn (for frequency see section 2):

Lipids (fasting):

- Total cholesterol
- LDL-cholesterol
- VLDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Free fatty acids
- Non-HDL cholesterol

Biochemistry:

- High sensitivity C reactive protein (hsCRP)

Glucose metabolism:

- HbA_{1c}
- FPG
- Fasting insulin
- Fasting C-peptide

8.5 Assessments for safety

The timing of the assessments are outlined in the flow chart (section 2).

8.5.1 Height

Height should be measured (centimetres or inches, one decimal) without shoes as two individual measurements performed by a single observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject should be repositioned between the two measurements.

8.5.2 Hypoglycaemic episodes

At V3, all subjects and their LAR must be instructed in symptom recognition and handling of hypoglycaemia.

Blood glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

should be recorded by the subject or their LAR. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 3 to visit 18.

The record should include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Date and time of last trial product administration prior to episode
- Type and dose of last trial product administration prior to episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other disease
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration[10].

Oral carbohydrates should not be given if the subject is unconscious.

If the question "Was subject able to treat him/herself?" is answered "No", the following information should be recorded:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose, other factors not listed, please specify or none)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[11]?
  - Autonomic: sweating, trembling, hunger or palpitations
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
  - General malaise: headache or malaise
- Did the subject experience other symptoms? Please specify

- Description of the episode, if applicable

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form (SIF) must also be filled in, see section 12.

8.5.2.1 Self-measured blood glucose (SMBG)

At V3, subjects are provided with a blood glucose (BG) meter including BG meter auxiliaries and instructions for use. The subjects or their LAR will be instructed in how to use and calibrate the device, according to the manufacturer's instructions. Instruction will be repeated as necessary during the trial.

The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

At each visit, the subject or subject's LAR must demonstrate how to use the BG meter device by measuring the subject's blood glucose value, preferably by using be the subject's own BG meter. The SMBG value must be documented in the subject's medical record.

During dose escalation the SMBG measurement must be done before instructing the subject in dose escalation (section 8.1.7). In case the value fulfils the criteria of a hypoglycaemic episode this must be recorded in the eCRF (section 8.5.2).

Subjects or their LAR must be instructed to do a SMBG in between visits in case a hypoglycaemic episode is suspected (section 8.5.2). The subjects must be instructed to contact the investigator in case of low SMBGs.

Subjects or their LAR should be instructed in how to record the results of the SMBGs in the diaries. The record of each SMBG should include date, time and value (section 8.7.3.2). All hypoglycaemic episodes from the diary must be transcribed into the eCRF.

8.5.3 Pulse

Pulse (beats per minute) must be recorded after resting for 5 minutes in a sitting position.

Any "abnormal, clinically significant" findings at screening must be recorded as medical history/concomitant illness in the eCRF and in the subject's medical record.

Any clinically significant worsening or new clinically significant findings after V2 must be reported as an AE in accordance with section 12.

8.5.4 Electrocardiogram – 12 lead

A 12-lead ECG must be performed and interpreted locally by the investigator. ECG print-outs must be evaluated, signed and dated by the investigator.

The evaluation of ECGs must follow the categories:

- Normal
- Abnormal, clinically significant yes/no

ECG performed for any reason unrelated to this trial within 12 weeks prior to V2 is acceptable provided no clinical symptoms suggestive of cardiac disease have been identified or occurred prior to enrolment. If an ECG is performed before the subject has signed the informed consent form, it must be documented in the subject's medical records that the reason for performing the procedure is not related to this trial. It is allowed to perform the screening ECG after V2 but prior to V3.

Any "abnormal, clinically significant" findings at screening must be recorded as medical history/concomitant illness in the eCRF and in the subject's medical record.

ECGs performed within 30 days prior to the subsequent visits where an ECG is scheduled is acceptable (section 2).

Any clinically significant worsening or new clinically significant findings after V2 must be reported as an AE in accordance with section 12.

8.5.5 Pregnancy tests

All females of childbearing potential must have pregnancy tests performed as described below. For documentation of menstrual periods see section 8.7.3.3.

8.5.5.1 Blood samples

At V2 and V19, a serum pregnancy test must be performed.

If a female subject becomes of childbearing potential during the trial, a serum pregnancy test must be performed as soon as possible or at the latest at the next visit.

8.5.5.2 Urine-sticks

At V3-V18, urine-stick pregnancy tests will be performed at the site if:

- Pregnancy is suspected
- A menstrual period is missed (unless this is a part of the mode of action of the contraceptive method)
- According to local requirements

The result of the urine-stick pregnancy test must be documented in the medical record.

8.5.5.3 Recording of menstrual periods

Documentation of the first date of the last menstrual period (if applicable) before V2 must be recorded in subject's medical record.

First date of all menstrual periods since last visit must be collected from all female subjects (section 8.7.3.3) and recorded in the eCRF.

8.5.6 Physical examination

Physical examination must include:

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

Any "abnormal, clinically significant" findings at screening V2 must be recorded as medical history/concomitant illness in the eCRF and in the subject's medical record.

Any clinically significant worsening or new clinically significant findings after V2 must be reported as an AE in accordance with section 12.

8.5.7 Blood samples for safety assessments

Any "abnormal, clinically significant" findings at V2 must be recorded as medical history/concomitant illness in the eCRF. The following blood samples must be drawn (for frequency see section 2):

Biochemistry:

- Creatinine
- Creatine kinase (CPK)
- Urea
- Albumin
- Bilirubin, total
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Sodium
- Potassium
- Calcium, total
- Calcium, albumin corrected
- Amylase
- Lipase

Haematology:

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes
- Differential count:
  - basophils
  - eosinophils
  - lymphocyte
  - monocytes
  - neutrophils

Hormones:

- Calcitonin (refer to Appendix C for actions taken if calcitonin is ≥ 20 ng/L)
- Prolactin
- Follicle stimulating hormone (FSH)
- Estradiol (females)
- Luteinizing hormone (LH)
- Testosterone (males)
- Thyroid stimulating hormone (TSH)
- Free T4
- Adrenocorticotropic hormone (ACTH)
- Cortisol
- Dehydroepiandrosterone sulfate (DHEAS)
- Carcinoembryonic antigen (CEA)
- Insulin-like growth factor-1 (IGF-1)

Pregnancy test:

Beta-human chorionic gonadotropin (beta-hCG)

8.5.8 Anti-liraglutide antibodies

Blood samples for determination of anti-liraglutide antibodies are collected from all subjects at randomisation (V3) and at the end of the 16-week double-blind period, see section 2. Only samples from subjects treated with liraglutide are analysed for anti-liraglutide antibody development. Depending on the number of subjects in the liraglutide treatment arm, baseline (randomisation V3) from subjects in the placebo group may be analysed for the purpose of determination of the assay cut points. At V19 and V20 antibody samples are collected and analysed from subjects treated with liraglutide only.

Blood samples for the determination of anti-liraglutide antibody must be drawn in a fasting state and prior to administrating trial product (see section 2). The anti-liraglutide antibody sample at V20 is to be taken minimum 2 hours after the last meal.

Samples are analysed by the special laboratory for anti-liraglutide antibody formation including cross reactivity to endogenous GLP-1. Furthermore samples from the follow up visit (V20) that are found to be positive for anti-liraglutide antibodies will be analysed for neutralising effect against liraglutide. Anti-liraglutide antibody positive samples from V20 that are also found to cross react with endogenous GLP-1 will in addition be analysed for neutralising effect against endogenous GLP-1. The neutralising antibody analyses will be performed by Novo Nordisk A/S. Baseline antibody samples collected at the randomisation visit will be included in the neutralising antibody analyses for assessment of assay cut points. See further information in sections 8.2 and 24.2.

8.5.9 Tanner staging

Pubertal development must be assessed by Tanner staging in accordance with stages 1-5[42] according to flow chart 2. The assessments must be conducted by site staff trained in pubertal assessments. Assessment of testicular volume (by orchidometer) for boys must be included.

Tanner staging can be performed up to 2 weeks before V10 and V19.

Evidence of accelerated pubertal development as judged by the investigator at V2 must be recorded as medical history/concomitant illness in the eCRF and in the subject's medical record.

Acceleration of pubertal development after V3 as judged by the investigator must be reported as an AE in accordance with section 12.

Tanner staging is not required once the subject reaches the Tanner stage 5, as judged by the investigator.

8.5.10 Mental health questionnaires (part A only)

The mental health of subjects will be assessed by the following questionnaires to meet the regulatory requirements (section 2):

- Columbia Suicide Severity Rating Scale (C-SSRS) Pediatric/Cognitively Impaired questionnaire[43]
- Patient Health Questionnaire 9 (PHQ-9) for children and adolescents[44]. The questionnaires will be available in a linguistically validated paper version.

Drugs for weight loss are one of the non-psychiatric drugs for which treatment-emergent suicidal ideation and behaviour as well as depression must be surveyed. Even though liraglutide has not been associated with suicidality or depression the two mental health questionnaires, C-SSRS and PHQ-9 have been included in part A of the present trial.

The questionnaires must be filled in and data must be entered into the eCRF. In case questionnaires cannot be completed because of mental incapacity, this must be documented in the subject's medical record and the eCRF.

8.5.10.1 C-SSRS

The investigator or delegated staff must complete the C-SSRS based on an interview with the subject. The investigator or delegated staff interviewing the subject must complete an online interviewer training prior to first interview.

The questionnaires completed at V2 must be used to exclude subjects from the trial with any suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent).

8.5.10.2 PHQ-9

The PHQ-9 should be completed by the subject without interruption.

The questionnaires completed at V2 must be used to exclude subjects with a PHQ-9 score ≥ 15 from the trial.

The investigator or delegated staff must review questionnaires for completeness and adverse events immediately following administration. The review must be documented in the subject's medical record. If clarification of entries or discrepancies in the questionnaire is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

8.5.10.3 Referral to mental health professional

If a subject has a PHQ-9 score from 10-14 both inclusive on any questionnaire the subject should be referred to a mental health professional (MHP) if judged relevant by the investigator. If referral is not deemed relevant, this must be documented in the subject's medical record.

A subject must be referred to a MHP if the subject has:

- a PHQ-9 score ≥ 15 or
- any suicidal behaviour or
- any suicidal ideation of type 4 or type 5 on any C-SSRS assessment
- if the opinion of the investigator it is necessary for the safety of the subject

If one or more of the above referral criteria are met the investigator should explain to the subject and/or the subject's LAR why the referral and psychiatric evaluation by a MHP is needed. If the subject and/or the subject's LAR refuses to be referred to a MHP, the decision should be documented in the medical record and the investigator must assess, if it is safe for the subject to continue in the trial, or if the subject should be discontinued from trial product (section 6.4 and 8.1.8).

If a subject's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the subject, at the discretion of the investigator (in agreement with the MHP), may continue in the trial. Otherwise, the trial product must be discontinued (section 6.4 and 8.1.8).

8.6 Additional safety assessments

8.6.1 In case of elevated calcitonin

If any calcitonin value post randomisation is above upper normal limit a repeated measurement of calcitonin should be taken within 4 weeks. All cases ≥ 20 ng/L will be reviewed by an external expert who will provide recommendations to the investigator whether further evaluation is indicated. For details, refer to appendix C.

8.6.2 Suspicion of acute pancreatitis

In case of acute, severe persistent abdominal pain leading to a suspicion of acute pancreatitis, the trial product should promptly be interrupted until the diagnosis of pancreatitis can be excluded. Appropriate additional examinations must be performed. Measurement of serum amylase and lipase activity levels must be done locally. If acute pancreatitis is ruled out, trial product should be re-initiated on same dose as when trial product was interrupted.

Pancreatitis is confirmed if as a minimum 2 of 3 criteria are met:

- Severe acute abdominal pain
- Serum amylase and/or lipase >3× upper normal limit
- Characteristic findings on relevant imaging e.g. computerised axial tomography/magnetic resonance imaging/ultrasound

If diagnosis of pancreatitis is confirmed the trial product must be discontinued (sections 6.4 and 8.6.3.3) and appropriate treatment(s) and careful monitoring of the subject should be initiated.

8.6.3 Adverse events requiring specific event forms in the eCRF

For some AEs the investigator must complete a specific event form in the eCRF in addition to the AE form. The AEs that require specific event forms are:

- Gallstone disease
- Neoplasms
- Pancreatitis

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly (section 12.1).

8.6.3.1 Gallstone disease

If an event of acute gallstone disease or clinical suspicion of this is observed during the trial, this must be recorded as an AE and on a specific gallstone event form in the eCRF. The following information should be obtained, if available as part of standard of care:

- Signs and symptoms of acute gallstone disease

- Specific laboratory test supporting a diagnosis of gallstone disease:
  - White blood cell count (WBC)
  - C-reactive protein (CRP)
  - Direct, indirect and total bilirubin
  - ALT and AST
  - Alkaline Phosphatase (ALP)
  - Amylase
  - Lipase
- Imaging performed and consistency with gallstone disease
- Treatment given for the condition
- Relevant risk factors for gallstone disease including:
  - History of gallstones
  - Family history of gallstones
  - Relevant surgery

8.6.3.2 Neoplasms

All events of benign, pre-malignant/carcinoma in-situ and malignant neoplasms must be reported during the trial. This must be recorded as an AE and on a specific neoplasm event form in the eCRF. The following information should be obtained if available as part of standard of care:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated to the event
- New diagnosis or recurrence/relapse of the neoplasm

8.6.3.3 Pancreatitis

If an event of pancreatitis is observed during the trial, this must be recorded as an AE and on a specific pancreatitis event form in the eCRF. The following information should be obtained if available as part of standard of care:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis:
  - Amylase
  - Lipase
  - ALT and AST
  - Bilirubin
  - Alkaline Phosphatase

- Imaging performed and consistency with pancreatic disease
- Treatment and complications to the event
- Relevant risk factors for pancreatic disease including:
  - History of gallstones
  - History of pancreatitis
  - Family history of pancreatitis
  - Trauma

8.7 Other assessments

8.7.1 Plasma concentration of liraglutide for pharmacokinetics

Blood samples for assessment of liraglutide plasma concentration are drawn from all subjects during the 16-week double-blind trial period as per section 2.

Subjects and subjects' LAR must be instructed to withhold their trial product dose in the morning until blood sampling is performed on the visit.

The subjects and subjects' LAR must be instructed to complete the dosing diary for liraglutide plasma concentration assessment (section 2) and the dose, date and exact time for sampling the blood must be recorded in the eCRF.

The blood sample taken at V20 for liraglutide plasma concentration assessment from subjects treated with liraglutide only is not part of the pharmacokinetic/pharmacodynamic modelling plan (section 17.5). The purpose of this assessment is to preclude any false negative antibody results. Hence recordings in the subject's dosing diary and eCRF are not requested for this sample.

Quality controlled data must be available for review by Development Bioanalysis prior to database lock (DBL).

8.7.2 Dietary and physical activity counselling

8.7.2.1 Dietary counselling

Subjects and subjects' LAR must receive individualised dietary counselling with the goal of obtaining a weight loss. The counselling must be performed by a certified dietitian according to local standard. Individuals with Prader-Willi Syndrome have a different body composition with less muscle mass and a higher percentage of body fat even if they are at a normal body weight. As a result, their caloric needs are significantly lower and caloric intake should be restricted.

If a BMI corresponding to < 25 kg/m^2 for adults by international cut-off points[45] is reached subjects should be assigned a maintenance diet.

Dietary counselling can be done in person or by phone/video conference according to the flowchart and must be documented in subject's medical record.

Dietary counselling should preferably take place within the visit window for the relevant visit.

Dietary compliance must be evaluated at every visit by the dietitian, using a numerical rating scale (NRS), and results must be provided to the investigator. The investigator or delegated staff must translate the NRS into a number and record the data into the eCRF.

8.7.2.2 Counselling in physical activity

At every site, there must be a qualified person (site staff trained in physical activity counselling) to provide instructions and advise on physical activity. An increase in physical activity is encouraged and reinforced at every visit.

8.7.3 Subject diary

Subjects will be provided with a paper diary to be completed at home. Only the subjects and/or the LAR must enter data in the diary. Subjects will be instructed by the investigator in when and how to complete the diary. It is important to explain to the subjects the necessity of accurate diary recording.

Review of diaries must be documented by the investigator, either on the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject and it is important to explain to the subjects the necessity of accurate diary recording.

All data from the diary must be transcribed into the eCRF.

The diary will include three different sections as specified in sections 8.7.3.1, 8.7.3.2 and 8.7.3.3

8.7.3.1 Dosing diary

Dosing diary should be completed by the subject on the last three days before a visit including a blood sampling for liraglutide plasma concentration (section 8.7.1 and section 2).

The last 3 doses of liraglutide must be recorded with:

- Dose

- Date
- Exact time

8.7.3.2 Hypoglycaemic episode diary

The hypoglycaemic episode diary should be completed if the subject recognises a hypoglycaemic episode, i.e. a hypoglycaemic form for each episode (section 8.5.2)

8.7.3.3 Menstrual period diary

The menstrual period diary forms should be completed by all female subjects of childbearing potential during the trial. The first day of all menstrual periods, if applicable, should be recorded in the diary.

8.8 Subject compliance

To ensure subject trial compliance, the investigator and/or delegated staff should remind the subjects to follow the trial procedures and requirements throughout the trial. If a subject is found to be non-compliant, the investigator and/or delegated staff should remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Subject treatment compliance is assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed, the subject should be asked to return all used, partly used and unused trial product. The investigator must assess the amount of trial product returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject (section 9.4)

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.

Liraglutide or liraglutide placebo must not be used, if it does not appear clear and colourless or almost colourless.

9.1 Trial products

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

Table 9–1 Trial products

Trial product Investigational medicinal product (IMP)	Strength	Dosage form	Route of administration	Delivery device
Liraglutide 6.0 mg/mL 3 mL cartridge	6.0 mg/mL	Solution for injection	Subcutaneous injection (s.c.)	3 mL FlexPen®
Liraglutide placebo 3 ml cartridge	N/A			

Liraglutide and liraglutide placebo are visually identical.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[46], local regulations and trial requirements.

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

The investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit (V3). At all subsequent drug dispensing visits, directions for use should be handed out to subjects, if needed.

9.3 Storage

Table 9–2 Storage

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Liraglutide 6.0mg/mL	Store in a refrigerator between 2°C to 8°C (36°F to 46°F) Protect from light Do not freeze	At temperatures below 30°C or in a refrigerator between 2°C to 8°C US: At room temperature (59°F to 86°F) or in a refrigerator (36°F to 46°F) Protect from light Do not freeze	Use within one month US: Use within 30 days
Liraglutide placebo			

* In-use time starts when first dose is taken or used as spare pen.

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.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

Subjects must be instructed to return all used, partly used and unused trial products including empty packaging material at each dispensing visit.

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.

Drug accountability is performed by using the IV/WRS drug accountability module. Only dispensed DUNs (= Dispensing Unit Numbers) returned by the subject (used/partly used or unused) are accounted for.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk in accordance with the TMM:

- Direction for Use for the FlexPen®
- Needles for the device with a maximum needle length of 8 mm
- Blood glucose meters (BG meters) and BG-meter auxiliaries

10 Interactive voice/web response system

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

IV/WRS is used for:

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

IV/WRS user manuals will be provided to each trial site.

DUNs will be allocated using IV/WRS. It is important to dispense the exact allocated DUNs to a subject. The subject's treatment allocation will be revealed using the IV/WRS at V10.

11 Randomisation procedure and breaking of blinded codes

Randomisation will be stratified according to pubertal status and by presence/absence of dysglycaemia. Stratification will be controlled by the IV/WRS. The stratification factors are:

Pubertal status:

- Tanner below 2 (defined as Tanner stage 1 with or without premature adrenarche) (part B only)
- Tanner 2 or 3 (part A only)
- Tanner 4 or 5 (part A only)

Glycaemic status:

- dysglycaemia yes
- dysglycaemia no

Dysglycaemia is defined as pre-diabetes with FPG 5.6 – 6.9 mmol/L (both inclusive) (100 - 125 mg/dL) (both inclusive) and/or HbA_{1c} 5.7 – 6.4 % (both inclusive). The HbA_{1c} and FPG results from V2 must be used.

At randomisation, the subjects will be randomised to one of two parallel treatment groups: liraglutide or placebo. The randomisation will be carried out in a 2:1 manner using the IV/WRS.

The trial is a double-blind trial for the first 16 weeks followed by a 36 weeks open-label treatment period. Only subjects treated with liraglutide will receive trial treatment in the 36-weeks open-label treatment period. The subject's treatment allocation will be un-blinded on an on-going basis after the double blind period at week 16 (V10).

11.1 Breaking of blinded codes

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

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

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS helpdesk should be contacted. Contact details are listed in Attachment I.
If the code has been broken the subject is allowed to continue in the trial. If the subject must be withdrawn from the trial, a withdrawal session must be completed in IV/WRS.

11.2 Laboratory access to blinded data

The special laboratories analysing the samples for anti-liraglutide antibodies and concentration of liraglutide will be provided with a randomisation list. This procedure will be described in a blinding plan.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

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

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

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

The following three definitions are used when assessing an AE:

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

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

- **Final outcome**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the subject is lost to follow-up.

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].

a. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

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

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

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

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

The following AEs must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x ULN and total bilirubin >2 x ULN, where no alternative aetiology exists (Hy's law).

Non-serious adverse event

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

Medical event of special interest

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

1. Medication errors concerning trial products:
   - Administration of wrong drug or use of wrong device.
   - Note: Use of wrong DUN is not considered a medication error.
   - Wrong route of administration, such as intramuscular instead of subcutaneous.
   - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
   - Accidental administration of a lower or higher dose than intended. These are doses lower or higher than 0.6, 1.2, 1.8, 2.4 and 3.0 mg respectively for subjects in part A and part B (children with a body weight ≥ 45 kg) and doses lower than 0.3, 0.6, 1.2, 1.8 and 2.4 mg respectively for subjects in part B (children with a body weight < 45 kg) (within 24 hours). 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.

When reporting a MESI, the following forms must be completed: the AE form, SIF and specific MESI form, as described in section 12.2 and illustrated in Figure 12–1.

Adverse events with additional data collection

AEs with additional data collection are AEs (SAE or non-serious AE) defined as important for the evaluation of product safety. These include:

- Gallstone disease
- Neoplasms
- Pancreatitis

A detailed description of additional data collection is described in section 8.6.3. When reporting adverse events with additional data collection, the following forms must be completed: the AE form, specific event form and if the event is serious the SIF as described in section 12.2 and illustrated in Figure 12–1.

Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (section 2). The events must be recorded in the applicable CRF 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: Liraglutide (NN8022) Weight Management Investigator's Brochure (IB) or any updates hereof.

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

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

AEs (SAE or non-serious AE) requiring additional data collection must be reported using both the AE form and the specific event form. The specific event form is a form tailored to collect specific information related to the individual event.

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

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

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

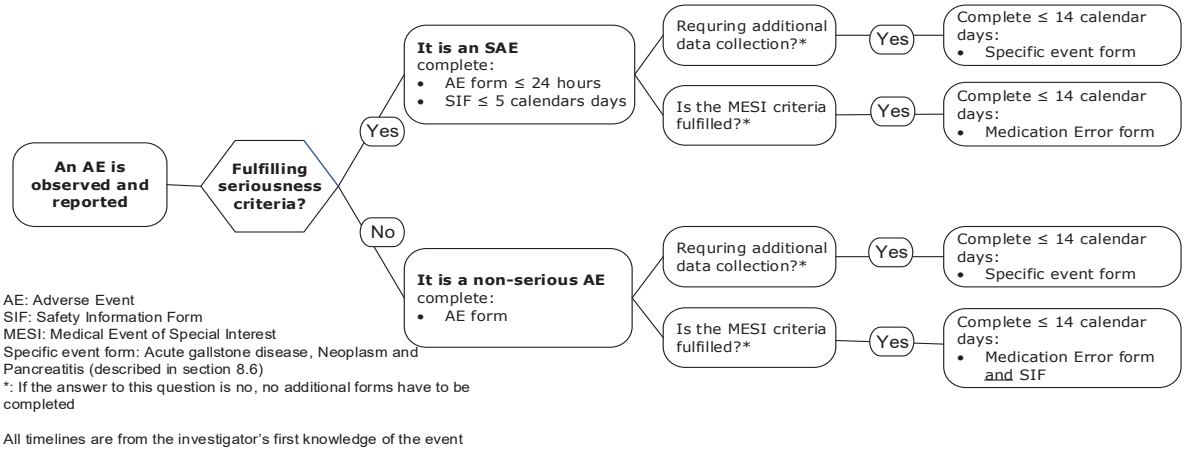
  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

- **SAEs fulfilling the MESI criteria:** In addition to above, the MESI form **within 14 calendar days** of the investigator's first knowledge of the AE.
- SAEs with additional data collection: In addition to above, the specific event form within 14 calendar days of investigator's first knowledge of the event.
- **Non-serious AE fulfilling the MESI criteria:** The AE form, SIF and MESI form **within 14 calendar days** of the investigator's first knowledge of the event.

- Non-serious AEs with additional data collection: The AE form and specific event 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[47]. 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[47], 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 should only include new (updated and/or additional) information that reflects the situation at the time of the investigator's signature.

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

- **SAEs**: The investigator must record follow-up information on all SAEs by updating the applicable form(s) in the eCRF (AE form, safety information form, specific event form and/or MESI form). 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:** The investigator must record follow-up information on non-serious AEs by updating the applicable form(s) in the eCRF (the AE form and/or the specific event form). 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 by updating the applicable form(s) in the eCRF (AE form, safety information form and/or MESI form). 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:

- Liraglutide FlexPen®
- Placebo FlexPen®
- Needles

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

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

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

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each coded batch number or for each DUN must be completed.

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

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. 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 coded batch number and, if available, the DUN.

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (section 9).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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

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

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

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

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

   Forms and timelines for reporting AEs:
   Non-serious AEs:
   – 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.

12.5.2 Pregnancies in female partners of male trial subjects (Applicable for US only)

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

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

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

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

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

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

   Forms and timelines for reporting AEs:

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

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

12.6 Precautions and/or overdose

From clinical trials and marketed use of liraglutide overdoses have been reported up to 24 times the recommended dose (72 mg). Generally, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. Severe hypoglycaemia has also been observed.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal liraglutide safety committee to perform ongoing safety surveillance. The liraglutide 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 independent 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 is composed of permanent members who are independent of Novo Nordisk and will cover relevant specialities (specialists in paediatrics, statistics and endocrinology) and they may request assistance from a number of additional ad hoc members, if needed.

The DMC is established to review PK data and unblinded safety data from the 16-week double-blind period of part A and recommend if the trial can proceed to part B. The DMC will also monitor safety throughout the trial on an ongoing basis, and recommend to Novo Nordisk whether to continue, modify, or terminate the trial as necessary. The composition of the DMC, objectives of the surveillance, meeting frequency and type, data to be analysed at the meetings and responsibilities with regard to information (such as meeting minutes) will be described in a DMC charter.

The DMC members will have direct contact with the Novo Nordisk Global Safety, and will have no direct interaction with trial management. The DMC recommendations should be addressed directly to Novo Nordisk Global Safety and the internal Novo Nordisk safety committee. It is the responsibility of the internal Novo Nordisk safety committee to take action for subject safety based on the DMC recommendations. DMC concerns relating to trial processes will be communicated to trial management via Novo Nordisk Global Safety.

13 Case report forms

In this trial a combination of electronic case report forms (eCRF) and paper CRFs will be used.

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:

- Pregnancy forms
- Technical complaint forms (only to be used as back-up for electronic reporting)
- AE forms (only to be used as back-up for electronic reporting)
- Safety information forms (only to be used as back-up for electronic reporting)

The paper version of the technical complaint form, AE form, safety information forms and special forms must only be used to ensure timely reporting when/if the electronic CRF is unavailable. The technical complaint form must be used for complaints that are not subject related.

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

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

13.1 Corrections to case report forms

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

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

13.2 Case report form flow

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

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

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV 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 CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP[47], but will not exceed 12 weeks for trial sites with active subjects (defined as subjects in screening, treatment, or follow-up).

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation other than the CRF.

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 investigator must make a reasonable effort to obtain additional information from external sources e.g. primary physician and other hospitals/departments to collect information required to evaluate all inclusion and exclusion criteria if not available in the subject’s medical record at the trial site and if not part of the screening assessments performed.

Considering the electronic source data environment, it is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore transcription to the diary from the glucometer is considered the source document for recordings of glucometer.

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

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

The monitor will ensure that the CRFs are completed.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Screen failure reason.
- SAEs

Monitors must review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF. 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. Data management may be delegated under an agreement of transfer of responsibilities to a contract research organisation (CRO).

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.

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.

Results from the statistical analysis will generally be presented by two-sided confidence intervals (CIs) with a confidence level of 95%. Superiority will be claimed if the two-sided p-value is less than 5% and the treatment estimate favours liraglutide.

The full analysis set (FAS) will be used in the analysis of the efficacy endpoints. For the safety endpoints, the safety analysis set (SAS) will be used. The definition of the analysis sets is given in Section 17.2.

For safety endpoints, summaries will be presented separately for the periods “in trial” and “on treatment” as defined in Section 17.4.1.2.

The baseline value will be defined as the last measured and available value from V3 (randomisation) and V2 (screening).

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

17.1 Sample size calculation

This is a superiority trial comparing liraglutide to placebo. Based on previous experience the treatment effect after 52 weeks is expected to be considerable larger than after 16 weeks. Therefore the sample size calculation below focuses alone on the first co-primary endpoint.

It is difficult to assess the anticipated effect of liraglutide in BMI SDS[48] in children and adolescents with PWS. It is anticipated that the effect is similar to the effect for adults.

The standard deviation (SD) is assessed based on publications[49,] and trial NN8022-3967 in adolescents with obesity aged 12−17 years. For the sample size scenarios, SDs of 0.15, 0.25 and 0.35 were investigated.

The effect of withdrawals is accounted for as a reduction of the anticipated treatment difference and increase of the SD. Since a conservative imputation method is planned for the main analysis of the primary endpoint, it is assumed that withdrawn subjects respond as if treated with placebo for the entire trial. The assumed withdrawal percentage at week 16 is 10% and 20% at week 52. This is lower than what was seen for trial NN8022-1839 in adults with obesity and adults with overweight. Since patients with Prader-Willi Syndrome are under close supervision by parents or institutional staff and for the lack of other therapeutic options, this assumption is considered reasonable. Let p_{WD} denote the probability of withdrawal. The adjustment for withdrawals is made by correcting the treatment difference Δ and variance σ^2 as

$$\Delta_{corr} = (1 - p_{WD})\Delta$$

$$\sigma^2_{corr} = \sigma^2 + \frac{2}{3} p_{WD}(1 - p_{WD})\Delta^2$$

The total number of subjects is shown for the investigated scenarios in the table below for 80%, 85% and 90% power.

Table 17–1 Sample size calculations for different scenarios; total number of subjects

Power	Treatment difference (completers)	SD		
		0.15	0.25	0.35
80%	-0.22	27	63	117
	-0.225	27	60	111
	-0.23	24	57	108
85%	-0.22	30	72	132
	-0.225	30	69	126
	-0.23	27	66	123
90%	-0.22	33	81	156
	-0.225	33	78	147
	-0.23	33	75	141

It seems realistic and conservative to assume a SD of 0.25 and a withdrawal rate of 10% after 16 weeks and 20% after 52 weeks. A withdrawal rate of 10% gives 57 subjects randomised. With this setting, a treatment difference of -0.23 corresponding to approximately a 5-6% decrease in BMI can be detected with a power of 80%. Assuming a withdrawal rate at 20% at week 52 a trial completion of 45 subjects, which is a regulatory requirement, is obtainable.

The distribution of the 57 subjects for randomisation on part A and B and the two treatment groups are shown in the table below.

Table 17–2 Overview of randomised subjects

	Liraglutide	Placebo	Total Liraglutide and Placebo	Expected number of subjects to complete treatment (at least 80%)	Minimum PIP requirement of subjects to complete treatment
Part A	22	11	33	28	28
Part B	16	8	24	19	17
Total	38	19	57	47	45

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline.

FAS: Includes all randomised subjects who have received at least one dose of trial product and have any post-randomisation data. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

SAS: Includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation “as treated”.

Data from nominal visits (V10x and V19x) will be used prior to imputation of remaining missing data unless otherwise stated.

Before data are locked for statistical analysis, a blind review of all data will take place. Any decision to exclude a subject or single observations from the statistical analysis is the joint responsibility of the trial statistician, the ITM and the medical specialist. Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

17.3 Primary endpoints

The two co-primary endpoints are:

- Change from baseline in BMI SDS[48] after 16 weeks of treatment
- Change from baseline in BMI SDS after 52 weeks of treatment

The hypotheses of equality between liraglutide and placebo for each of the two endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. The implication is that liraglutide will only be considered statistically significantly better than placebo at 52 weeks if it is considered statistically significantly better with respect to the first primary endpoint.

The primary analysis will include subjects from all strata, i.e. both from part A and part B (provided that the external DMC recommends that part B will be conducted).

BMI SDS will be summarised using descriptive statistics according to the stratification factor for Tanner stage and stratification factor for glycaemic category. In case there are a very low number of subjects within one glycaemic category, the description may be done according to stratification factor for Tanner stage alone.

The analysis of each of the co-primary endpoints will use the same approach and is described below.

The objective is to show that liraglutide is superior to placebo in obtaining weight loss.

Let $\mu_{liraglutide}$ and $\mu_{placebo}$ denote mean change in BMI SDS for liraglutide and placebo respectively. The null-hypothesis and the alternative hypothesis are:

H_0: $\mu_{liraglutide} = \mu_{placebo}$ against the alternative H_A: $\mu_{liraglutide} \neq \mu_{placebo}$

The null-hypothesis will be rejected on a 5% level if the two-sided 95% confidence interval of the treatment difference $\mu_{liraglutide} - \mu_{placebo}$ excludes 0. If the upper limit is below 0 superiority of liraglutide against placebo can be concluded.

The hypothesis will be tested using an analysis of covariance (ANCOVA) with treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects and baseline BMI SDS and baseline age as covariates. Part A of the trial includes Tanner stage 2-5 or hormonally-induced puberty, and part B includes Tanner stage below 2 and subjects with premature adrenarche. The stratification factor for Tanner stage includes three levels; stage below 2 (defined as Tanner stage 1 with or without premature adrenarche) (corresponding to part B), stage 2 and 3 together, and stage 4 and 5 together (the last two corresponds to part A). The baseline glycaemic category includes two levels; presence and absence of dysglycaemia.

Missing data will in the main analysis be handled by the following multiple imputation (MI) method. A pattern mixture model approach is applied where withdrawn subjects with missing

values are assumed to respond as if treated with placebo for the entire trial. Multiple copies (N = 1000) of the full dataset will be generated by imputing missing values based on estimated parameters for the placebo group. This will be done as follows.

- In the first step, N = 1000 copies of the dataset will be generated.
- In the second step, an enriched ANCOVA model with sex, region, stratification factor for Tanner stage, baseline glycaemic category and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects and baseline BMI SDS, as covariate is fitted to the change from baseline in BMI SDS at 16 weeks (or 52 weeks) for the completers in the placebo group only.
- For each of the N copies of the dataset, the estimated parameters and their variances from this model are used to impute missing values at 16 weeks (or 52 weeks) for subjects in both treatment arms, based on their factor levels and the values of the covariates.
- For each of the N complete datasets, the change from baseline in BMI SDS at 16 weeks (or 52 weeks) is analysed using the main ANCOVA model with treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, and baseline BMI SDS and baseline age as covariates.
- The estimates and SDs for the N data sets are pooled to one estimate m_{MI} and associated SD_{MI} using Rubin's formula:

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

where m_i and SD_i are the estimated means and standard deviations for the N copies of the dataset. From m_{MI} and SD_{MI}, the 95% CI for the treatment difference and the associated p-value are calculated.

If N = 1000 copies are insufficient to obtain stable results, a higher number will be used.

The MI method assumes that withdrawn subjects with missing values in the placebo arm have a response similar to the completers in the in the placebo arm given similar baseline characteristics. In the active arm the assumption is that withdrawn subjects with missing values behave as if they have been in the placebo arm during entire trial regardless of the time of withdrawal. In this way the assumptions are differential and conservative for estimating the treatment effect. The estimate in the primary analysis can be said to be an intention to treat (ITT) estimator or an effectiveness estimand of the add-on effect of liraglutide to dietary and physical activity counselling.

If the imputation ANCOVA model cannot be estimated due to too few placebo subjects with available data, explanatory variables will be removed in the following order until the model is

estimable: region, sex, baseline BMI SDS, Tanner stage, baseline glycaemic category and interaction between baseline glycaemic category and stratification factor for Tanner stage.

Sensitivity analysis

To investigate the sensitivity of the results of the main analysis of the primary endpoint with regard to the handling of missing data, the following sensitivity analyses will be performed:

- An ANCOVA will be performed with imputation of missing values according to the last observation carried forward (LOCF) method. The model will include terms for treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage, and baseline BMI SDS and baseline age as covariates. The response variable will be the last available measurement of BMI SDS obtained within the 16-week double-blind period of the trial. Data from nominal visits (V10x and V19x) will not be used for this analysis.
- The same type of ANCOVA as above will be performed, but using an imputation of missing values according to the baseline observation carried forward (BOCF) method. Missing measurements of BMI SDS at 16 weeks will with this method be imputed by the corresponding baseline values.
- The same type of ANCOVA as above will be performed without imputation by only including subjects who completed the 16-week double-blind period.
- A mixed model for repeated measurements (MMRM) will be applied where all post baseline BMI SDS measurements obtained at planned visits during the 16-week double-blind period will enter as the dependent variables, and visit, treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage will be included as fixed effects, and baseline BMI SDS and baseline age as covariates. All these factors and covariates will be nested under visit, which is technically the same as introducing the corresponding interaction terms in the model. An unstructured covariance matrix for the BMI SDS measurements within subject will be employed.

The sensitivity analyses will be repeated for the week 52 co-primary endpoint.

The ANCOVA model with LOCF assumes that post treatment discontinuation, the body weight is on average stable in both treatment arms. If the assumption holds, the treatment effect (effectiveness estimand) in each arm and the treatment difference can be estimated from this analysis unbiased. If the withdrawal and the development in both arms are similar, the treatment difference can be estimated from this analysis unbiased. If the development in body weight after treatment discontinuation differs between active and placebo, this analysis might provide an optimistic or over-conservative estimate, depending on the actual circumstances. The analysis is included to be

able to compare the results with legacy obesity programs, where this analysis was the main analysis of the primary endpoints.

The ANCOVA model with BOCF assumes that post treatment withdrawn subjects with missing values returns to a body weight in the proximity of their baseline body weight regardless of the timing of withdrawal. This analysis is expected to provide a conservative estimate (effectiveness estimand) of the treatment effect (in each arm). The impact of this assumption on the treatment difference depends on withdrawal pattern over time and development of body weight post withdrawal and reason for withdrawal. The analysis is typically expected to provide a conservative estimate of the treatment difference (effectiveness estimand).

The MMRM model assumes that withdrawn subjects, had they completed the trial, would not have behaved differently than completing subjects from the same treatment arm with the same baseline characteristics and change in body weight at time of withdrawal. This analysis estimates the treatment difference had all subjects stayed on the randomised treatment (efficacy estimand).

The ANCOVA analysis in completers is expected to give more positive results than the primary analysis. However, this analysis has its own clinical interpretation and will serve as a benchmark and provide an estimate of the efficacy estimand in the population that tolerate the trial product and endure the diet and exercise counselling program.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

The planned secondary endpoints will be analysed as outlined in this section.

17.4.1.1 Efficacy endpoints

BMI

The changes in BMI from baseline at 16 and 52 weeks will be analysed separately with the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, but with the baseline BMI as covariate instead of the baseline BMI SDS.

In addition, the following categorical endpoints related to BMI will be evaluated:

- Percentage of subjects achieving ≥ 5% reduction in baseline BMI at 16 weeks
- Percentage of subjects achieving ≥ 5% reduction in baseline BMI at 52 weeks
- Percentage of subjects achieving ≥ 10% reduction in baseline BMI at 16 weeks
- Percentage of subjects achieving ≥ 10% reduction in baseline BMI at 52 weeks

These endpoints will be analysed separately using a logistic regression model. The response will be a binary outcome (yes/no) indicating for each subject whether the respective minimum reduction in BMI has been achieved. The model will include treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, and baseline BMI and baseline age as covariates. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

For the analysis of the categorical endpoints, missing BMI values will be imputed using the 100 complete datasets from the MI performed for the corresponding analysis on the continuous change in BMI. The logistic regression will be performed on each of these datasets. Rubin's formula will then be applied on the 100 estimates of the log odds ratio and the associated SDs to produce a pooled estimate and SD. These pooled values will lastly be used to calculate the 95% CI for the odds ratio.

BMI SDS: No increase

The percentage of subjects with no increase in BMI SDS at 16 and 52 weeks will be analysed using the same statistical method as the one used for the categorical endpoints related to BMI, but with the baseline BMI SDS as covariate instead of the baseline BMI.

Hyperphagia questionnaire outcome

The questionnaire on hyperphagia will be evaluated similarly to the primary endpoint. That is, the change in hyperphagia score (hyperphagia total score and hyperphagic behaviour, drive and severity score respectively), from baseline at 16 and 52 weeks will be analysed separately using the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, but with the corresponding baseline hyperphagia score instead of the baseline BMI SDS as covariate.

Glycaemic category

The change in glycaemic category (normoglycaemia, pre-diabetes, T2DM) from baseline at 16 and 52 weeks will be summarised using descriptive statistics.

Furthermore, two separate analyses will be performed on the binary variable normoglycaemia (yes/no) at 16 and 52 weeks, using a logistic regression model with the factors treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage , and baseline age as

covariate. Missing data will be handled by a MI method similar to the one used for the main analysis of the primary endpoint, but adapted to the logistic regression model. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

Other efficacy endpoints

The following other efficacy variables will be evaluated:

- Body weight
- Waist circumference
- Waist to hip circumference ratio
- CV biomarker (hsCRP)
- Fasting lipids (TC, LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol, VLDL cholesterol, TG and FFA)
- Systolic and diastolic blood pressure
- Quantitative glucose metabolism parameters (HbA_{1c}, FPG, fasting insulin, C-peptide, HOMA-B and HOMA-IR)

The changes in these variables from baseline at 16 and 52 weeks will be analysed using the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, but with the baseline value of the corresponding variable instead of the baseline BMI SDS as covariate. Each endpoint will be analysed separately. For hsCRP, fasting lipids, fasting insulin, C-peptide, HOMA B and HOMA IR, the response and baseline values will be log transformed prior to the analysis.

17.4.1.2 Safety endpoints

Adverse events

AEs will be summarised for the safety analysis set separately for two periods:

- In trial: defined as events with onset date on or after the first day of trial product administration and no later than the last study visit.
- On treatment: defined as events with onset date on or after the first day of trial product administration and no later than whatever comes first: a) 14 days after the last day on trial product, b) FU visit (subjects with trial product discontinued), or c) last study visit (early withdrawn subjects without FU visit).
- A treatment emergent adverse event (TEAE) is defined as an event that occurs in the 'on treatment' period .

The AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA). They will be presented in terms of the number and percentage of subjects with at least one event, the number of events and the event rate per 1000 years. AEs in the screening period will be presented in listings.

Hypoglycaemic episodes

The hypoglycaemic episodes will be summarised descriptively by severity and treatment in terms of the number and percentage of subjects with at least one event and the total number of events. In the same way as for AEs, there will be separate summaries for the "in trial" and "on treatment" periods. Hypoglycaemic episodes in the screening period will be presented in listings.

Classification of Hypoglycaemia:

Treatment emergent: Hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 14 days after the last day on trial product.

Nocturnal hypoglycaemic episodes: Are episodes occurring between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the American Diabetes Association (ADA) classification of hypoglycaemia (see Figure 17–1).

Novo Nordisk classification of hypoglycaemia

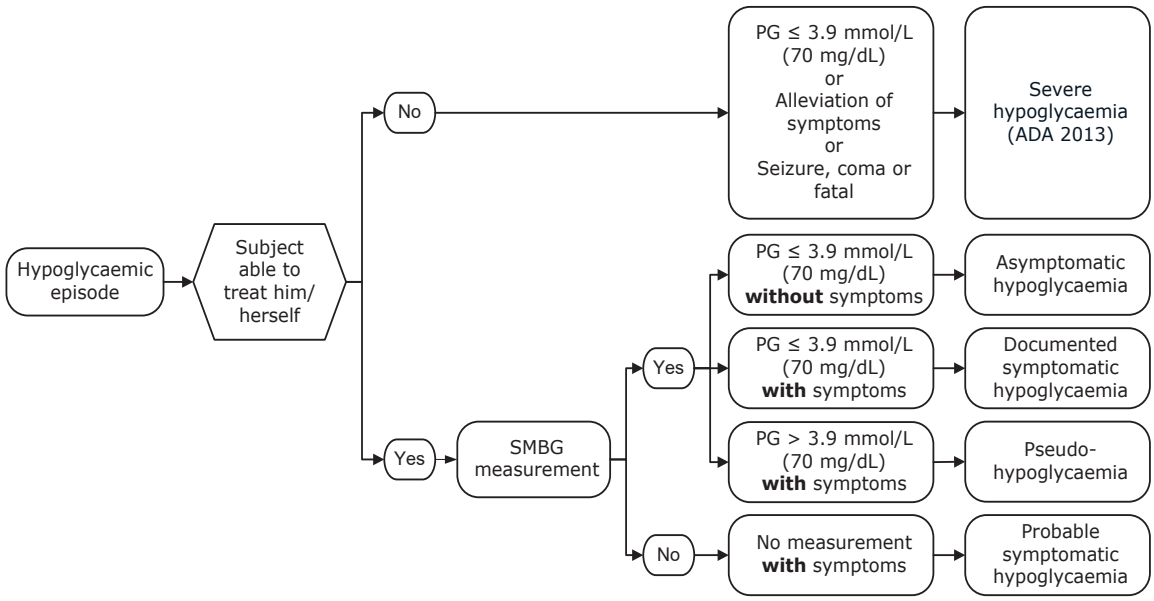
In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[50]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification[51].
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value < 3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[51] or BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[51] or BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia.

ADA classification[2] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 ADA classification of hypoglycaemia

Anti-liraglutide antibodies

Anti-liraglutide antibodies will be summarised in terms of the number and percentage of subjects at each visit that are antibody-positive and antibody-negative. Similarly, subjects with cross-reactivity against endogenous GLP-1 and in vitro neutralising effect will be summarised.

In addition, a comparison of the change in HbA_{1c} and body weight between antibody-positive and antibody-negative subjects will be performed using descriptive statistics and graphs. Listings with the individual antibody results will also contain information about the HbA_{1c} levels and body weight measurements. The impact of anti-liraglutide antibodies on safety will be similarly assessed by descriptive comparisons between antibody-positive and antibody-negative subjects.

ECG

Summary statistics and the frequencies of shifts in ECG status from baseline at 16 and 52 weeks will be tabulated for each treatment group.

Pulse

Summary statistics and the frequencies of shifts from baseline to 16 and 52 weeks will be tabulated for each treatment group. In addition, statistical analyses similar to those made for blood pressure will be performed.

Laboratory parameters

Summary statistics will be tabulated for each laboratory parameter. The distributions will also be presented graphically using box plots by treatment and week.

For each laboratory parameter, the values will be compared to the relevant reference range. The results will be presented as follows:

- Shifts from baseline at 16 and 52 weeks will be tabulated. The shift tables will include the number of subjects below, within and above the reference range at each visit
- The proportion of subjects with laboratory values outside the reference range will be tabulated per visit and treatment group
- Individual values outside the reference range (abnormal values) will be listed by treatment and subject

For amylase and lipase two statistical analyses will be applied, respectively. The relative change (100*value/baseline) will be analysed with an MMRM model as described under sensitivity analysis in section 17.3. The response and baseline values will be log transformed prior to the analysis. Subjects having a measurement above 3UNR anytime during treatment (yes/no) will be analysed using a logistic regression. For the evaluation of the response, all measurements obtained during treatment will be included and these measurements are defined as any scheduled or un-

scheduled measurements obtained from, but not including, baseline and until, and including, end of treatment (visit 19). The model will include treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, and baseline value of the variable and baseline age as covariates. Separate analyses will be made for amylase and lipase. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

Pubertal status

Tanner stage at screening as well as changes in Tanner stage at 16 and 52 weeks will be summarised using descriptive statistics.

Physical examination

Physical examination at screening and changes in physical examination will be summarised.

Mental health questionnaires

Results from the mental health questionnaires PHQ-9 and C-SSRS from part A will be summarised using descriptive statistics and the frequencies of shifts from baseline to 16 and 52 weeks will be tabulated for each treatment group.

17.4.1.3 Pharmacokinetic endpoints

See section 4.2.2.2.

17.5 Interim analysis

No interim analysis is planned for the efficacy data in this trial. PK data from part A will be included in a population PK analysis also including historical data for other populations to aid dose selection for part B. Modelling results and safety data will be reviewed by the DMC before subjects in Part B will be enrolled in the trial. Before the randomisation code break, modelling results will only be communicated to DMC and to individuals involved in dose selection for part B.

17.6 Pharmacokinetic and/or pharmacodynamic modelling

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk A/S. A more technical and detailed elaboration of the population PK analysis will be done in the modelling analysis plan (MAP), which will be finalised before DBL. The population PK analysis will be reported in a modelling analysis report separate from the CTR. The model-derived AUC and CL/F will be summarized in the CTR, referring to the modelling analysis report, which will be included as an appendix to the CTR.

The objective of this modelling analysis is to study the liraglutide exposure in paediatric subjects with PWS and to investigate the effects on liraglutide plasma concentrations of pre-specified

covariates for these subjects. The analyses will be based on sparse liraglutide plasma concentration samples from all subjects, dosing history, body measurements and demographic data. Data from pre-defined historical trials in relevant populations (for example adults with obesity) might be included in the analysis to allow for the comparison with relevant populations. No pre-defined time of day is specified for the sampling, but the exact date and time of sampling will be recorded by the investigator.

The pharmacokinetics of liraglutide will be evaluated using population PK analysis methods to aim for the estimation of the apparent clearance (CL/F) and apparent distribution volume (V/F). $AUC_{(0\text{-}24hr,\ ss)}$ and t½ will be derived from the model parameter estimates. Due to the sparseness of the data, V/F might not be estimable, and hence, t½ cannot be derived. In case, CL/F will be estimated, while other model parameters may be set to prior pre-defined estimates (based on data from other trials). The number and timing of samples has been optimised to allow for the estimation of CL/F.

The individual estimates of $AUC_{(0\text{-}24hr,\ ss)}$ will be derived from CL/F, and used to verify adequate exposure in patients in part A and B.

The pre-specified analysis will explore the effects of covariates on liraglutide exposure. The covariates of interest, such as body weight, sex and age group, will be tested on CL/F.

Exposure-response analysis

The PK and PD data may be included in exploratory analyses of PK and exposure-response relationships, which may also include data from other trials.

17.7 Health economics and/or patient reported outcomes

The questionnaire of hyperphagia score will be evaluated as described in Section 17.4.1.1 The evaluation of the mental health questionnaires PHQ-9 and C-SSRS is described in Section 17.4.1.2.

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial will be conducted in compliance with ICH GCP[47], applicable regulatory requirements and in accordance with the Declaration of Helsinki.[4]

Current treatment options for paediatrics with obesity are limited and include lifestyle modifications and orlistat. Both treatment options are associated with suboptimal adherence, which in the case of orlistat is due to gastrointestinal adverse reactions[52-56]. In a head-to-head comparison of liraglutide 3.0 mg and orlistat in adults with obesity, liraglutide effected significantly greater mean weight loss after one year (3.8 kg more than orlistat, $p<0.0001$) and enabled a greater proportion of subjects to lose >5% of baseline body weight[57].

The present trial design will be conducted in children only after the safety has been confirmed in adolescents with obesity who have a documented history of failing to lose weight with lifestyle modifications. Trial subjects will have access to experimental intensified treatment, liraglutide, which has been shown to induce weight loss and improve cardio metabolic and quality of life parameters in adults with obesity at a dose of liraglutide 3.0 mg.

To date, two randomised, controlled PK/PD trials with liraglutide have been completed in paediatric subjects; trial NN2211-1800 (liraglutide 1.8 mg in subjects with T2DM (10 to < 18 years, duration of 5-6 weeks) and trial NN8022-3967 (liraglutide 3.0 mg in subjects with obesity and without T2DM (12 to < 18 years), duration of 5-6 weeks). In both trials, liraglutide was generally well tolerated, and there were no unexpected safety or tolerability issues identified.

The safety and efficacy experience with liraglutide in adult and paediatric subjects is described in details in the current version of the Investigator's Brochure[58] and any updates hereof.

Identified and expected risks
With respect to the key risks of liraglutide, the most frequently reported adverse events in subjects treated with liraglutide 3.0 mg were gastrointestinal (nausea and diarrhoea), with onset in weeks 1-4; these were mild to moderate, and transient. Other gastrointestinal adverse events included: dyspepsia, vomiting, constipation, and abdominal pain. During the post-marketing safety surveillance of post-marketing reports from marketed liraglutide (Victoza®), Novo Nordisk A/S identified reports containing events related to altered renal function using the standardised MedDRA query (SMQ) Acute renal failure. These events are mainly transient and related to dehydration and were more frequent in patients with pre-existing renal impairment. Based on the known risk associated with subcutaneous administration of proteins and peptides, reported adverse events related to allergic reactions and due to the potential severity of these events, allergic reactions is an identified risk.

An association between the use of GLP-1RAs and pancreatitis has been suggested based on case reports received in clinical trials and during the post-marketing experience with liraglutide (in T2DM) and other GLP-1RAs. Few events of pancreatitis have been reported in clinical trials with liraglutide in weight management. Cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) were reported more commonly in adult subjects treated with liraglutide 3.0 mg compared to placebo. From literature, it is well-known that obesity carries an increased risk of cholelithiasis and that an association between rapid and or marked weight loss and the development of cholelithiasis is present[59-62].

Potential risks

There is currently no evidence in humans supporting a causal relationship between liraglutide treatment and any of the following potential risks.

C-cell tumours induced in mice and rats following dosing of liraglutide are believed to be caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive. The relevance for humans is likely to be low. No reports of MTC have been identified as having a clear causal relationship to liraglutide. Data from the intensive monitoring of calcitonin (a marker for MTC) in plasma in the liraglutide clinical development programmes do not support an effect of liraglutide effect on calcitonin levels in humans.

Subjects with obesity and subjects with overweight have an increased risk of certain types of cancer. In the weight management programme, the reporting rate of neoplasm events confirmed by external independent event adjudication was similar with liraglutide and placebo. Based on a limited number of reports in the weight management programme, a numerical imbalance was observed for events of breast neoplasms in females and colorectal adenomas in males.

In the clinical development programme, mean increase in resting pulse (by 2-3 beats per minute) as well as a decrease in systolic blood pressure has been observed. The long-term clinical effects of the increase in resting pulse have not been established. There was no indication that the effect on resting pulse was dose dependent. However, as the long-term clinical effects of the increase in resting pulse have not been established, cardiovascular disorders are an important potential risk also for liraglutide in weight management.

Trial-specific risk mitigation

Adrenal insufficiency has been reported in patients with PWS. Although uncommon, the clinical manifestations are serious[63]. Therefore it is important to ensure patients enrolled in the trial do not have this condition. As an inclusion criterion, subjects are required to have had testing performed to evaluate for adrenal insufficiency before enrolment in the trial, see Section 8.1.1.1.

All participating subjects will be monitored closely through frequent site visits and telephone/video conference contact. Blood sampling frequency and volume will be minimised for subjects' safety and convenience. The duration of the double-blind trial period is set to 16 weeks in an effort to limit the duration of placebo injections and reduce unnecessary subject discomfort/inconvenience (Section 5.2).

In order to improve gastrointestinal tolerability of liraglutide, a weekly dose-escalation scheme will be used during the initial 4-8 weeks. In contrast to the scheme used for adult subjects, for children with PWS subjects, the liraglutide dose will be escalated only if the previous dose is tolerated (as judged by the investigator). Furthermore, to resolve tolerability issues, the investigator is allowed to down-titrate to the previously given dose or to prolong a dose step for one additional week (see section 5.3 for details). Subjects treated with liraglutide should be advised of the potential risk of dehydration, renal impairment and acute renal failure, in relation to gastrointestinal AEs and take precautions to avoid fluid depletion. Subjects with PWS will not necessarily present with gastrointestinal symptoms but are at risk of delayed gastric emptying and treatment with liraglutide may exacerbate this. With the potential risk of gastric rupture, the Investigator must pay special attention to subjects who vomit or have persistent, severe abdominal pain.

Hypoglycaemic episodes will be assessed in this trial as part of routine safety monitoring. If a subject develops T2DM during the trial, he/she will be allowed to remain in the trial if glycaemic control can be achieved diet and exercise with additional metformin.

Subjects with a history of acute or chronic pancreatitis will be excluded from trial participation. Trial participants will be informed of the characteristic symptoms of acute pancreatitis. Furthermore, serum lipase and amylase activity levels will be monitored on a regular basis during the course of the trial. If pancreatitis is suspected, liraglutide/liraglutide placebo will be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated. Subjects that are diagnosed with acute pancreatitis must have their trial product withdrawn.

Subjects with a personal or family history of MTC and subjects with Multiple Endocrine Neoplasia Syndrome type 2 are excluded from this trial. In addition, subjects with a screening calcitonin (a specific biomarker for C-cell activation) level $\geq$ 50 ng/L will be excluded from the trial, as hormone concentrations above this threshold are indicative of C-cell neoplasia[64]. During the trial, calcitonin levels will be measured at pre-specified trial visits and levels above upper normal range will be flagged by the laboratory, and reported to the investigator and Novo Nordisk.

It is assumed that the benefits and risks associated with long-term liraglutide treatment will be the same for the paediatric population with PWS as for the adult populations with the exception of any unforeseen effects on growth and pubertal development. In non-clinical studies, dosing liraglutide from post-natal day 21 to 91 in juvenile rats caused a dose-dependent delay in sexual maturation,

defined in females as age of animals for vaginal opening, and for males as preputial separation (both onset and end) that was most pronounced in females. A delay in age of sexual maturation is known to occur in rats and humans under caloric restriction/increased energy expenditure[7]. Estrous cycle length was slightly extended among high-dose female rats during treatment but returned to normal after two weeks of recovery.

Pubertal and growth related hormonal levels, biochemical parameters of bone metabolism and growth and pubertal development will be monitored in the present trial. An external independent DMC will be established to review and evaluate accumulative data from an ongoing clinical trial in order to protect the safety of the subjects and to evaluate the evolving risk-benefit profile of liraglutide. Additionally an expert in paediatric calcitonin will review abnormal levels as described in Appendix C.

Conclusion

Given the scarcity and limitations of available treatment options for paediatric obesity, and obesity associated with PWS, the potential weight loss and cardio-metabolic benefits of liraglutide and its acceptable safety/tolerability profile noted in the short-term paediatric trials, it is concluded that the potential benefits from participating in the present trial outweigh the potential risks. Based on the tolerability seen and model-estimated steady-state liraglutide exposure in the previous PK/PD trials in children 10 to less than 18 years with T2DM and 12 to less than 18 years with obesity, a starting dose of 0.6 mg has been chosen in children ≥ 12 and < 18 years. Dosing in children ≥ 6 and < 12 years of age will be determined based on the results of the NN8022-4181 trial and on the DMC review of PK and safety data from the 16-week double-blind period of part A of this trial.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[47] and the requirements in the Declaration of Helsinki[4].

Before any trial-related activity, the investigator must give the subject and/or the subject's legally acceptable representative (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. In addition to the information given to the subject's LAR, the child or adolescent must be given information according to his/her capacity to understand, always taking into consideration the subject's presumed willingness to participate in a clinical trial.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial. The informed consent/assent must be signed at least one day prior to V2 as the subject must attend this visit fasting.

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.

If the minor reaches legal age while participating in the trial and has only signed an age specific informed consent/child assent form, the subject has to re-consent to the informed consent form signed by the subject's LAR.

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 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.

18.4 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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the DMC, 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
- 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: 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 for US sites
- All investigators, as described above, wil 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 if more than one site is involved in the trial.

By signing the protocol, each investigator agrees to comply fully with ICH GCP[47], applicable regulatory requirements and the Declaration of Helsinki[4].

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 unauthorised persons can get access to the data.

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[35].

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[34].

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

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[35] (sometimes referred to as the Vancouver Criteria).

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 biospecimens

Anti-liraglutide antibody samples are taken during the trial (section 2). The samples are sent via central lab to a special lab, where they are analysed. Samples from V19 that are anti-drug antibody positive as well as a number of anti-drug antibody negative baseline samples will be sent from the special lab to Novo Nordisk for further analysis. Only personnel from the special lab and Novo Nordisk will have access to the samples. The samples may be stored until marketing authorisation by regulatory authorities (USA and EU) but no longer than 15 years after end of trial as further characterisation of the antibody response may be requested by the health authorities.

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 be informed by Novo Nordisk about the

results if the findings are deemed clinically relevant. In this 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 clinical trial report synopsis to the IRB/IEC.

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

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

Regulatory Authorities:

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

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

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

Netherlands: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015, 24 november 2014 (Decree compulsory insurance in medical research involving human subjects 2015, 24 November 2014).

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Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Appendix A

Liraglutide
NN8022-4179

Body mass index for age

Table of Contents

Page

List of in-text tables

Page

1 Introduction

According to protocol inclusion criterion no. 5 subjects must have a BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points and ≥ the 95th percentile for age and sex. Table 1, table 3 and table 4 must be used to determine subject eligibility.

Table 2 should be used if subjects are assigned a maintenance diet.

2 International BMI cut of points

Table 1 International cut off points for body mass index for obesity by sex for children between 6 and 18 years, defined to pass through BMI of 30 kg/m^2 at age 18. Obtained by averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore, and United States[1]

Age : Years	Body mass index 30 kg/m^2 Males	Body mass index 30 kg/m^2 Females
6	19.78	19.65
6.5	20.23	20.08
7	20.63	20.51
7.5	21.09	21.01
8	21.60	21.57
8.5	22.17	22.18
9	22.77	22.81
9.5	23.39	23.46
10	24.00	24.11
10.5	24.57	24.77
11	25.10	25.42
11.5	25.58	26.05
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84
18	30	30

Table 2 International cut off points for body mass index for obesity by sex for children between 6 and 18 years, defined to pass through BMI of 25 kg/m^2 at age 18. Obtained by averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore, and United States[1]

Age : Years	Body mass index 25 kg/m^2 Males	Body mass index 25 kg/m^2 Females
6	17.55	17.34
6.5	17.71	17.53
7	17.92	17.75
7.5	18.16	18.03
8	18.44	18.35
8.5	18.76	18.69
9	19.10	19.07
9.5	19.46	19.45
10	19.84	19.86
10.5	20.20	20.29
11	20.55	20.74
11.5	20.89	21.20
12	21.22	21.68
12.5	21.56	22.14
13	21.91	22.58
13.5	22.27	22.98
14	22.62	23.34
14.5	22.96	23.66
15	23.29	23.94
15.5	23.60	24.17
16	23.90	24.37
16.5	24.19	24.54
17	24.46	24.70
17.5	24.73	24.85
18	25	25

Determination of a subject's BMI > 95th percentile[2]

Table 3 BMI-for-age GIRLS 6 to 18 years (percentiles)

Year: Month	Month	95th percentile (BMI in kg/m^2)
6:0	72	18.4
6:1	73	18.4
6:2	74	18.4
6:3	75	18.5
6:4	76	18.5
6:5	77	18.5
6:6	78	18.6
6:7	79	18.6
6:8	80	18.6
6:9	81	18.7
6:10	82	18.7
6:11	83	18.8
7:0	84	18.8
7:1	85	18.9
7:2	86	18.9
7:3	87	19.0
7:4	88	19.0
7:5	89	19.1
7:6	90	19.1
7:7	91	19.2
7:8	92	19.2
7:9	93	19.3
7:10	94	19.3
7:11	95	19.4
8:0	96	19.4
8:1	97	19.5
8:2	98	19.6
8:3	99	19.6

Year: Month	Month	95th percentile (BMI in kg/m^2)
8:4	100	19.7
8:5	101	19.8
8:6	102	19.8
8:7	103	19.9
8:8	104	20.0
8:9	105	20.0
9:10	106	20.1
9:11	107	20.2
9:0	108	20.2
9:1	109	20.3
9:2	110	20.4
9:3	111	20.5
9:4	112	20.5
9:5	113	20.6
9:6	114	20.7
9:7	115	20.7
9:8	116	20.8
9:9	117	20.9
9:10	118	21.0
9:11	119	21.1
10:0	120	21.1
10:1	121	21.2
10:2	122	21.3
10:3	123	21.4
10:4	124	21.5
10:5	125	21.5
10:6	126	21.6
10:7	127	21.7
10:8	128	21.8
10:9	129	21.9
10:10	130	22.0

Year: Month	Month	95th percentile (BMI in kg/m^2)
10:11	131	22.1
11:0	132	22.2
11:1	133	22.2
11:2	134	22.3
11:3	135	22.4
11:4	136	22.5
11:5	137	22.6
11:6	138	22.7
11:7	139	22.8
11:8	140	22.9
11:9	141	23.0
11:10	142	23.1
11:11	143	23.2
12:0	144	23.3
12:1	145	23.4
12:2	146	23.5
12:3	147	23.6
12:4	148	23.7
12:5	149	23.8
12:6	150	23.9
12:7	151	23.9
12:8	152	24.0
12:9	153	24.1
12:10	154	24.2
12:11	155	24.3
13:0	156	24.4
13:1	157	24.5
13:2	158	24.6
13:3	159	24.7
13:4	160	24.8
13:5	161	24.9

Year: Month	Month	95th percentile (BMI in kg/m^2)
13:6	162	25.0
13:7	163	25.1
13:8	164	25.1
13:9	165	25.2
13:10	166	25.3
13:11	167	25.4
14:0	168	25.5
14:1	169	25.6
14:2	170	25.6
14:3	171	25.7
14:4	172	25.8
14:5	173	25.9
14:6	174	25.9
14:7	175	26.0
14:8	176	26.1
14:9	177	26.1
14:10	178	26.2
14:11	179	26.3
15:0	180	26.3
15:1	181	26.4
15:2	182	26.5
15:3	183	26.5
15:4	184	26.6
15:5	185	26.6
15:6	186	26.7
15:7	187	26.7
15:8	188	26.8
15:9	189	26.8
15:10	190	26.9
15:11	191	26.9
16:0	192	27.0

Year: Month	Month	95th percentile (BMI in kg/m^2)
16:1	193	27.0
16:2	194	27.1
16:3	195	27.1
16:4	196	27.1
16:5	197	27.2
16:6	198	27.2
16:7	199	27.2
16:8	200	27.3
16:9	201	27.3
16:10	202	27.3
16:11	203	27.4
17:0	204	27.4
17:1	205	27.4
17:2	206	27.4
17:3	207	27.5
17:4	208	27.5
17:5	209	27.5
17:6	210	27.5
17:7	211	27.6
17:8	212	27.6
17:9	213	27.6
17:10	214	27.6
17:11	215	27.6
18	216	27.7

Table 4 BMI-for-age-BOYS[2] 6 to 18 years (percentiles)

Year: Month	Month	95th percentile (BMI in kg/m^2)
6:0	72	17.9
6:1	73	17.9
6:2	74	17.9
6:3	75	17.9
6:4	76	18.0
6:5	77	18.0
6:6	78	18.0
6:7	79	18.1
6:8	80	18.1
6:9	81	18.1
6:10	82	18.2
6:11	83	18.2
7:0	84	18.3
7:1	85	18.3
7:2	86	18.3
7:3	87	18.4
7:4	88	18.4
7:5	89	18.5
7:6	90	18.5
7:7	91	18.6
7:8	92	18.6
7:9	93	18.7
7:10	94	18.7
7:11	95	18.8
8:0	96	18.8
8:1	97	18.9
8:2	98	18.9
8:3	99	19.0
8:4	100	19.0
8:5	101	19.1

Year: Month	Month	95th percentile (BMI in kg/m^2)
8:6	102	19.1
8:7	103	19.2
8:8	104	19.2
8:9	105	19.3
9:10	106	19.3
9:11	107	19.4
9:0	108	19.5
9:1	109	19.5
9:2	110	19.6
9:3	111	19.6
9:4	112	19.7
9:5	113	19.8
9:6	114	19.8
9:7	115	19.9
9:8	116	20.0
9:9	117	20.0
9:10	118	20.1
9:11	119	20.2
10:0	120	20.2
10:1	121	20.3
10:2	122	20.4
10:3	123	20.4
10:4	124	20.5
10:5	125	20.6
10:6	126	20.7
10:7	127	20.7
10:8	128	20.8
10:9	129	20.9
10:10	130	21.0
10:11	131	21.0
11:0	132	21.1

Year: Month	Month	95th percentile (BMI in kg/m^2)
11:1	133	21.2
11:2	134	21.3
11:3	135	21.4
11:4	136	21.4
11:5	137	21.5
11:6	138	21.6
11:7	139	21.7
11:8	140	21.8
11:9	141	21.8
11:10	142	21.9
11:11	143	22.0
12:0	144	22.1
12:1	145	22.2
12:2	146	22.3
12:3	147	22.3
12:4	148	22.4
12:5	149	22.5
12:6	150	22.6
12:7	151	22.7
12:8	152	22.8
12:9	153	22.9
12:10	154	23.0
12:11	155	23.1
13:0	156	23.1
13:1	157	23.2
13:2	158	23.3
13:3	159	23.4
13:4	160	23.5
13:5	161	23.6
13:6	162	23.7
13:7	163	23.8

Year: Month	Month	95th percentile (BMI in kg/m^2)
13:8	164	23.9
13:9	165	24.0
13:10	166	24.0
13:11	167	24.1
14:0	168	24.2
14:1	169	24.3
14:2	170	24.4
14:3	171	24.5
14:4	172	24.6
14:5	173	24.7
14:6	174	24.7
14:7	175	24.8
14:8	176	24.9
14:9	177	25.0
14:10	178	25.1
14:11	179	25.1
15:0	180	25.2
15:1	181	25.3
15:2	182	25.4
15:3	183	25.5
15:4	184	25.5
15:5	185	25.6
15:6	186	25.7
15:7	187	25.8
15:8	188	25.8
15:9	189	25.9
15:10	190	26.0
15:11	191	26.1
16:0	192	26.1
16:1	193	26.2
16:2	194	26.3

Year: Month	Month	95th percentile (BMI in kg/m^2)
16:3	195	26.3
16:4	196	26.4
16:5	197	26.5
16:6	198	26.5
16:7	199	26.6
16:8	200	26.7
16:9	201	26.7
16:10	202	26.8
16:11	203	26.8
17:0	204	26.9
17:1	205	27.0
17:2	206	27.0
17:3	207	27.1
17:4	208	27.1
17:5	209	27.2
17:6	210	27.2
17:7	211	27.3
17:8	212	27.3
17:9	213	27.4
17:10	214	27.4
17:11	215	27.5
18	216	27.5

3 References

1 Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000; 320(7244):1240-1243.

2 World Health Organisation. BMI for age, 2007 WHO reference. 22 Jul 2011.

Appendix B

Liraglutide
NN8022-4179

Blood pressure ranges

Table of Contents

Page

List of in-text figures

Page

List of in-text tables

Page

1 Introduction

According to exclusion criterion no.20 subjects should be excluded from the trial in case they have uncontrolled treated or untreated hypertension >99th percentile for age and gender in children, according to "The fourth report on the: Diagnosis, evaluation, and treatment of high blood pressure in children and adolescents"[1]. The hypertension percentiles used are based on age, gender and height percentile according to CDC Growth Charts[2]

2 Determination of a subject's hypertension > 99th percentile

In order to determine whether a subject is > the 99th percentile for age and gender the investigator must define the subjects height percentile according to Figure 1 for males and Figure 2 for females.

Based on the subject's age, and height percentile, it can be determined if the blood pressure is above the 99th percentile by using Table 1 for males and Table 2 for females.

Table 1 Blood Pressure Levels for Boys by Age and Height Percentile[2]

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean. For research purposes, the standard deviations in appendix table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in table 3 (i.e., the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in appendix B. For children with height percentiles other than these, follow steps 1–4 as described in appendix B.

Figure 1 Height for age percentiles in boys[1]

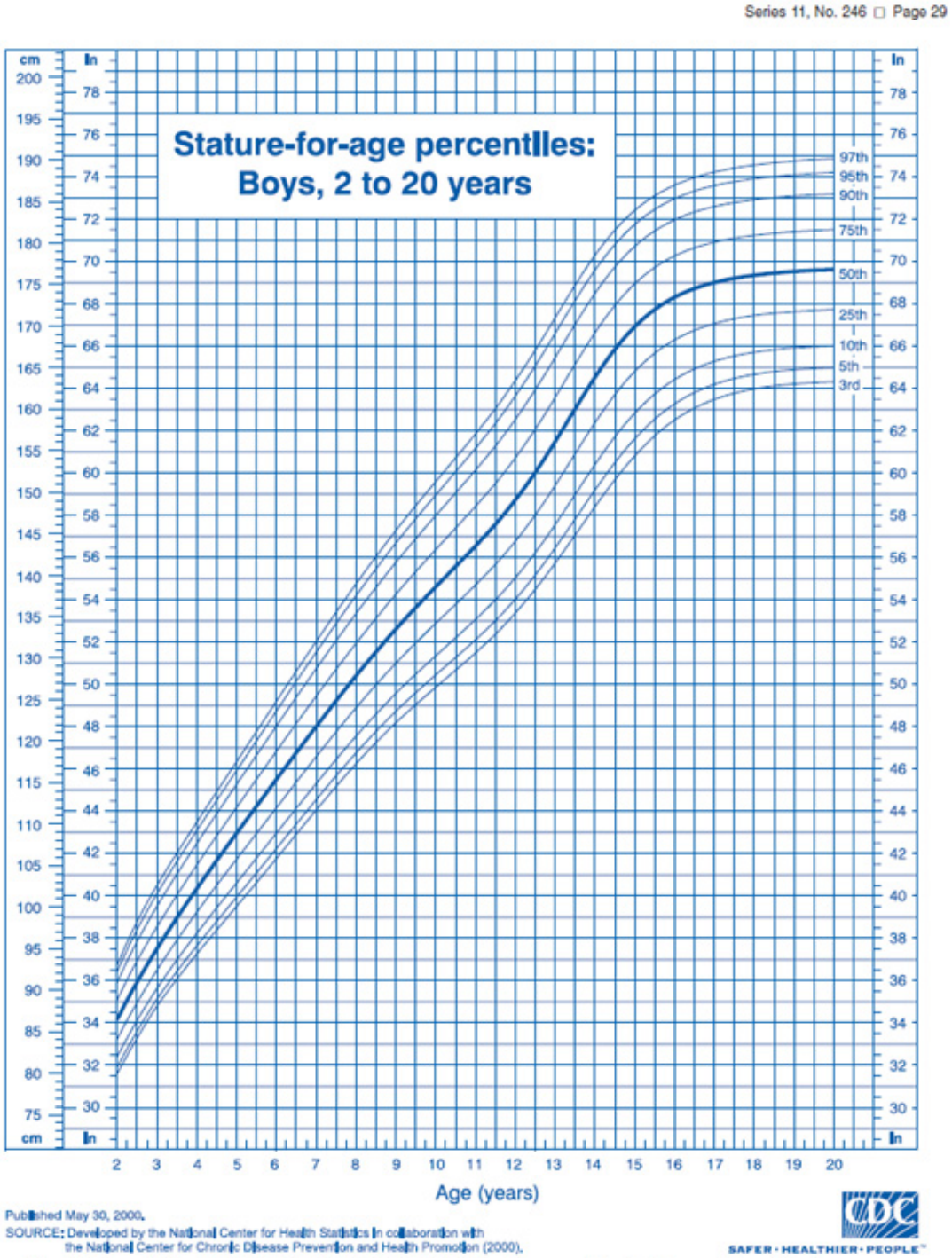

Figure 11. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, 2 to 20 years: Boys stature-for-age

Table 2 Blood Pressure Levels for Girls by Age and Height Percentile[1]

Blood Pressure Levels for Girls by Age and Height Percentile*

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean. For research purposes, the standard deviations in appendix table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in table 4 (i.e., the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in appendix B. For children with height percentiles other than these, follow steps 1–4 as described in appendix B.

Figure 2 Height for age percentiles in girls[2]

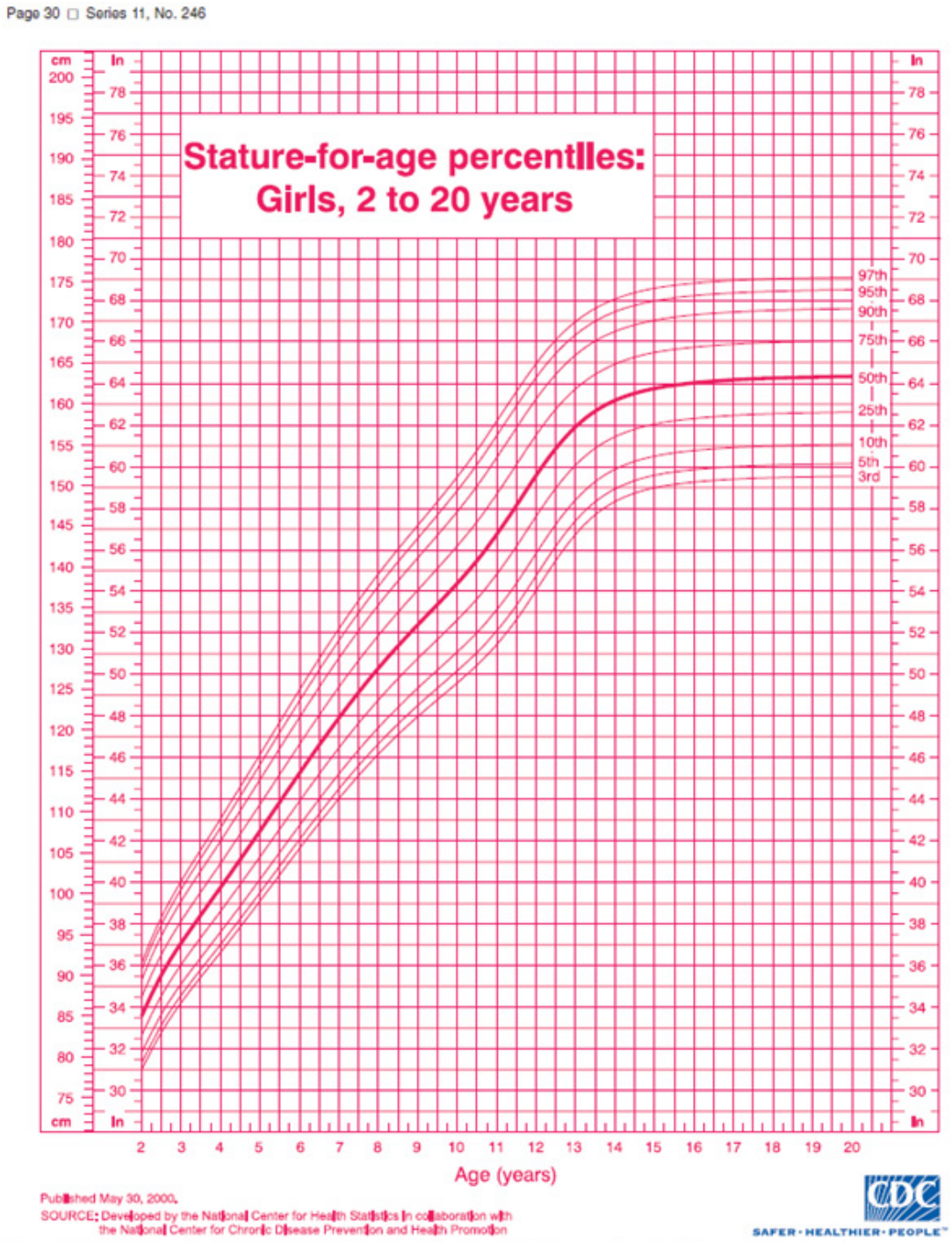

Figure 12. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, 2 to 20 years: Girls stature-for-age

3 References

1 THE FOURTH REPORT ON THE: Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. 1 May 2011.

2 National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. CDC Growth Charts. 2012.

Appendix C

Liraglutide
NN8022-4179

Calcitonin Monitoring

Table of Contents

Page

1 Background

Non-clinical experiments conducted in rodents have demonstrated that liraglutide has the potential to stimulate growth and proliferation of thyroid C-cells. It is unknown whether Liraglutide causes thyroid C-cell neoplasms, including medullar thyroid carcinoma (MTC) in humans, as human relevance could not be ruled out by clinical or nonclinical studies.

However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with liraglutide.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) as likely indicative of C-cell neoplasia[1] the interpretation of values between the upper normal range and 100 ng/L can become problematic.
There is little information available on normal calcitonin levels in children. The available information suggests that children in the age range included in this clinical trial (6 to less than 18 years) will have calcitonin levels indistinguishable from adults[2].

There are several known factors affecting calcitonin levels, namely renal dysfunction, smoking, several drug classes (proton pump inhibitors, beta-blockers, insulin secretagogues). Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

2 Calcitonin and C-cell abnormalities - evaluation and follow-up

Subjects with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2) or with a screening calcitonin ≥ 50 ng/L at V2 must be excluded from the trial. Subjects who are screen failures and have a calcitonin level above the normal range should be referred to their primary care physician and consideration given to referring the subject to a paediatric endocrinologist or thyroid specialist for further evaluation.

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. Calcitonin levels will be reviewed monthly by the International Medical Director (IMD) for this project or their surrogate. Calcitonin levels above upper normal limit will be flagged by the central laboratory at the laboratory report, and reported to the investigator, the International Trial Manager (ITM), and IMD. Subject with a calcitonin level post randomisation above the normal limit should be repeated within 4 weeks for confirmation.

If the repeat calcitonin level, or a calcitonin level obtained at a visit is initially ≥ 20 ng/L, the subject's abnormal level and clinical data will be forwarded to an external expert. The external expert will report their recommendation to the investigator, the IMD and ITM whether further evaluation is indicated (e.g., referral to a paediatric endocrinologist or thyroid specialist), and whether the subject should discontinue with trial product.

Subjects who have a calcitonin level above the normal range as the last value taken during the trial, should be referred to their primary care physician and consideration given to referring the subject to a paediatric endocrinologist or thyroid specialist for further evaluation.

3 References

1 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007; 92(2):450-455.

2 Basuyau JP, Mallet E, Leroy M, Brunelle P. Reference intervals for serum calcitonin in men, women, and children. Clin Chem 2004; 50(10):1828-1830.