Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02918279
Sponsor trial ID:	NN8022-4180
Official title of study:	Effect of liraglutide for weight management in pubertal adolescent subjects with obesity
Document date:	11-December-2019

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID: NN8022-4180

Effect of liraglutide for weight management in pubertal adolescent subjects with obesity

56-week, double-blind, randomised, parallel-group, placebo-controlled multi-national trial followed by a 26-week period off study-drug

Trial phase: 3a

Protocol originator

[redacted]

Table of Contents

Table of Figures

Page

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Table of Tables

Page

List of abbreviations

ACTH	adrenocorticotropic hormone
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BOCF	baseline observation carried forward
BMI	body mass index
BUN	Blood urea nitrogen
CEA	carcinoembryonic antigen
CI	confidence interval
CRF	case report form
CLAE	clinical laboratory adverse event
C-SSRS	Columbia Suicidality Severity Rating Scale
CTX1	type I collagen C-telopeptide
DHEAS	dehydroepiandrosterone sulfate
DMC	data monitoring committee
DUN	dispensing unit number
ECG	electrocardiogram

eCRF	electronic case report form
FAS	full analysis set
FDAAA	Food and Drug Administration Amendment Act
FFA	free fatty acids
FPFV	first patient first visit
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high density lipoprotein
HOMA-B	homeostasis model assessment of beta-cell function
HOMA-IR	homeostasis model assessment of insulin resistance
hsCRP	high sensitivity C reactive protein
IB	investigator's brochure
ICH	International Conference on Harmonisation
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
ISPAD	international society for pediatric and adolescent diabetes
ITT	intention-to-treat
IWRS	interactive web response system
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
LAR	legally acceptable representative
LDL	low density lipoprotein
LH	luteinising hormone
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPLV	last patient last visit
MAP	modelling analysis plan
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia type 2
MHP	mental health professional
MI	multiple imputation
MMRM	mixed model for repeated measurements
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
NRS	numerical rating scale
NTX1	type I collagen N-telopeptide
P1NP	procollagen 1 N-terminal propeptide

PD	pharmacodynamic
PDCO	Paediatric Committee
PHQ-9	Patient Health Questionnaire 9
PK	pharmacokinetic
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(ly)
SD	standard deviation
SDS	standard deviation score
SIF	safety information form
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
T4	thyroxine
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglycerides
TMM	Trial Materials Manual
TPD	trial product discontinuation
TSH	thyroid stimulating hormone

ULN	upper limit of normal
UTN	Universal Trial Number
VLDL	very low density lipoprotein
WBC	white blood cell count

1 Summary

Objectives

Primary objective

- To compare the efficacy of liraglutide versus placebo on weight loss in adolescent subjects with obesity after 56 weeks of treatment

Secondary objectives

- To compare the efficacy of liraglutide versus placebo on glycaemic control and cardiovascular risk factors in adolescent subjects with obesity after 56 weeks of treatment
- To compare the safety of liraglutide versus placebo in adolescent subjects with obesity after 56 weeks of treatment

Primary endpoint

Change in body mass index (BMI) standard deviation score from baseline (randomisation) to 56 weeks.

Key secondary efficacy endpoints:

- Percent of subjects achieving ≥5% reduction in baseline BMI at week 56
- Percent of subjects achieving ≥10% reduction in baseline BMI at week 56
- Change from baseline to 56 weeks
  - BMI
  - Body weight (kilogram [kg], pounds [lb]
  - Body weight (percent [%])
  - Systolic and diastolic blood pressure
  - Glucose metabolism: glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose
  - Number of treatment emergent adverse events

Trial design:

This is a 56-week double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug. The trial will be conducted in pubertal adolescents with obesity aged 12 to less than 18 years. Subjects will be randomised 1:1 to receive liraglutide or placebo. The randomisation will be stratified according to pubertal and glycaemic status.

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to those in the European Union. All subjects will undergo counselling in healthy nutrition and physical activity for weight loss and must be prescribed a structured programme from the beginning of the 12-week run-in period and continuing through the 26-week follow-up period off trial drug.

Trial population:
A planned total of approximately 342 subjects will be screened. A planned total of 228 subjects will be randomised.

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.
- Male or female, age 12 to less than 18 years at the time of signing informed consent and less than 18 years at date of randomisation
- BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points and ≥the 95th percentile for age and sex (for diagnosis of obesity)
- Stable body weight during the previous 90 days before screening V2 (<5 kg self-reported weight change)
- History of failing to lose sufficient weight with lifestyle modification as judged by the investigator and documented in subject's medical record

Key exclusion criteria:
- Pre-pubertal subjects (Tanner stage 1) at screening V2
- Type 1 diabetes mellitus (T1DM)
- Family or personal history of multiple endocrine neoplasia type 2 (MEN2)
- Medullary thyroid carcinoma (MTC)
- History of pancreatitis (acute or chronic)
- Subjects with secondary causes of obesity (i.e., hypothalamic, genetic or endocrine causes)
- Treatment with medications within 90 days before screening V2 that, based on the investigator's judgement, may cause significant weight change. This should also include treatment with any of the following medications: pramlintide, orlistat, zonisamide, topiramate, lorcaserin, phenteremine, bupropion, naltrexone, glucagon-like peptide-1 (GLP-1) receptor agonists, or metformin (used as treatment for obesity)
- Anti-diabetic treatment other than metformin
- History of major depressive disorder within 2 years before screening V2

Key randomisation criteria:
- BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points and ≥the 95th percentile for age and sex (for diagnosis of obesity).
- Compliance with run-in procedures and visit schedule as judged by the investigator.

Assessments:

Efficacy:

- Body weight
- Systolic and diastolic blood pressure
- Patient reported outcome (Impact of Weight on Quality of Life-Kids)
- HbA_{1c}
- Fasting plasma glucose
- Fasting C-peptide

Safety

- Adverse events
- Biochemistry and haematology
- Mental health related questionnaires (Patient Health Questionnaire 9 and Columbia Suicidality Severity Rating Scale)
- Pubertal assessments (Tanner staging)
- Hormones
- Antibodies against liraglutide
- Pulse
- Bone age (x-ray)

Trial products:

The following trial products will be supplied by Novo Nordisk A/S. Denmark:

- Liraglutide 6 mg/mL, solution for injection, 3 mL PDS290 pre-filled pen-injector
- Placebo, solution for injection, 3 mL PDS290 pre-filled pen-injector

2 Flowchart

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance											End of Treatment	Follow-up (FU)						TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
Visit number	1	2	3	4[1]	5	6[1]	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	19 x	25 x	30 x
Timing of visit (weeks)	-15	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	20	25	30	34	38	42	46	51	56	58	64	70	76	82	30	56	82
Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	± 2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
SUBJECT RELATED INFO/ASSESSMENTS																																	
Informed consent and assent 18.2	X																																
In/exclusion criteria 6.2 6.3		X	X																														
Randomisation criteria 6.4									X																								
Criteria for premature discontinuation of trial product 6.5										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Demography 8.2.1		X																															
Concomitant illness and medical history 8.2.2		X[2]																															
History of psychiatric disorders 8.2.2.1		X																															
Concomitant medication 8.2.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tobacco use 8.2.5		X																	X						X					X			
Childbearing potential 8.2.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
EFFICACY																																	
Body weight 8.3.1.1		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hip and waist circumference 8.3.1.2									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Systolic and diastolic blood pressure 8.3.2		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Lipids 8.5.3		X							X						X				X			X			X					X			

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance												End of Treatment	Follow-up (FU)						TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
Visit number	1	2	3	4[1]	5	6[1]	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	19 x	25 x	30 x
Timing of visit (weeks)	-15	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	20	25	30	34	38	42	46	51	56	58	64	70	76	82	30	56	82
Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	± 2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
hsCRP 8.5.3		X							X						X				X			X			X					X			
Glucose metabolism 8.5.3		X						X							X				X			X			X					X			
IWQOL-Kids 8.3.3									X						X				X			X			X								
SAFETY																																	
Height 8.4.1		X						X	X						X				X			X			X					X	X	X	X
Adverse events 8.4.10		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints 12.4										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Additional safety assessments, if applicable 8.4.10		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes 8.4.13 and SMPG 8.4.2										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Pulse 8.4.3		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECG 8.4.4		X																	X						X								
Pregnancy test[3] 8.2.4.1 and 8.2.4.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
First day of menstrual period[4] 8.4.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination 8.4.6		X							X						X				X			X			X					X			
Biochemistry 8.5.4		X							X						X				X			X			X					X			
Haematology 8.5.4		X							X						X				X			X			X					X			
Hormones[5] 8.5.4									X						X				X			X			X					X			
Calcitonin 8.4.12, 8.5.4 and Appendix C		X							X						X				X			X			X					X			
Biomarkers (bone age) 8.5.4									X						X				X			X			X					X			

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance											End of Treatment	Follow-up (FU)						TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
Visit number	1	2	3	4[1]	5	6[1]	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	19 x	25 x	30 x
Timing of visit (weeks)	-15	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	20	25	30	34	38	42	46	51	56	58	64	70	76	82	30	56	82
Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	± 2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
Anti-liraglutide antibodies 8.5.5									X										X						X	X		X		X			
Tanner staging 8.4.7		X							X										X						X					X			
Bone age (x-ray) 8.4.8									X																X[6]								
PHQ-9 and C-SSRS 8.4.9		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
OTHER ASSESSMENTS																																	
Liraglutide plasma concentration 8.6.1														X	X	X			X			X			X	X		X		X			
Counselling in healthy nutrition and physical activity 8.6.2			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	X[7]	X	X[7]	X[7]	X	X[7]	X[7]	X	X[7]	X[7]	X	X[7]	X	X	X	X
Healthy nutrition compliance 8.6.2.1				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
TRIAL MATERIAL																																	
Dispensing visit 9									X				X	X	X	X	X	X	X	X	X	X	X	X									
Hand-out direction for use for trial product 8.1.7, 9.2									X				X	X	X	X	X	X	X	X	X	X	X	X									
Drug accountability 9.4									X				X	X	X	X	X	X	X	X	X	X	X	X	X								
IWRS session 10	X								X				X	X	X	X	X	X	X	X	X	X	X	X	X								
New dose of trial product 8.1.8										X	X	X	X																				
REMINDERS																																	
Training in trial product and pen handling (including injection technique)[8] 8.1.7									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance												End of Treatment	Follow-up (FU)						TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
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Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	±2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
Hand-out BG meter 8.4.2									X																								
BG meter finger prick test 8.4.2									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Hand-out diary, females 8.6.3		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Collect diary, females 8.6.3									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hand-out diary, males 8.6.3									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Collect diary, males 8.6.3										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Attend visit fasting 8.1.2		X						X	X						X				X			X			X	X[9]		X[9]		X			
End of trial (EoT)																														X			

Footnotes:

[1] Can be performed as phone visit.

[2] At V2, all pre-existing conditions should be reported as medical history or concomitant illness.

[3] At V2 and V25 performed as serum pregnancy test and from V3-V24 and V26-V30 performed as urine-stick pregnancy test, if applicable (see Section 8.2.4.1 and 8.2.4.2).

[4] At screening the first date of last menstrual period should be collected. For other visits, first date of all menstrual periods since the last visit should be collected.

[5] Estradiol for female subjects only and testosterone for male subjects only

[6] An x-ray will not be performed at V25 for subjects for whom the bone age evaluation at randomisation indicates that the epiphyses are fused.

[7] Can be performed by phone

[8] At V3-V24, training in trial product and pen handling (including injection technique) is at the investigator's discretion.

[9] Only 2 hour fasting before blood sampling.

3 Background information and rationale for the trial

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

In the case of Mexico, the above will include the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:

- Investigation follow-up
- Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;
- Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;
- To present in a timely manner the information required by the Health Authority.

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

The prevalence of obesity in children and adolescents, as well as in adults, has been increasing steadily during the past three decades and has reached alarming proportions worldwide[3-5]. The American Medical Association as well as a number of leading institutions such as the National Institutes of Health (1998), The Obesity Society (2008) and the American Association for Clinical Endocrinology (2012) now classify obesity as a disease, calling for dedicated efforts in prevention, diagnosis and treatment[6]. Paediatric obesity is associated with a number of complications, including hypertension, type 2 diabetes mellitus (T2DM), early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems[7]. Furthermore, paediatric overweight/obesity is an independent risk factor for obesity in adulthood[8], thus predisposing to future comorbid conditions and reduced life expectancy[9, 10]. In studies conducted in paediatric subjects with obesity, weight loss has been associated with improvements in cardiometabolic risk factors, including measures of glycaemic control, beta-cell function, insulin sensitivity/resistance, lipid profile, systolic/diastolic blood pressure and metabolic syndrome[11-14].

Paediatric obesity remains a major public health challenge as treatment options are limited. Although lifestyle modification is the recommended first-line treatment, widespread adoption of this treatment method and long-term compliance are problematic[15-17] and treatment intensification may be needed. Currently, orlistat is the only pharmacotherapy with FDA approval for the management of obesity in the paediatric population and is indicated for those aged ≥12 years[18]. However, orlistat effects modest weight loss in adolescents and treatment compliance is low due to gastrointestinal adverse events (AEs)[17-19]. No medication is currently approved for the treatment of

obesity in individuals <18 years in the European Union. For paediatric subjects with severe obesity, long-term success of lifestyle interventions and pharmacotherapy has been disappointing, indicating the need for more aggressive options such as bariatric surgery[20]. However, procedural complications and the risk of long-term nutritional deficiencies due to suboptimal compliance with post-operative lifestyle changes may outweigh the benefits of surgically-assisted weight reduction[21]. Thus, effective weight loss treatments with optimised safety/tolerability profiles which do not discourage compliance are urgently needed for the paediatric population.

Liraglutide

Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) analogue with 97% homology to human GLP-1[22, 23]. The derivatisation of a fatty acid to GLP-1 resulted in a compound with protracted pharmacokinetic properties and made liraglutide suitable for once-daily injection at any time of the day[22, 23]. Liraglutide has been approved for the treatment of adults with T2DM at doses up to 1.8 mg/day in approximately 90 countries under the brand name Victoza®. The moderate dose-dependent weight loss observed in the T2DM development programme, together with improvements in other cardiometabolic risk factors (e.g., glycaemic parameters, systolic blood pressure, lipid profile), have prompted the investigation of liraglutide's potential use for weight management[24].

The weight management clinical development programme has shown that liraglutide induces weight loss through a decrease in appetite and subsequent energy intake, and not through an increase in energy expenditure[25]. In the phase 2 dose-finding trial, the 3.0 mg dose of liraglutide was the most efficacious in terms of weight loss and improvements in cardiometabolic and health-related quality of life endpoints. The safety profile of liraglutide 3.0 mg was generally similar to that of liraglutide at lower doses in the T2DM programme. The only types of AEs found to be dose-dependent were gastrointestinal disorders. The 3.0 mg dose was further investigated for weight management in adults with overweight and obesity (with and without other weight-related co-morbidities) in 4 phase 3 trials.

In the weight management development programme, treatment with liraglutide 3.0 mg, as adjunct to diet and exercise, resulted in significantly greater weight loss than diet and exercise alone in subjects with overweight and obesity with at least one weight-related co-morbidity. Liraglutide 3.0 mg met the pre-specified mean and categorical weight-loss endpoints in each of the phase 2 and 3 individual trials. In each trial, more than 35% of subjects in the group assigned to liraglutide 3.0 mg achieved the 5% weight loss benchmark set forth in the FDA guidance, and the proportion achieving the benchmark was more than twice that of the group assigned to placebo (i.e., diet and exercise alone)[26, 27]. Weight loss with liraglutide 3.0 mg was accompanied by positive effects on multiple secondary efficacy parameters, including waist circumference, insulin resistance, fasting and postprandial glycaemic control, prevalence of pre-diabetes and progression to T2DM, systolic blood pressure, lipids and cardiovascular biomarkers, and health-related quality of life. Apart from a small increase in gallbladder disease, the safety profile of liraglutide 3.0 mg in adults was consistent

with that observed with doses up to 1.8 mg in T2DM; transient gastrointestinal events were reported most frequently[26, 27].

Non-clinical studies

Liraglutide has been tested for toxicity in single-dose studies in mice, rats and monkeys, and in repeated-dose studies for up to 3 months in mice, 6 months in rats and up to 12 months in monkeys. In all studies, reductions in food consumption as well as reductions in body weight gain were observed in the first 2 weeks. These effects can be ascribed to the pharmacological effect of liraglutide.

In 2-year carcinogenicity studies, liraglutide caused dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice. Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose in vivo micronucleus tests in rats. Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells.

In a 2-year repeat-dose carcinogenicity study of liraglutide injected subcutaneously (s.c.) once a day in CD-1 mice, a treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis (the body surface used for drug injection) in males in the 3.0 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6.0 mg/mL) is 10 times higher than the concentration in the formulation used to administer 3.0 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

Liraglutide had no adverse effect on fertility, but an increase in early embryonic deaths occurred at 1.0 mg/kg/day in female rats. Embryo-foetal toxicity was observed in rats and rabbits at or below human systemic exposures. Liraglutide dose-dependently delayed onset of puberty more markedly in juvenile female than male rats. Subcutaneous administration of liraglutide to juvenile rats for 10 weeks produced adverse signs of toxicity among females at a dose level of 0.25 mg/kg/day and above, resulting in a marked delay in the attainment of sexual maturation at 0.25 and 1.0 mg/kg/day. Males were lesser affected than females. Ovary weights were slightly reduced at treatment end but normal after a 4 week off-study-drug recovery period. Following mating after a 4 week off-study-drug period, slightly low implantation counts and post-partum litter size were noted in females previously dosed at 1.0 mg/kg/day, for which a relationship to treatment could not be discounted. There were no toxicologically significant changes observed among liraglutide-treated male rats.

Further information regarding the clinical and non-clinical findings for liraglutide can be found in the latest edition of the Liraglutide 3.0 mg (Saxenda®) Weight Management investigator's brochure (IB)[28] or any updates hereof.

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

3.2 Rationale for the trial

This trial is part of a Paediatric Investigation Plan for treatment of obesity submitted to and agreed with the Paediatric Committee (PDCO), a committee of EMA. The trial is also a post marketing requirement from the FDA.

Paediatric obesity is associated with multiple complications/co-morbidities and adverse long-term health consequences[7, 8, 10, 29]. In clinical studies, weight loss in paediatric subjects with obesity led to improvements in these weight-related complications/co-morbidities[11-14].

Liraglutide (Victoza®) is approved for the treatment of T2DM in adults at doses up to 1.8 mg[22, 23]. Liraglutide (Saxenda®) is approved for weight management in adults at doses up to 3.0 mg[30, 31].

To date, two 5-6 week randomised, controlled trials with liraglutide have been completed in paediatric subjects. 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[32]. Liraglutide's safety/tolerability and pharmacokinetic (PK) 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, the present large, longer-term trial will investigate the efficacy and safety of liraglutide (doses up to 3.0 mg) in inducing weight loss and improving glycaemic control in adolescents with obesity (12 to less than 18 years).

4 Objectives and endpoints

4.1 Objectives

Primary objective

- To compare the efficacy of liraglutide versus placebo on weight loss in adolescent subjects with obesity after 56 weeks of treatment

Secondary objectives

- To compare the efficacy of liraglutide versus placebo on glycaemic control, cardiovascular risk factors and Impact of Weight on Quality of Life-Kids (IWQOL-Kids) in adolescent subjects with obesity after 30 and 56 weeks of treatment
- To compare the safety of liraglutide versus placebo in adolescent subjects with obesity after 30 and 56 weeks of treatment
- To examine the potential rebound effect from end of treatment at week 56 to week 82

4.2 Endpoints

4.2.1 Primary endpoint

Change in body mass index (BMI) standard deviation score (SDS) from baseline (randomisation) to 56 weeks[33].

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary efficacy endpoints

- Percent of subjects achieving ≥5% reduction in baseline BMI at weeks 30, 56* and 82[34, 35]
- Percent of subjects achieving ≥10% reduction in baseline BMI at weeks 30, 56* and 82
- Change in BMI SDS from baseline to 30 and 82 weeks and change from 56 weeks to 82 weeks
- Change from baseline to 30 and 56 weeks and change from 56 weeks to 82 weeks in:
  - BMI*
  - Body weight (kilogram [kg], pounds [lb] and percent [%])*
  - Waist circumference
  - Waist-to-hip circumference ratio
  - Cardiovascular risk factors: high sensitivity C-reactive protein (hsCRP) and 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 and homeostasis model assessment of beta-cell function and insulin resistance parameters (HOMA-B and HOMA-IR)

– Patient reported outcome (PRO) assessed by Impact of Weight on Quality of Life-Kids (IWQOL-Kids)

4.2.2.2 Supportive secondary safety endpoints

- Number of treatment emergent adverse events*
- Number of treatment emergent hypoglycaemic episodes:
  - According to ADA/ISPAD classification
  - According to Novo Nordisk/ISPAD classification
- Occurrence of anti-liraglutide antibodies
- Change from baseline to 56 weeks in bone age assessment
- Change from baseline to 30 and 56 weeks and change from 56 weeks to 82 weeks in:
  - Pulse
  - Electrocardiogram (ECG)[a]
  - Laboratory parameters:
    - Haematology: haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count (eosinophils, neutrophils, basophils, lymphocytes, monocytes)
    - Biochemistry: creatinine, creatinine kinase, urea (BUN), albumin, bilirubin (total), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), sodium, potassium, calcium total, calcium, albumin- corrected, amylase, lipase, and carcinoembryonic antigen (CEA)
    - Hormone levels: calcitonin, insulin-like growth factor-1 (IGF-1), thyroid stimulating hormone (TSH), free thyroxine (free T4), dehydroepiandrosterone sulfate (DHEAS), luteinising hormone (LH), follicle stimulating hormone (FSH), estradiol (females), testosterone (males), prolactin, adrenocorticotropic hormone (ACTH), cortisol
    - Bone metabolism markers: Type 1 collagen N-telopeptide (NTX1), type 1 C-telopeptide (CTX1), procollagen 1 N-terminal propeptide (P1NP), alkaline phosphatase (bone)
  - Pubertal status
  - Physical examination
  - Height standard deviation score (SDS)
  - Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Reported Health Questionnaire 9 (PHQ-9)

[a]Not assessed at week 82 and does not have associated endpoints.

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

5 Trial design

5.1 Type of trial

This is a 56-week double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug. The trial will be conducted in pubertal adolescents with obesity aged 12 to less than 18 years. Subjects will be randomised 1:1 to receive liraglutide or placebo. The randomisation will be stratified according to pubertal and glycaemic status (see Sections 5.2 and 11).

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to those in the European Union. All subjects will undergo counselling in healthy nutrition and physical activity for weight loss and must be prescribed a structured programme from the beginning of the 12-week run-in period and continuing through the 26-week follow-up period off trial drug. The trial design is shown schematically below:

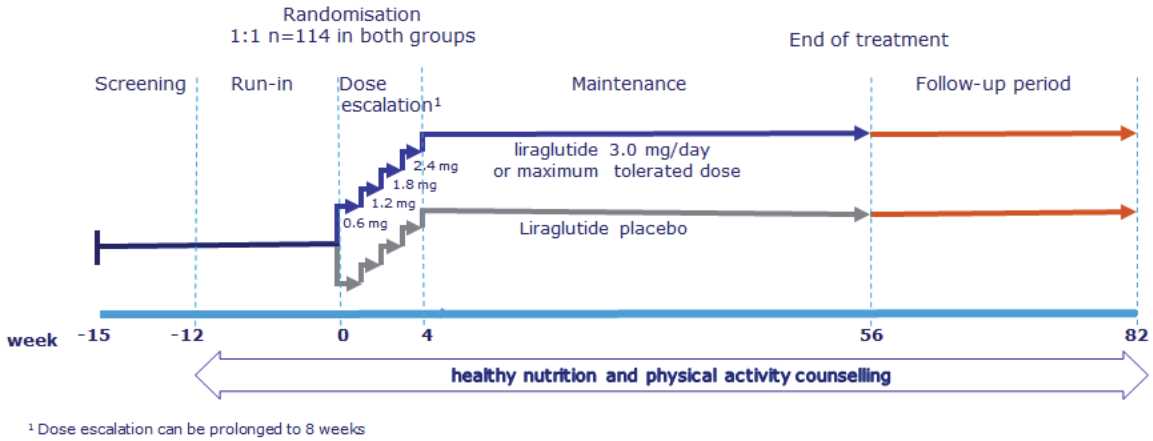


Figure 5–1 Trial design

5.2 Rationale for trial design

This trial is designed in accordance with regulatory requirements[35] and guidelines[34] ,[36]

The primary endpoint, change in BMI SDS, is selected based on EMA's recommendation for a primary endpoint in the assessment of efficacy of new medicinal products for the treatment of obesity in children[34]. The primary endpoint is assessed at the end of the 56 week double blind period. Secondary endpoints are assessed at the end of 30, 56, and 82 weeks. The assessment of secondary endpoints at 30 weeks, including BMI SDS, is included as there is a likelihood of a high attrition rate in this population of adolescents. Efforts will be made to encourage retention.

First-line therapy in primary obesity should always be lifestyle modification, rather than pharmacotherapy. To reflect this, a 12-week run-in period has been included in the trial design. During the run-in period, a structured counselling programme in healthy nutrition and physical activity is implemented in alignment with CHMP guidelines[34].

The 56-week treatment period is designed to be double-blind in order to avoid/minimise bias during the assessment of the primary endpoint. Randomisation is another measure used to minimise bias and is expected to lead to comparable subject populations at baseline in the liraglutide and placebo groups. Stratification according to Tanner staging as described in Section 8.4.7 will be used to enable the examination of treatment effect consistency across trial population subgroups. Stratification will also be performed according to glycaemic status: normoglycaemia versus dysglycaemia (pre-diabetes and T2DM).

Table 5–1 Glycaemic category

Normoglycaemia	FPG <5.6 mmol/L (<100 mg/dL) and/or HbA_{1c} <5.7%
Pre-diabetes	FPG 5.6−6.9 mmol/L (both inclusive), FPG 100–125 mg/dL (both inclusive) or HbA_{1c} 5.7−6.4% (both inclusive)
Type 2 diabetes (T2DM)	FPG ≥7.0 mmol/L (≥126 mg/dL) and/or HbA_{1c} ≥6.5%

Adapted from[37]

The stratification is controlled by interactive web response system (IWRS); see Section 11.

Dysglycaemia is expected to occur frequently in this trial population. No interaction was observed between glycaemic status and body weight in the adult trial (NN8022-1839: Effect of liraglutide on body weight in non-diabetic subjects with obesity or overweight subjects with co-morbidities), and a similar pattern of AEs was observed in sub-populations by pre-diabetes status at screening.

The 56-week duration of liraglutide treatment is consistent with regulatory authorities' recommendations for the estimation of safety and stabilisation of treatment effect of a weight-management product (1 year) and also includes a 4-8 week dose escalation period[34, 38].

The 26-week duration of the off-study-drug follow-up period is aligned with regulatory recommendations[34] and is considered to be sufficient to assess effect maintenance and any evidence of rebound, as well as to monitor post-treatment safety.

5.3 Treatment of subjects

Subjects will undergo a 12-week run-in period during which they will receive counselling in healthy nutrition and physical activity. This counselling will continue throughout the 56-week blinded period and the 26-week off-study-drug follow-up period.

Subjects who are eligible for randomisation will be administered liraglutide or placebo by a once-daily s.c. injections. Placebo contains the same excipients as liraglutide, but no active drug substance. Subjects randomised to receive placebo will receive s.c. injections with injection volumes corresponding to the liraglutide dose.

The injections can be done either in the abdomen, thigh, or upper arm. Injection region consistency is not required throughout the trial.

Injections can be administered at any time of day irrespective of meals. It is recommended that the time of injection for a subject is consistent throughout the trial.

Based on the results of the NN8022-3967 PK trial in pubertal adolescents with obesity (aged 12-17 years), including model-estimated steady-state exposure, treatment with liraglutide will be initiated with 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until a maximum tolerated dose (MTD) or the 3.0 mg dose of liraglutide (highest allowed liraglutide dose) is reached. Dose escalation will be based on tolerability as judged by the investigator and the duration will be from 4-8 weeks (see Section 8.1.8.1).

Subjects and their legally acceptable representative (LAR) will be instructed in symptom recognition and handling of hypoglycaemia, and in blood glucose measurements at randomisation (see Section 8.4.13).

Medications that should not be used within 90 days before screening and during the trial are listed in Sections 6.3 and 6.5.

Subjects who at screening have a diagnose of T2DM can enter the trial. The only allowed anti-diabetic treatment is metformin.

If a subject develops T2DM (Table 5–1) during the course of the trial, he/she will be allowed to remain on trial product if glycaemic control can be achieved through healthy nutrition and physical activity, according to local standard of care. Furthermore, additional treatment with metformin is allowed, at the discretion of the investigator.

If diabetes treatment other than healthy nutrition, physical activity and metformin is required for glycaemic control, the trial product must be discontinued (see Sections 6.5 and 8.1.10).

If a dose is missed, treatment should be resumed as prescribed at the next scheduled dose. An extra dose or increase in dose should not be taken for the missed dose. If more than 3 consecutive days have elapsed since the last dose, subject should resume dosing at the discretion and direction of the investigator.

5.4 Treatment after discontinuation of trial product

In the 26-week off-study-drug follow-up period, subjects will continue to receive counselling in healthy nutrition and physical activity.

After the end of the trial, subjects will be encouraged to continue following healthy nutrition and physical activity guidance, at the discretion of their healthcare provider. If trial product is discontinued prematurely (see Sections 6.5 and 8.1.10), this also applies.

5.5 Rationale for treatment

As liraglutide will be administered by s.c. injections the same route of administration will be used for placebo in order to maintain blinding. The relatively slow absorption and half-life of approximately 13 hours make liraglutide suitable for once-daily administration, at any time of the day[22, 23].

The 3.0 mg dose of liraglutide is chosen as the target maintenance dose in the present trial. In the phase 2 dose-finding trial (NN8022-1807) in adults, the 3.0 mg dose of liraglutide (as adjunct to diet and exercise) was the most efficacious in terms of weight loss and improvements in cardiometabolic and quality of life endpoints. The safety profile of liraglutide 3.0 mg was generally similar to that of liraglutide at lower doses; the only types of AEs found to be dose-dependent were gastrointestinal disorders that were generally transient. In the subsequent phase 3 trials, liraglutide 3.0 mg, as an adjunct to a reduced calorie diet along with increased physical activity, induced a mean weight loss from baseline of ≥5% that was superior to placebo (i.e., diet and exercise alone). Weight loss with liraglutide 3.0 mg was accompanied by positive effects on multiple glycaemic and non-glycaemic secondary endpoints.

Clinical trials in adults with or without obesity and with or without T2DM have demonstrated that liraglutide should be initiated at a daily dose of 0.6 mg, with subsequent dose escalation in 0.6 mg weekly increments in order to improve gastrointestinal tolerability. Based on the results of the NN8022-3967 PK trial in adolescents with obesity aged 12-17 years, liraglutide treatment will be initiated at the 0.6 mg dose and will be escalated in weekly increments of 0.6 mg. Given the more vulnerable nature of the pediatric population, the liraglutide dose will be escalated only if the present dose is tolerated.

In case of tolerability issues, the investigator has an option of prolonging the dose escalation period or reducing the trial product dose as described in Section 8.1.8.1. The dose may also be reduced to previous dose level in case of intermittent illness as described in Section 8.1.8.2.

Lifestyle modification is the recommended first-line treatment for overweight/obesity in the paediatric population[15,16]. Therefore a 12-week run-in period with structured counselling in healthy nutrition and physical activity is included in the trial. Only subjects who, after this lifestyle modification attempt, still fulfil the definition of obesity can be randomised (as defined by inclusion

and randomisation criteria). Currently, no pharmacologic agents are approved for weight management in the paediatric population with obesity in the European Union. Although orlistat has FDA approval for the above-mentioned indication in adolescents aged ≥12 years, its weight loss efficacy is modest and treatment compliance is low due to gastrointestinal adverse effects[17-19]. Therefore, a placebo comparator group will be used to evaluate whether liraglutide, in combination with healthy nutrition and physical activity, is more efficacious for the treatment of obesity than healthy nutrition and physical activity alone.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 342

Number of subjects planned to be randomised: 228 (~ 33% screening failure rate)

For Mexico only: Out of the 228 subjects, approximately 40 subjects are planned to be randomised in Mexico.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age 12 to less than 18 years at the time of signing informed consent and less than 18 years at date of randomisation
3. BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points and ≥ the 95th percentile for age and sex (for diagnosis of obesity)
4. Stable body weight during the previous 90 days before screening V2 (<5 kg self-reported weight change)
5. History of failing to lose sufficient weight with lifestyle modification as judged by the investigator and documented in subject's medical record

6.3 Exclusion criteria

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

1. Pre-pubertal subjects (Tanner stage 1) at screening V2
2. Body weight ≤ 60 kg
3. Type 1 diabetes mellitus
4. Calcitonin ≥50 ng/L
5. Family or personal history of multiple endocrine neoplasia type 2 (MEN2)
6. Medullary thyroid carcinoma (MTC)
7. History of pancreatitis (acute or chronic)
8. Subjects with secondary causes of obesity (i.e., hypothalamic, genetic or endocrine causes)
9. Treatment with medications within 90 days before screening V2 that, based on the investigator's judgement, may cause significant weight change. This should also include treatment with any of

the following medications: pramlintide, orlistat, zonisamide, topiramate, lorcaserin, phenteremine, bupropion, naltrexone, GLP-1 receptor agonists, or metformin (used as treatment for obesity)

10. Anti-diabetic treatment other than metformin
11. Diet attempts using herbal supplements or over-the-counter medications within 90 days before screening V2
12. Participation in an organised weight reduction program (e.g., Weight Watchers®) within 90 days before screening V2
13. Previous surgical treatment for obesity (excluding liposuction if performed >1 year before screening V2)
14. History of major depressive disorder within 2 years before screening V2
15. Any lifetime history of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
16. PHQ-9 score of ≥ 15 at screening V2
17. Any suicidal ideation of type 4 or 5 based on the baseline C-SSRS questionnaire at screening V2
18. Any suicidal behaviour within 30 days before screening V2
19. Any lifetime history of suicidal attempt
20. Uncontrolled treated or untreated hypertension >99th percentile for age and gender in children. If white-coat hypertension is suspected at screening V2, a repeated measurement at V3 prior to other trial-related activities is allowed (last measurement being conclusive)
21. Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the investigator
22. Subjects with confirmed bulimia nervosa disorder
23. Diagnosis of malignant neoplasms within the last 5 years prior to screening V2 (except basal and squamous cell skin cancer)
24. Known or suspected abuse of alcohol or narcotics
25. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures
26. Known or suspected hypersensitivity to trial product or related products
27. Previous participation in this trial. Participation is defined as signed informed consent.
28. Subjects from the same household participating in the trial
29. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening V2
30. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice)

    For Sweden only: Oral (except low-dose gestagen [lynestrenol and norestisteron]), injectable, or implanted hormonal contraceptives, intrauterine device, intrauterine system (for example, progestin-releasing coil), vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate). Use of contraception is not required for female subjects who have not yet made their sexual debut and/or are not sexually active.

For Belgium only: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some intrauterine devices, true sexual abstinence (i.e., refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

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

6.4 Randomisation criteria

To be randomised, all randomisation criteria must be answered "yes".

1. BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points and ≥the 95th percentile for age and sex (for diagnosis of obesity).
2. Compliance with run-in procedures and visit schedule as judged by the investigator.
3. PHQ-9 score < 15 at randomisation
4. No suicidal ideation of type 4 or 5 since last visit based on the C-SSRS questionnaire at randomisation

6.5 Criteria for premature discontinuation of trial product

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Randomised subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only in case a subject or subject's LAR decline any further contact with the site in relation to the trial this will be considered as withdrawn from the trial.

The subject may be prematurely discontinued from trial product, at the discretion of the investigator, due to a safety concern. The subject must be prematurely discontinued from trial product if the following applies:

1. Safety concern (not covered by any of below criteria) or unacceptable intolerability to trial product, as judge by the investigator.
2. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomisation criteria
3. Pregnancy
4. Intention of becoming pregnant
5. In case of code break (see Section 11.1)
6. Suspicion of pancreatitis (see Sections 8.4.10.5 and 8.4.11). Subjects may restart on trial product should the suspicion not be confirmed.
7. Diagnosis of medullary thyroid carcinoma
8. Weight loss attempts other than what is agreed with the dietitian as part of the trial intervention
9. If diabetes treatment other than healthy nutrition, physical activity and metformin addition is initiated.

10. Initiation of treatment with medications that, based on the investigator's judgement, may cause significant weight change. This should also include treatment with any of the following medications: pramlintide, orlistat, zonisamide, topiramate, lorcaserin, phenteremine, bupropion, naltrexone, GLP-1 receptor agonists, or metformin (used as treatment for obesity)
11. Anti-diabetic treatment other than metformin
12. Initiation of diet attempts using herbal supplements or over-the-counter medications
13. Inadequate psycho- and/or pharmaco therapeutic treatment of a subject's psychiatric disorder (see Section 8.4.9.3)
14. The subject and/or the subject's LAR refusal of referral to a mental health professional (MHP) and it, in investigator's opinion, is unsafe for the subject to continue in the trial (see Section 8.4.9.3)
15. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
16. The subject treated with 0.6 mg trial product experiences persistent intolerance as judged by the investigator

See Section 8.1.10 for procedures to be performed for subjects discontinuing trial product prematurely.

6.6 Withdrawal from trial

The subject may withdraw consent at will at any time either by the subject and/or by the subject's LAR. The subject's request to withdraw from the trial must always be respected.

See Section 8.1.9 for procedures to be performed for subjects withdrawing consent.

For Mexico only: Should the subject, his/her family members parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

6.7 Subject replacement

Subjects who discontinue trial product prematurely or withdraw consent will not be replaced.

6.8 Rationale for trial population

In the weight management programme, liraglutide 3.0 mg as an adjunct to a reduced calorie diet along with increased physical activity produced clinically relevant and sustained weight loss in adults with overweight or obesity with or without diabetes. Weight loss with liraglutide 3.0 mg was accompanied by beneficial effects on multiple secondary efficacy parameters (i.e., glycaemia, blood pressure, lipid profile).

As with adults, the prevalence of overweight/obesity has tripled in the adolescent population during the past three decades and current projections predict a further increase[3, 7, 39]. Paediatric obesity is associated with a number of complications, including hypertension, T2DM, early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems[7]. Furthermore, paediatric overweight/obesity is an independent risk factor for obesity in adulthood[8], thus predisposing to future comorbid conditions and reduced life expectancy[10, 29]. In the paediatric population, weight loss has been associated with improvements in cardiometabolic risk factors, including measures of glycaemic control, beta-cell function, insulin sensitivity/resistance, lipid profile, systolic/diastolic blood pressure and metabolic syndrome[11-14].

No safety/tolerability concerns for adolescents with obesity aged 12−17 years were raised in the 5-6 week NN8022-3967 trial investigating the safety/tolerability and pharmacokinetics of liraglutide doses up to 3.0 mg. Data from the NN8022-3967 trial, as well as the PK modelling analysis based on this trial, have resulted in the decision to use a starting dose of 0.6 mg in the current trial. The present trial will investigate the efficacy and safety of liraglutide for weight management in the same subject population.

7 Milestones

Planned duration of recruitment period is 52 weeks from global first patient first visit (FPFV).

End of trial is defined as last patient last visit (LPLV).

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 IWRS in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flowchart (see Section 2).

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[40], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE) [41], the Food and Drug Administration Amendment Act (FDAAA)[42], European Commission Requirements[43-45] 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 that must be performed during this trial. The overview of when they must be performed is included in the flowchart (see Section 2).

8.1 Visit procedures

It is the responsibility of the investigator to ensure that all site visits and phone 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.

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

8.1.1 Information visit, visit 1

Informed assent and informed consent from the subject's LAR(s) must be obtained before any trial-related activity; 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 IWRS. Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

All subjects must be reminded to attend the screening visit in a fasting state. Screening must take place at least 1 day after the information.

8.1.2 Fasting

The subjects must attend some visits fasting; see Section 2. Fasting is defined as having consumed no food or drink except for water for the last 8 hours before blood sampling. For V26 and V28, only 2 hours fasting (i.e. no food or drink except for water) is needed before blood sampling for anti-liraglutide antibodies and liraglutide plasma concentrations.

Any prescribed medication which should be taken with or after a meal should be withheld on the day of the visits attended fasting, until blood sampling and body weight measurements have been performed. Trial product can be taken as usual in relation to visits attended fasting except V14, V15, V16, V19, V22, and V25; see Section 8.6.1.

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, visit 2

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

All screening assessments as described in Section 2 must be performed and data recorded in the eCRF. For screening failures, please refer to Section 8.1.5.

8.1.4 Run-in visits

Subject's eligibility according to the in- and exclusion criteria must be evaluated before the 12-week run-in period is initiated.

V4 and V6 can be performed as phone visits. All subjects must be reminded to attend V8 and the randomisation visit in a fasting state.

During the run-in period the investigator should evaluate the subject's compliance with the run-in procedures and visit schedule. If deemed acceptable, as judged by the investigator, the subject can proceed to randomisation visit. If not, the subject is a screening failure (8.1.5).

All run-in assessments as described in Section 2 must be performed and data recorded in the eCRF. For screening failures, please refer to Section 8.1.5.

8.1.5 Screening failures

A screening failure is a subject who does not fulfil one or more of the inclusion and/or exclusion and/or randomisation criteria. For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious adverse events (SAE) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section 12. A screening failure session must be made in the IWRS. The case book must be signed.

8.1.6 Re-screening

Re-screening is NOT allowed if the subject has failed one of the inclusion, exclusion criteria or randomisation criteria, this includes re-sampling if the subject has failed one of the exclusion criteria related to laboratory parameters.

8.1.7 Randomisation and initial trial product dose

Subjects' eligibility according to the randomisation criteria must be evaluated before randomisation. To randomise a subject, a randomisation session must be performed in IWRS. Tanner stage, HbA_{1c} and FPG status from V8 must be entered in IWRS; see Section 11.

All subjects must be instructed in handling of the device and the trial product; see Section 9. This should include training in injection site (see Section 5.3) and injection technique. Subjects should be instructed to perform an air shot before the use of a new pre-filled pen. At all subsequent visits, subjects should be re-trained at the investigator's discretion.

The initial dose of trial product must be injected by the subject or the subject's LAR at the site and this must be documented in the subject's medical record. The initial dose of trial product must be injected post blood sampling.

For training in symptom recognition and handling of hypoglycaemia; see Section 8.4.13. For instruction in handling of the BG meter including auxiliary supplies and self-measured plasma glucose (SMPG); see Section 8.4.2.

8.1.8 Dose escalation

Treatment with trial product will be initiated at randomisation with 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until MTD or the 3.0 mg dose of trial product (highest allowed dose) is reached. Ideally, subjects will reach maximum dose of 3.0 mg at V13.

The SMPG measurement performed during dose escalation visits (Section 8.4.2) must be performed before instructing the subject in dose escalation.

8.1.8.1 Dose escalation and tolerability

Dose escalation is based on tolerability as judged by the investigator.

The trial product dose escalation should continue to next dose level only if the present dose is tolerated. If, after increasing to next dose level, the dose is poorly tolerated, it is allowed to be lowered to the previously dose level.

If a subject has tolerability issues with a given dose level, it is allowed to remain at that 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 investigators to judge when the subject has reached MTD.

Escalation of the trial product is not allowed if the subject has a self-measured plasma glucose (SMPG) < 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 or during the dose escalation visits, or during contacts (i.e.,

via telephone). Hypoglycaemic episodes must be reported in the eCRF according to Section 8.4.2, 8.4.13, 8.5.3 and 12.1.1.

Visits to the clinic occur weekly during the first 4 weeks of dose escalation at V10-V13. Ideally, subjects will reach maximum dose of 3.0 mg at V13.

In those cases where more than one week is needed at any dose escalation step, the subject must still follow the visit schedule (V10-V13). For the remaining dose escalation step(s) after V13, is it at the discretion of the investigator to be in frequent contact (e.g., by phone) with the subject to ensure correct dose settings. The dose escalation process must be finalised no later than V14.

Contacts regarding dose escalation must be documented in the subject's medical record.

8.1.8.2 Tolerability at maximum tolerated dose

In case a subject experiences tolerability issues at the MTD during the trial, as judged by the investigator, the trial product dose may be lowered to the next, lower dose level as needed: 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.

The reason for lowering the trial product dose must be documented in the subject's medical record.

If the cause of the subject's tolerability issues is intermittent illness or otherwise transient, as judged by the investigator, the subject is allowed to return to MTD again.

If a subject treated with 0.6 mg experiences persistent intolerance, as judged by the investigator, the trial product must be discontinued.

8.1.8.3 Recording of trial product dose levels in eCRF

The investigator must record the trial product dose, date of dose level changes and reason for changes in the eCRF throughout the trial.

8.1.9 Withdrawal from trial

If a subject and/or the subject's LAR(s) withdraw consent, the investigator must aim to undertake procedures similar to those for the end of treatment (V25) as soon as possible, and a follow-up visit (V26) two weeks later.

If a subject and/or the subjects LAR(s) withdraw consent after end of treatment (V25), the investigator must aim to undertake procedures similar to those for the end of trial (V30) as soon as possible.

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 IWRS. The case book must be signed.

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

8.1.10 Premature discontinuation of trial product

If a subject prematurely discontinues trial product, the investigator must aim to undertake procedures similar to those for the end of treatment (V25) as soon as possible, and a follow-up visit (V26) two weeks later.

The subjects must be asked to attend additional visits depending on when the trial product discontinuation takes place during the trial:

- If the trial product is discontinued before V19 subjects must be asked to attend three additional visits (V19x, V25x and V30x) taking place weeks 30, 56 and 82 after randomisation, respectively.
- If the trial product is discontinued after V19 and before V25 subjects must be asked to attend two additional visits (V25x and V30x) taking place weeks 56 and 82 after randomisation, respectively.

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

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (screening visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product. 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 AEs.

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. Following medical history should be reported as a minimum if applicable: diagnose of T2DM, 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.

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

8.2.2.1 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.

8.2.3 Concomitant medication

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

Details of any concomitant medication must be recorded at screening. 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, 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.

8.2.4 Childbearing potential

It must be recorded in the eCRF whether female subjects are of child-bearing potential.

Female subjects of child-bearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1week after end of treatment.

Pregnancy testing must be performed on female subjects of child bearing potential (females who have had their first menstrual period) as described in Sections 8.2.4.1 and 8.2.4.2.

8.2.4.1 Blood sample for pregnancy testing

At screening and/or V25, a serum pregnancy test must be performed.

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

8.2.4.2 Urine-sticks pregnancy testing

Urine-stick pregnancy tests will be performed at the site during the trial if pregnancy is suspected, if a menstrual period is missed (unless this is a part of the mode of action of the contraceptive method) or if in accordance with local requirements.

Documentation of result of urine-stick pregnancy test must be recorded in the eCRF.

8.2.5 Tobacco use

Details of tobacco use must be recorded according to Section 2. Smoking is defined as smoking at least one cigarette or equivalent daily.
Smoking status:

- Never smoked
- Previous smoker, smoking stop date
- Current smoker

8.3 Efficacy assessments

The timing of the assessments is outlined in the flowchart; see Section 2. The assessments performed at randomisation are the baseline measurement, unless otherwise specified.

8.3.1 Body measurements

8.3.1.1 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 digital 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.

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

Weight measured at screening is used for the calculation of BMI, whereas weight measured at randomisation is used as baseline for assessment of change in body weight. BMI is calculated in the eCRF.

8.3.1.2 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 of both hip and waist circumference must be performed in the following order: hip, waist, hip, waist, hip, waist; these must be measured in the horizontal plane using a non-stretchable measuring tape and rounded up or down to the nearest 0.5 cm or 0.2 inches. All three measurements must be recorded in the eCRF.

The circumference should be measured when the subject is in a standing position wearing light clothing. The subject should have an empty bladder. The subject should be standing, feet together with arms down their side and hip and waist 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.

8.3.2 Systolic and diastolic blood pressure

For blood pressure at screening, three measurements must be performed. The mean value is calculated by the eCRF and must be used to evaluate eligibility of the subject; see Section 6.3 and Appendix B. For the subsequent visits, only one measurement needs to be performed.

If the investigator suspects white coat hypertension at screening one re-assessment at V3 of the systolic and diastolic blood pressure (using the same procedure as described below) is allowed as described in the exclusion criterion (Section 6.3).

The method for measuring systolic and diastolic blood pressure should follow the standard clinical practise 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 (or V3, if applicable) 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 screening must be reported as AEs in accordance with Section 12.

8.3.3 Patient-reported outcome questionnaire, IWQOL-Kids

The Impact of Weight on Quality of Life-Kids (IWQOL-Kids) is a disease-specific questionnaire which measures the impact of weight on quality of life in adolescents and is validated in youth ages 11 years and older[46]. The four concepts captured are:

- the impact of weight on an individual's physical mobility and comfort (Physical Comfort)
- how an individual feels about themselves and their body (Body Esteem)
- how an individual is treated in their social environment (Social Life)
- the individual's perception of what family members may think and feel about them (Family Life).

The questionnaire has 27 items and a total, as well as domain-specific score(s), can be derived. The scaled scores range from 0–100, with higher scores representing better health-related quality of life.

The questionnaire is a self-administered questionnaire. It must be completed by the subject using an electronic device; see Section 13.3, and it must be completed without assistance of the investigator or delegated staff.

At fasting visits, the questionnaire should be completed after all fasting-related activities, but before any other visit-related procedures are conducted. Only subjects can make changes in the questionnaire.

After completion, the questionnaire must be reviewed by the investigator or delegated staff on the same day for potential AEs, including any overall change in health and concomitant medication. When reviewing the questionnaires, the investigator should not influence or question the subject on the content of the subject's response to the questionnaire questions. Review of questionnaires must be documented in the subject's medical record.

8.4 Safety assessments

The timing of the assessments is outlined in the flowchart; see Section 2. The assessments performed at randomisation are the baseline measurement, unless otherwise specified.

8.4.1 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.

8.4.2 Self-measured plasma glucose (SMPG)

At randomisation, subjects will be provided with a blood glucose (BG) meter including auxiliary supplies as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated at regular intervals as indicated in the flowchart; see Section 2.

The blood glucose 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.

Only the blood glucose meter provided by Novo Nordisk should be used for the measurements required in the protocol.

At each visit, the subject must demonstrate how to use the BG meter device by measuring their SMPG. The measured SMPG value must be recorded in the subject's medical record.

During dose escalation the SMPG measurement must be done before instructing the subject in dose escalation; see Section 8.1.8.

Subjects must be instructed to do a SMPG in between visits in case a hypoglycaemic episode is suspected and to report hypoglycaemic episodes in the diary (Section 8.6.3.2). Subjects must contact the investigator in case of low SMPGs.

8.4.3 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 screening must be reported as AEs in accordance with Section 12.

8.4.4 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

If abnormal, a comment must be given. The evaluation should be based on the investigator's judgement.

ECGs performed for any reason unrelated to this trial within 12 weeks prior to screening are acceptable, provided no clinical symptoms suggestive of cardiac disease have been identified or have 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.

The ECG from screening is considered baseline. It is allowed to perform the screening ECG after screening, but prior to randomisation.

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.

Any clinically significant worsening or new clinically significant findings after screening must be reported as AEs in accordance with Section 12.

8.4.5 Recording of menstrual periods

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

First date of all menstrual periods since last visit must be collected from all female subjects (see Section 8.6.3.3) and recorded in the eCRF.

8.4.6 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 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 screening must be reported as AEs in accordance with Section12.

8.4.7 Tanner staging

Pubertal development must be assessed by the Tanner staging in accordance with stages 1-5[47]. The assessments must be conducted by site staff trained in pubertal assessments. Assessment of testicular volume (by orchidometer) stages for males must be included.

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

Acceleration of pubertal development after screening as judged by the investigator must be reported as AEs in accordance with Section 12

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

8.4.8 Bone age (x-ray)

An x-ray of left hand and wrist will be performed at randomisation and V25 for all subjects for evaluation of bone age. An x-ray will not be performed at V25 for subjects for whom the bone age evaluation at randomisation indicates that the epiphyses are fused.

The x-ray imaging data will be submitted to a supplier selected for central medical imaging services and will be analysed by an independent paediatric radiology expert assigned by the supplier for bone age assessment.

A bone age x-ray performed within 2 weeks prior to the scheduled assessments is acceptable.

8.4.9 Mental health questionnaires

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, Columbia Suicide Severity Rating Scale (C-SSRS) and Patient Health Questionnaire 9 (PHQ-9), have been included in the present trial. Data collection will be done using an electronic device (Section 13.3).

8.4.9.1 C-SSRS

The investigator 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 screening and randomisation 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).

8.4.9.2 PHQ-9

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

The questionnaires completed at screening and randomisation 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 AEs 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.

8.4.9.3 Potential 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 an 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, in 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 why the referral and psychiatric evaluation by an MHP is needed. If the subject refuses to be referred to a MHP, the subject's decision should be documented in subject's medical record and the investigator must assess if the trial product should be discontinued due to safety reasons; see Section 6.5.

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.

8.4.10 Adverse events

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

8.4.10.1 Medication error

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

- Trial products involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episode and/or AE(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors; see Section 12.1.4.

8.4.10.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute gallstone disease
- Neoplasm
- Pancreatitis

In case any of these events fulfil the criteria for a SAE, please report accordingly; see Section12.

8.4.10.3 Acute gallstone disease

If an event of acute gallstone disease or clinical suspicion of this is observed during the trial, the following additional information should be reported if available on the acute gallstone disease form:

- Signs and symptoms of acute gallstone disease
- Specific laboratory test supporting a diagnosis of gallstone disease
- Imaging performed and consistency with gallstone disease
- Treatment given for the event
- Relevant risk factors associated with the event

8.4.10.4 Neoplasm

All events of benign, pre-malignant/carcinoma *in-situ* and malignant neoplasms must be reported during the trial and the following additional information should be obtained if available as part of standard of care on the neoplasm form:

- Type of neoplasm
- Signs and symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment given for the event
- Participation in screening programs
- Relevant risk factors associated with the event

8.4.10.5 Pancreatitis

If an event of pancreatitis, acute or chronic is observed during the trial, the following information must be reported, if available on the pancreatitis form:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis
- Imaging performed and consistency with pancreatic disease
- Treatment given for the event
- Relevant risk factors associated with the event

8.4.11 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 presences of pancreatitis can be excluded. See Section 6.5. Appropriate additional examinations must be performed. Measurement of amylase and lipase must be done locally. If acute pancreatitis is ruled out, subject should resume dosing at the discretion and direction of the investigator. Trial product dose changes must be recorded in the eCRF.

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

- Severe acute abdominal pain
- Blood amylase and/or lipase >3x upper limit of normal (ULN)
- Characteristic findings on relevant imaging (e.g., computerised axial tomography/magnetic resonance imaging/ultrasound)

8.4.12 Elevated calcitonin

If any calcitonin value post randomisation is ≥ ULN a repeat 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.

8.4.13 Hypoglycaemic episodes

At randomisation, all subjects must be instructed in symptom recognition and handling of hypoglycaemia.

Plasma 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) occurring in conjunction with hypoglycaemic symptoms

should be reported in the diary according to the instructions below throughout the trial from randomisation to V25. See Section 8.6.3.2.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[48].

A SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must trigger a hypoglycaemic episode form to be completed by the subject. Repeated SMPG measurements and/or symptoms, occurring within a period of 60 min after onset on a hypoglycaemic episode, will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported on one hypoglycaemic episode form. SMPG measurements ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms after the 60 min period shall trigger the reporting of a new hypoglycaemia episode and prompt the subject to fill out a new hypoglycaemic episode form until a succeeding measurement is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved.

In case of several low SMPG values within the 60 minutes interval, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode but the start time of the episode will remain as the time for the first SMPG value and/or symptom.

The record should include the following information:

- Start date and time of the hypoglycaemic episode.
- The plasma glucose level before treating the episode (if available) and any follow up measurements.
  The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode. The remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No).
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experience symptoms later during the episode.
- Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)? [49] (Layman language used in the diaries: Was the low blood glucose episode associated with symptoms severe enough to result in unconsciousness or a seizure and was glucagon (an injection) or IV glucose/sugar (drip) needed for your child to recover?).
  If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia.
- Date, time and dose of last trial product administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Change in any concomitant illness.
- Any sign of fever and/or other acute disease.
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

If the question "Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?" is answered "YES", the hypoglycaemic episode is classified as “severe”[49] and the following information should be recorded:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?

- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), other factors not listed or unknown).
- Did the subject experience seizure?
- Did the subject experience loss of consciousness?
- Did the subject experience any of the following symptoms[49] (layman term used in the diary is specified in brackets if different from the protocol term)?
  - Autonomic: Shakiness, sweatiness, trembling, palpitations (Rapid and irregular heart beat) and pallor (extreme paleness)
  - Neuroglycopenic: Poor concentration, blurred or double vision, disturbed colour vision, difficulty hearing, slurred speech, poor judgment and confusion, problems with short-term memory, dizziness and unsteady gait
  - Behavioural signs and symptoms: Irritability, erratic behaviour, agitation (restlessness associated with irritability and tension), nightmares, inconsolable crying
  - Non-specific symptoms: Hunger, headache, nausea, tiredness
  - Other symptoms?

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

If the subject experiences a severe hypoglycaemic episode, the subject or LAR should be instructed to contact the investigator as soon as possible after recovery for further guidance.

The investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[50, 51].

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in; see Section 12.

8.5 Laboratory assessment

Blood samples may be drawn on another day than the day of the actual visit, as long as it is within the visit window outlined in the flowchart (see Section 2).

Laboratory assessments will be 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.

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

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis. If additional laboratory sampling is needed, e.g. to follow-up on AEs, this must be done at a local laboratory.

All laboratory samples must be sent to the central laboratory and the results will be reported to the investigator on an ongoing basis. Anti-liraglutide antibody results and the results of the liraglutide plasma concentration analysis will not be provided to the investigator, as these results will not be used for any clinical evaluation during the trial and would potentially unblind the treatment.

Antibody samples will be stored as described in Section 24.2.

HOMA-B and HOMA-IR results (calculated by Novo Nordisk A/S) will not be reported to investigators during the trial but will be included in the clinical trial report.

For Mexico only: The handling, transportation and storage of biological samples are described in the laboratory manual (for central laboratory details; see Attachment I).

8.5.1 Total blood volume for laboratory assessments

Approximately 197 mL blood will be collected from each subject during the entire trial period. Blood collection should be performed in accordance with the guidelines in EU Directive 2001/20/EC[52].

8.5.2 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 (signed and dated) either on the document or in the subject's medical record. The evaluation of screening results must be dated and signed prior to randomisation 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 reports and evaluations must be retained as source documentation.

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 Sections 8.2.2 and 12.

8.5.3 Laboratory assessments for efficacy

Any "abnormal, clinically significant" findings at screening 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
- FFA
- Non-HDL cholesterol (calculated value from central lab)

Biochemistry:
- hsCRP

Glucose metabolism (The measurement performed at V8 is considered baseline**):**
- HbA_{1c}
- FPG[a]
- Fasting insulin
- Fasting C-peptide

HOMA-B and HOMA-IR will be calculated on glucose metabolism parameters to asses beta-cell function and insulin resistance.

[a]**Fasting plasma glucose**
An FPG result ≤ 3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator; see Section 12.1.1.

8.5.4 Laboratory assessments for safety

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

Pregnancy test:
- hCG (see Section 8.2.4.1)

Biochemistry:
- Creatinine
- Creatine kinase
- Urea (BUN)
- Albumin
- Bilirubin, total
- ALT
- AST
- ALP
- Sodium
- Potassium
- Calcium, total
- Calcium, albumin corrected
- Amylase
- Lipase
- CEA

Haematology:
- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes
- *Differential count:*
  - basophils
  - eosinophils
  - lymphocytes
  - monocytes

– neutrophils

Hormones:

- Calcitonin (values above ULN); refer to Section 8.4.12 and Appendix C
- Prolactin
- FSH
- Estradiol (female subjects)
- LH
- Testosterone (male subjects)
- TSH
- free T4
- ACTH
- Cortisol
- DHEAS
- IGF-I

Bone metabolism markers

- NTX1
- CTX1
- P1NP
- alkaline phosphatase (bone)

8.5.5 Anti-liraglutide antibodies

Blood samples for determination of anti-liraglutide antibodies should be collected from all subjects and sent via central laboratory to special laboratory for analysis; see Section 2. Only samples from subjects treated with liraglutide will be analysed for anti-liraglutide antibody development. A randomisation list will be provided to the special laboratory.

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

Samples are analysed by the special laboratory for anti-liraglutide antibody formation including cross reactivity to endogenous GLP-1. Follow up samples that are found to be positive for anti-liraglutide antibodies will be analysed for in vitro neutralising effect to liraglutide. Antibody positive follow up samples that are found to cross react with endogenous GLP-1 will, in addition, be analysed for in vitro neutralising effect against endogenous GLP-1. The last-mentioned analyses will be performed by Novo Nordisk A/S. See Sections 8.5.4 and 24.2.

8.6 Other assessments

8.6.1 Plasma concentration of liraglutide

Blood samples for assessment of liraglutide plasma concentration should be collected and sent via central laboratory to special laboratory for analysis; see Section 2. A randomisation list will be provided to the special laboratory. Samples from randomised subjects will be analysed for liraglutide plasma concentration.

Subjects must be instructed to withhold their trial product dose in the morning until blood sampling is performed on the visit. Any dose taken by mistake in the morning before the visit must be recorded in the eCRF Section made for the purpose.

The subjects must be instructed to complete the dosing diary for liraglutide plasma concentration assessment (see Section 8.6.3.1). The doses, dates and exact time for blood sampling must be recorded in the eCRF.

The blood samples taken at V26, V28 and V30 for liraglutide plasma concentration assessments are not part of the liraglutide pharmacokinetic and pharmacodynamic modelling plan (see Section 17). The purpose of these assessment are to preclude any false negative antibody results. Hence recordings in the subjects' dosing diary and eCRF are not requested for these samples.

8.6.2 Counselling in healthy nutrition and physical activity

8.6.2.1 Counselling in healthy nutrition

Subjects (and subjects' LAR, as applicable) must receive individualised counselling in healthy nutrition with the goal of obtaining a weight loss. The counselling must be performed by a certified dietitian according to local standard. The focus of the counselling in healthy nutrition must be facilitating healthier food choices.

If a BMI corresponding to ≤ 25 kg/m^2 for adults by international cut-off point[53] is reached, subjects should be assigned a maintenance diet, at the discretion of the investigator. For details, refer to Appendix A.

Counselling in healthy nutrition can be done by phone and must be documented in subject's medical record.

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

8.6.2.2 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 with a goal of 60 minutes of moderate to high intensity physical activity per day[54].

8.6.3 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 either on the document 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.

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

The diary will include three different Sections as specified in Sections 8.6.3.1, 8.6.3.2 and 8.6.3.3.

8.6.3.1 Trial product dosing diary

Trial product dosing diary pages should be completed by the subject on the last three days before a visit including a blood sampling for liraglutide plasma concentration (see Section 8.6.1).

The last 3 doses of trial product should be recorded in the diary with:

- Dose
- Date
- Exact time for dosing

8.6.3.2 Hypoglycaemic episode diary

The hypoglycaemic episode diary pages should be completed if the subject recognises a hypoglycaemic episode in between visits (see Section 8.4.2).

8.6.3.3 Menstrual period diary

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

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the

investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance: 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 investigational medicinal products (IMP). The investigator must assess the amount of IMPs returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject (see 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 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	Strength	Dosage form	Route of administration	Delivery device
Liraglutide Investigational medicinal product (IMP)	6 mg/mL	Solution for injection	Subcutaneous injection (s.c.)	PDS290 pen-injector for liraglutide/placebo (0.6 mg/ 1.2 mg/1.8 mg/2.4 mg/ 3.0 mg)
Placebo Investigational medicinal product (IMP)	0 mg/mL			

Liraglutide and placebo are visually identical.

If metformin is used by the subjects, it will be regarded as a concomitant medication and will not be provided by Novo Nordisk.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[55], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to enrolment and randomisation.

The investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit and at all subsequent dispensing visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Liraglutide 6 mg/mL Placebo	Store in a refrigerator 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 2°C to 8°C **US only**: At room temperature (59°F-86°F) or in a refrigerator (36°-46°F) Protect from light Do not freeze	Use within one month **US only:** Use within 30 days

[a] In-use time starts when the product is taken out of the refrigerator at subjects home.

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g., outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Drug accountability is performed using the IWRS drug accountability module. The trial products must be accounted for at pen level and either recorded as used/partly used, unused or lost. Returned pens must be sent for destruction, thus may not be re-allocated to new subjects.

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

9.5 Auxiliary supplies

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

- Direction for use for PDS290 pen-injector for trial product
- Needles for the device (maximum length to be used is 8 mm)
- BG meters and BG-meter auxiliary supplies

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

10 Interactive web response system

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

IWRS is used for:

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

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

At randomisation, the subjects will be randomised to one of two parallel treatment groups: liraglutide 3.0 mg or placebo. The randomisation will be carried out in a 1:1 manner using the IWRS.

The randomisation will be stratified according to pubertal and glycaemic status (see Sections 5.2). Stratification will be controlled by the IWRS. The strata are:

Table 11–1 Strata

Tanner 2 or 3	Dysglycaemia yes
Tanner 2 or 3	Dysglycaemia no
Tanner 4 or 5	Dysglycaemia yes
Tanner 4 or 5	Dysglycaemia no

Dysglycaemia is defined as T2DM or pre-diabetes with FPG ≥ 5.6 mmol/L (≥100 mg/dL) and/or HbA_{1c} ≥ 5.7% (see Table 5–1). The laboratory results from V8 must be used for this purpose.

11.1 Breaking of blinded codes

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

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

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

If the code has been broken, the subject must discontinue treatment with trial product (see Section 6.5) and a treatment discontinuation session must be completed in IWRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

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

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form; see Section 8.4.13.

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 products:
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

12.1.2 Serious adverse event

A 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 dyscrasia 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).

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug 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), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 0.6, 1.2, 1.8, 2.4 and 3.0 mg respectively (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 occur.

Medication errors must be reported on an AE form and a specific event form (medication error form); see Section 8.4.10.1.

12.1.5 Adverse event requiring additional data collection

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

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

- Acute gallstone disease
- Neoplasm
- Pancreatitis

For details; see Section 8.4.10.2.

12.1.6 Technical complaints

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (week 82). The events must be recorded in the applicable eCRF forms in a timely manner; see timelines below and Figure 12–1.

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

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

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

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

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest.

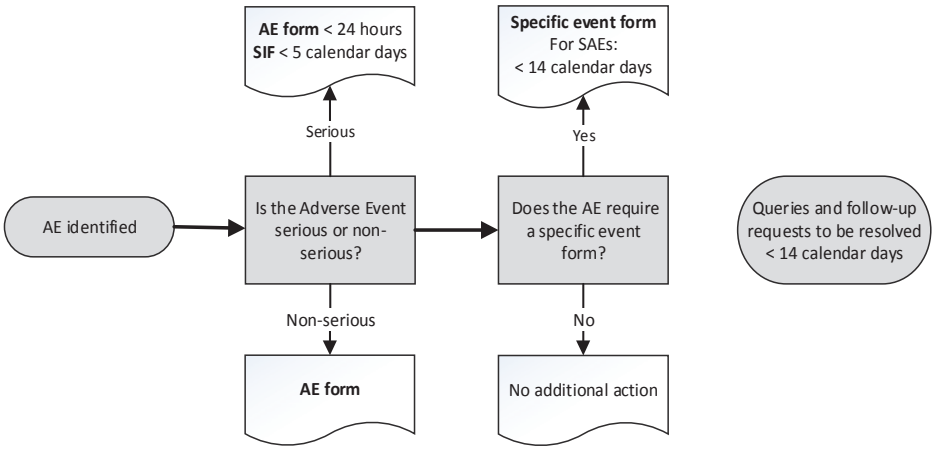
Timelines for initial reporting of AEs:
The investigator must complete the following forms in the eCRF within the specified timelines:

SAEs: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form:In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF. See Section 13.

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



Timelines are for the completion of forms from the time of investigator's awareness
AEs requiring specific event forms are descibed in Section 12.1.4 and 12.1.5
AE: Adverse event
SAE: Serious adverse event
SIF: Safety information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:
Novo Nordisk assessment of expectedness is performed according to the following reference documents: Company Core Data Sheet (CCDS), current version and any updates thereto.

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

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

Novo Nordisk products used as concomitant medication or non-investigational medicinal product:
If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product or 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 AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

  The SAE follow-up information should only include new (e.g., corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

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

of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- liraglutide PDS290 pre-filled pen injector
- Placebo PDS290 pre-filled pen injector
- Novo Nordisk 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 and/or SAEs.

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

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

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

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

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint

Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

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

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

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

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

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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

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

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

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

2. Reporting of AE information

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

<u>Forms and timelines for reporting AEs:</u>

Non-serious AEs:

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

SAEs:

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

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

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

12.5.2 Pregnancies in female partners of male subjects – US only

Male subjects must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening and run-in 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). One case of a [redacted]-fold overdose ([redacted] mg daily) given for [redacted] months has been reported. Generally, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. None of the reports included severe hypoglycaemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical

signs and symptoms. Refer to the latest edition of the Liraglutide 3.0 mg (Saxenda®) Weight Management investigator's brochure (IB)[28] or any updates hereof.

When initiating treatment with liraglutide, the subject may, in some cases, experience loss of fluids/dehydration (e.g., in cases of vomiting, nausea or diarrhoea). It is important to avoid dehydration by drinking plenty of fluids.

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 an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad-hoc. This is in order to protect the safety of the subjects and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on trial continuation, modification or termination.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

13 Case report forms

For 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 EDC Data Entry Guideline.

The following will be provided as paper CRFs:

- Pregnancy forms

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not subject related [e.g., discovered at trial site before allocation]).

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

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

13.1 Corrections to case report forms

Corrections to the 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.

13.3 Electronic questionnaires

Novo Nordisk will use a SitePad at sites for electronic recording of PROs (see Section 8.3.3) and mental health questionnaires (see Section 8.4.9). The SitePad and related support services will be provided by an external supplier that will be working under the direction and supervision of Novo Nordisk.

Subjects will be instructed in the use of the SitePad before entering any data. The SitePad will contain built in edit checks, to ensure that all relevant questions are answered. The SitePad device is not intended to support the subsequent review and modification of completed entries. In case of need for corrections of the transferred data, a query flow must be initiated by the investigator. An audit trail will be maintained.

All data entered will be transferred automatically from the device to an electronic database from where a certified copy will be saved on a CD-ROM and shipped to the sites after completion of the trial. A secure web portal will be the source data. Data entered on the devices will upon confirmation of a successful back-up be deleted from the device.

Data in the electronic database will be viewable to relevant site and Novo Nordisk staff through a secure and password-protected web portal. Data will be transferred to Novo Nordisk clinical database at defined intervals.

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 eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks for trial sites with active subjects (defined as subjects in screening, treatment, or follow up).

The monitor must be given direct access to all source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone). All data must be verifiable in source documentation other than the eCRF. For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

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

The original of the completed diaries must not be removed from the trial site.

The monitor will ensure that the eCRFs are complete.

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

- Date for obtaining informed consent
- Screen failure reason

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

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

15 Data management

Data management is the responsibility of Novo Nordisk. 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. The SAP will be finalised before database lock.

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 are given in Section 17.2.

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

The baseline value will be defined as the last measured and available value from randomisation (V9) and end of run-in (V8), if not otherwise specified.

17.1 Sample size calculation

This is a superiority trial comparing liraglutide to placebo. Superiority will be claimed if the p-value is less than 5% and the treatment favours liraglutide.

It is anticipated that the effect of liraglutide in adolescents with obesity will be similar to the effect observed in adults. The anticipated treatment difference for BMI SDS[33] is based on the results from trial NN8022 1839 in adults with overweight and obesity. For the sample size scenarios, treatment differences of -0.24, -0.26, and -0.28 were investigated.

The standard deviation (SD) is assessed based on publications by Reinehr et al. 2009[13] Berkowitz et al. 2003[56] and trial NN8022-3967 in adolescents with obesity aged 12−17 years. For the sample size scenarios, SD of 0.25, 0.35 and 0.45 were investigated.

The effect of withdrawals on the analysis 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 for this paediatric trial is 40% at week 56. A higher withdrawal percentage is assumed for this trial than what was seen in trial NN8022-1839 in adults, because this trial will include an adolescent trial population.

The total number of subjects is shown for the investigated scenarios in Table 17–1 for 90% and 99% power.

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

POWER	Treatment difference (completers)	SD		
		0.25	0.35	0.45
90%	-0.24	144	266	428
	-0.26	124	*228*	366
	-0.28	110	200	318
99%	-0.24	248	462	746
	-0.26	216	398	638
	-0.28	190	346	554

Based on the above mentioned references, it seems realistic and conservative to assume an SD of 0.35 and a treatment difference of −0.26. The minimum requirement in the Paediatric Investigation Plan is 154 randomised subjects while FDA requires a minimum of 100 subjects exposed to liraglutide. A sample size of 228 randomised subjects gives a power of 90%. Thus, the number of randomised subjects should be 228.

17.2 Definitions of analysis sets

The following analysis sets are defined in accordance with the ICH E95[57].

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 (V19x, V25x and V30x) will be used prior to imputation of remaining missing data unless otherwise stated. For AEs, summaries will be presented separately for the periods “run-in”, “in-trial” and “on-treatment”, as defined in Section 17.4.1.2.

Before data are locked for statistical analysis, a blinded 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 Novo Nordisk trial statistician, the international trial manager and the international 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 endpoint

The primary endpoint is change from baseline in BMI SDS after 56 weeks of treatment[33].

The objective is to show that liraglutide is superior to placebo in obtaining weight loss. Let $\mu_{liraglutide}$ and $\mu_{placebo}$ denote the mean change in BMI SDS for liraglutide and placebo, respectively. The null-hypothesis and the alternative hypothesis are:

H0: $\mu_{liraglutide} = \mu_{placebo}$ against the alternative HA: $\mu_{liraglutide} \neq \mu_{placebo}$

The null-hypothesis will be rejected on a 5% level if the two-sided 95% CI of the treatment difference $\mu_{liraglutide}$ - μplacebo 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) 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 baseline glycaemic category includes two levels: presence and absence of dysglycaemia. The stratification factor for Tanner stage includes two levels: stages 2 and 3 together, and stages 4 and 5 together.

Missing data in the main analysis will be handled by the following multiple imputation (MI) method. A pattern mixture model approach is applied where withdrawn subjects without a follow-up visit are assumed to respond as if treated with placebo for the entire trial. Multiple copies (100 copies) 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, 100 copies of the dataset will be generated.
- In the second step, an enriched ANCOVA model with 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, baseline waist circumference, baseline age and baseline HbA_{1c} as covariates will be fitted to the change from baseline in BMI SDS at 56 weeks for the completers in the placebo group only.
- For each of the 100 copies of the dataset, the estimated parameters and their variances from this model will be used to impute missing values at 56 weeks for subjects in both treatment arms, based on their factor levels and the values of the covariates.
- For each of the 100 complete datasets, the change from baseline in BMI SDS at 56 weeks will be 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 100 data sets are pooled to one estimate and associated SD using Rubin's formula:

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

where m_i and SD_i are the estimated means and SDs for the 100 copies of the dataset, and m_{MI}, SD_{MI} are the pooled estimates. From m_{MI} and SD_{MI} , the 95% CI for the treatment difference and the associated p-value will be calculated.

The MI method does not assume missing at random. It assumes that withdrawn subjects in the placebo arm have a response similar to the completers in the placebo arm given similar baseline characteristics. In the active arm, the assumption is that withdrawn subjects behave as if they have been in the placebo arm during the entire trial regardless of the time of their 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 ITT estimator or an effectiveness estimand of the add-on effect of liraglutide to healthy nutrition and physical activity counselling.

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 analysis 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 56-week double-blind period of the trial.
- 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 56 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 56 weeks 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 56-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 ANCOVA model with LOCF assumes that post treatment discontinuation, the body weight is on average stable in both treatment arms. This assumption can be evaluated over the 26 weeks follow-up period in completers. 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 withdrawal differs between active and placebo, this analysis might provide an optimistic or over-conservative estimate, depending on the actual circumstances. The ANCOVA model with BOCF assumes that post treatment withdrawn subjects return 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 effect and 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.

17.4 Secondary endpoints

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

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

BMI SDS at 30 and 82 weeks

The change in BMI SDS from baseline to 30 and 82 weeks and from 56 weeks to 82 weeks will be analysed using the same statistical method as used for the main analysis of the primary endpoint.

BMI

The changes in BMI from baseline at 30 and 56 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. Change from 56 weeks to 82 weeks will be summarised using descriptive statistics.

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

- Percentage of subjects achieving ≥5% reduction in baseline BMI at 30, 56 and 82 weeks
- Percentage of subjects achieving ≥10% reduction in baseline BMI at 30, 56 and 82 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 results 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.

PRO outcome

The PRO questionnaire IWQOL-Kids will be evaluated similarly to the primary endpoint. That is, the change in PRO score from baseline at 30 and 56 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 PRO score instead of the baseline BMI SDS as covariate.

Glycaemic category

The change in glycaemic category (normoglycaemia, pre-diabetes, T2DM) from baseline at 30 and 56 weeks and change from 56 weeks to 82 weeks will be summarised using descriptive statistics.

Furthermore, two separate analyses will be performed on the binary variable normoglycaemia (yes/no) at 30 and 56 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 an MI method similar to the one used for the main analysis of the primary endpoint, but adapted to the logistic regression model. The results will be presented as odds ratios together with the associated 95% CIs.

Other supportive secondary efficacy endpoints

The following other efficacy variables will be evaluated:

- Body weight
- Waist circumference
- Waist-to-hip circumference ratio
- Cardiovascular 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, fasting C-peptide, HOMA-B[a] and HOMA-IR[a])

The changes in these variables from baseline at 30 and 56 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, fasting C-peptide, HOMA-B and HOMA-IR, the response and baseline values will be log transformed prior to the analysis. The change in these variables from 56 weeks to 82 weeks will be summarised using descriptive statistics.

[a] The calculation of the HOMA endpoints will be done as follows:

- Beta-cell function (%) = 20·fasting insulin[mU/L]/(FPG[mmol/L]-3.5)
- Insulin resistance (%) = fasting insulin [mU/L]·FPG [mmol/L]/ 22.5.

17.4.1.2 Safety endpoints

Adverse events

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

- Run-in period: defined as events with onset date between V2 (included) and the first day of trial product administration (not included).
- In-trial period: defined as events with onset date between the first day of trial product administration and the last study visit.
- On-treatment period: defined as events with onset date between the first day of trial product administration and whatever comes first: a) 14 days after the last day on trial product , b) follow-up visit (V26 for subjects with trial product discontinued), or c) last study visit (subjects withdrawn without follow-up 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 (prior to randomisation) will be presented in listings.

Hypoglycaemic episodes

Hypoglycaemic episodes will be summarised descriptively by severity and treatment in terms of the number and percentage of subjects with at least one episode and the total number of episodes. Separate summaries will be made by severity (the ISPAD criterion for severe hypoglycaemia[49]). 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 23:00 and 07:00 both inclusive.

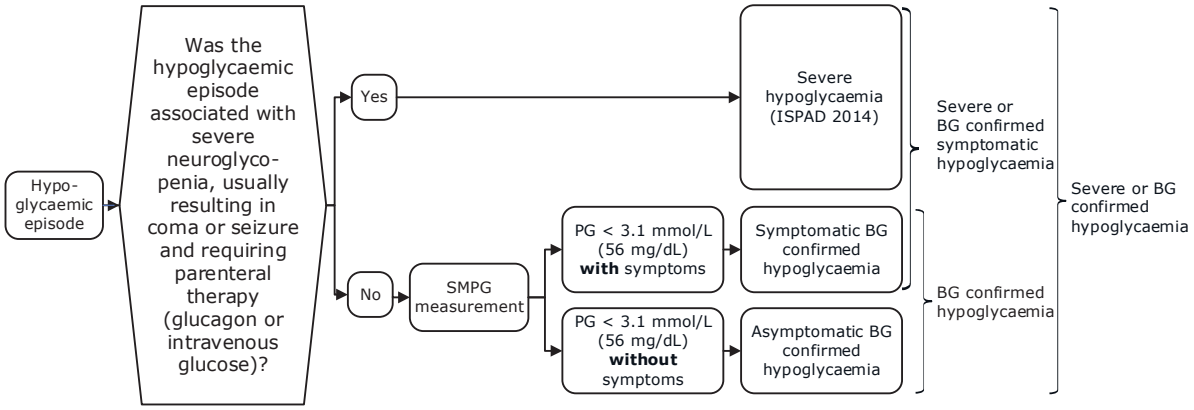
Hypoglycaemic episodes are classified according to ISPAD's definition of severe hypoglycaemia[49] as well as the Novo Nordisk classification of hypoglycaemia; see Figure 17–1 and the ADA classification of hypoglycaemia; see Figure 17–2).

Novo Nordisk classification of hypoglycaemia in paediatrics

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[58]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG-confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ISPAD classification[49]: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- 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 ISPAD classification[49] 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 ISPAD classification[49] or BG-confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



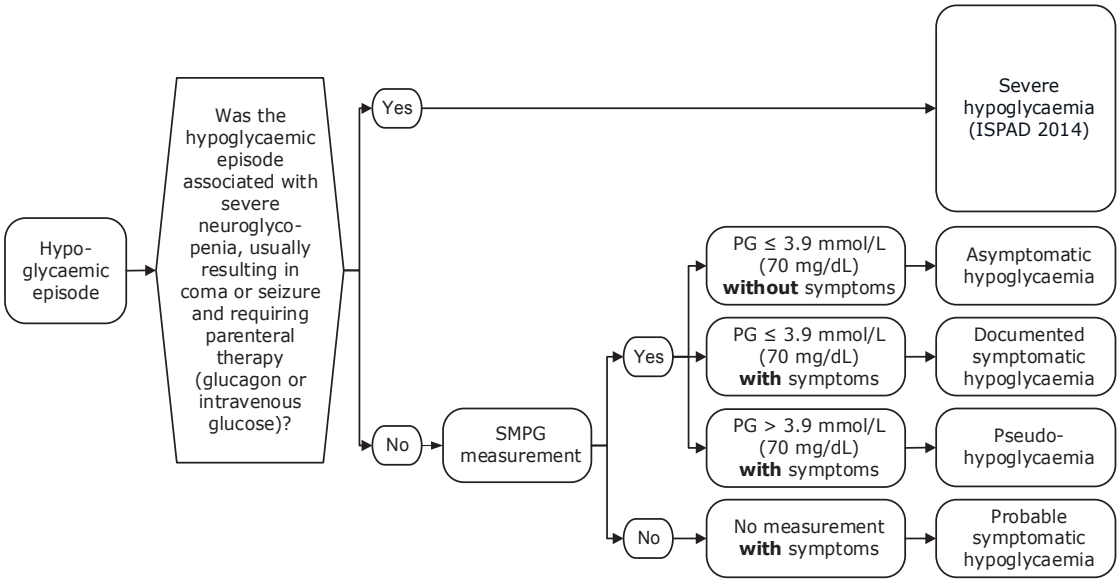
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

BG: blood glucose PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–1 Novo Nordisk classification of hypoglycaemia in paediatric subjects

ADA/ISPAD classification of hypoglycaemia in paediatric subjects[48, 49]

- Severe hypoglycaemia according to the ISPAD classification[49]:Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- 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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA/ISPAD classification of hypoglycaemia in paediatrics

Anti-liraglutide antibodies

Anti-liraglutide antibodies will be summarised in terms of the number and percentage of subjects per visit that are antibody-positive, antibody-negative, cross-reacting and in vitro neutralising.

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.

Bone age assessment

Bone age assessment at baseline and change in bone age assessment will be summarised using descriptive statistics.

ECG

Summary statistics and the frequencies of shifts from baseline at 30 and 56 weeks will be tabulated for each treatment group.

Pulse
Summary statistics and the frequencies of shifts from baseline to 30 and 56 weeks and from 56 weeks to 82 weeks will be tabulated for each treatment group. In addition, statistical analyses similar to those made for blood pressure will be performed for change from baseline to 30 and 56 weeks.

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 ranges. The results will be presented as follows:

- Shifts from baseline at 30 and 56 weeks and from 56 weeks to 82 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

Pubertal status
Tanner stage at screening as well as changes in Tanner stage at 30 and 56 weeks and change from 56 weeks to 82 weeks, will be summarised using descriptive statistics.

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

Height SDS
Height SDS[59] at screening and changes in height SDS will be summarised.

Mental health questionnaires
Results from the mental health questionnaires PHQ-9 and C-SSRS will be summarised using descriptive statistics and the frequencies of shifts from baseline to 30 and 56 weeks and from 56 weeks to 82 weeks will be tabulated for each treatment group.

17.5 Pharmacokinetic and pharmacodynamic modelling

Liraglutide concentrations from samples drawn at site visits will be used to describe the liraglutide exposure in pubertal adolescent subjects with obesity (12 to less than 18 years) and to investigate the effects of covariates on the pharmacokinetics. Data from pre-defined historical trials in relevant populations (i.e., adult 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 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 data base lock.

The pre-specified analysis will explore the effects of covariates on liraglutide exposure. The structural model and covariate relationships will be predefined in detail in the MAP. In brief, a previously-developed population PK model for liraglutide will be used. For the PK model, the apparent clearance will be estimated, while other model parameters may be set to prior pre-defined estimates (based on data from other trials). Area under the plasma concentration-time curve in steady state will be derived from the apparent clearance. The covariates of interest, such as body weight, sex and age group (adolescent/adult), will be tested on the apparent clearance.

The selected covariates will be incorporated into the population PK model and results will be presented using criteria which will be specified in the MAP. The population PK analysis will be reported in a separate stand-alone document.

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

17.6 Health economics and patient reported outcomes

The PRO questionnaire IWQOL-Kids 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[1], applicable regulatory requirements and in accordance with the Declaration of Helsinki[2].

Current treatment options for paediatric 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[15-19]. 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[26].

Participation in the present trial is restricted to adolescents who have obesity and who have a documented history of failing to lose weight with lifestyle modifications. Subjects will have access to experimental intensified treatment, liraglutide 3.0 mg, which has been shown to induce weight loss and improve cardiometabolic and quality of life parameters in adults with obesity. Subjects in the placebo group will have access to counselling in healthy nutrition and physical activity throughout the duration of the trial.

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 less than 18 years, duration of 5-6 weeks) and trial NN8022-3967 (liraglutide 3.0 mg in subjects with obesity without T2DM, 12 to less than 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 latest edition of the Liraglutide 3.0 mg (Saxenda®) Weight Management IB[28] or any updates hereof.

Identified and expected risks
With respect to the key risks of liraglutide, the most frequently reported AEs in subjects treated with liraglutide 3.0 mg were gastrointestinal (nausea and diarrhoea), with onset in weeks 1-4; these were of mild to moderate severity, and transient. Other gastrointestinal AEs 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 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 s.c. administration of proteins and peptides, allergic reactions are an identified risk due to the potential severity of these events.

An association between the use of GLP-1 receptor agonists 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-1 receptor agonists. 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/marked weight loss and the development of cholelithiasis is present[60-63].

Potential risks

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

Based on potential cross-reactivity of anti-liraglutide antibodies with an endogenous counterpart (GLP-1), anti-liraglutide antibody formation is a potential risk. Based on feedback from EMA, immune complex-related AEs are to be considered separately from those related to allergic reactions. No imbalance or safety concern has been seen regarding immune complex disorders for liraglutide in weight management. However, in alignment with liraglutide for T2DM, immune complex disorders are considered a potential risk for liraglutide in weight management.

It is unknown whether liraglutide causes thyroid C-cell tumours, including MTC, in humans, as human relevance has not been determined either by clinical or nonclinical studies. Cases of MTC in patients treated with liraglutide have been reported in the post-marketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans. Data from the intensive monitoring of calcitonin (a marker for MTC) in plasma in the liraglutide clinical development programme do not support a liraglutide-effect on calcitonin in humans, as mean calcitonin levels remained stable over time and well below the ULN of normal for both genders.

Subjects with overweight and obesity have an increased risk of certain types of cancer. In the weight management programme, the reporting rate of neoplasm events confirmed by 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. Pancreatic cancer has been added as a separate potential risk in the risk management plan as per EMA's request, although there is currently no evidence from clinical trials that GLP-1-based therapies increase this risk.

In the clinical development programme, mean increase in resting pulse (by 2–3 beat per minute), as well as a decrease in systolic blood pressure, have 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
All participating subjects will be monitored closely through frequent site visits. Blood sampling frequency and volume will be minimised for subjects' safety and convenience. The duration of the double-blind trial period is set to 56 weeks in an effort to limit the duration of placebo injections and reduce unnecessary subject discomfort/inconvenience (see Section 5.2).

An external independent DMC will be established and will perform review of unblinded safety data at regular intervals throughout the trial.

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 adolescent subjects, the trial product 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 lower to the previously given dose or to prolong a dose step for one additional week (see Section 8.1.8.1). Subjects treated with trial product 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.

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 with healthy nutrition, physical activity and 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, the trial product should promptly be interrupted until the presences of pancreatitis can be excluded (see Section 8.4.11) and appropriate treatment should be initiated. Subjects that are diagnosed with acute pancreatitis must have their trial product discontinued. Subjects with a personal or family history of MTC and subjects with MEN2 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. During the trial, calcitonin levels will be measured at pre-specified trial visits and levels above ULN 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 as they are for the adult populations with the exception of any unforeseen effects on growth and pubertal development. In nonclinical studies, dosing liraglutide from post-natal day 21 to 91 in juvenile rats caused a dose-dependent delay in sexual maturation

rate that was most pronounced in females. A delay in sexual maturation is known to occur in humans under caloric restriction/increased energy expenditure[64].

Pubertal- and growth-related hormonal levels, biochemical parameters of bone metabolism and growth and pubertal development will be monitored in the present trial.

Conclusion
Given the scarcity and limitations of available treatment options for paediatric obesity, the potential weight loss and cardiometabolic benefits of liraglutide and its acceptable safety/tolerability profile in the short-term paediatric trials, it is concluded that the potential benefits from participating in the present trial outweigh the potential risks. A starting dose of 0.6 mg has been chosen based on the tolerability seen in this population and model-estimated steady-state liraglutide exposure.

18.2 Informed consent

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

Before any trial-related activity, the investigator must give the subject and the subject's LAR verbal and written information about the trial and the procedures involved in a form that the subject and the subject's LAR can read and understand. The information given to the subjects must always be given in according to his/her capacity to understand, always taking into consideration the subject's presumed willingness to participate in a clinical trial. This includes the use of an impartial witness where required according to local requirements.

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

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial. The subject must only be included in the trial if both the subject and subject's LAR agree to have the subject participating.

A voluntary, signed and personally dated informed consent must be obtained from the subject and the subject's LAR before any trial-related activity. The informed consent/assent must be signed at least one day prior to screening as the subject must attend this visit fasting (see Section 8.1.2).

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

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

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

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

18.4 Information to subjects during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject, at the discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject may receive letters during the trial.

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

18.5 Premature termination of the trial and/or trial site

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

If the trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have

participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the trial database.

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

19.2 Prevention of missing data

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

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

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

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of investigator's brochure or SmPC or similar labelling as appropriate
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)
- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

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

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

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

22 Responsibilities

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

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

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

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list must be kept in a secure locked facility, so no unauthorized persons can get access to the data.

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[41].

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[40].

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the

results of interim analyses, because the release of such information may influence the results of the entire trial.

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

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[41] (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.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems 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 at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

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

24.2 Retention of human biosamples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons.

The samples will be stored either at the special laboratory or at Novo Nordisk AS after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

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

Only staff from the special laboratory or specialised staff at Novo Nordisk A/S will have access to the stored antibody samples.

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements, updates to investigator's brochure[28], 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.

26.1 For Belgium only

Law concerning experiments on the human person of 07 May 2004 - Article 29:
§1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

26.2 For Mexico only

Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.

If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the trial medication and/or a trial procedure that otherwise would not have been part of his/her regular care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required.

In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the trial by his own will or by a decision from the investigator.

By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

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Appendix A

Liraglutide
NN8022-4180

Body mass index (BMI) for age

Table of Contents

Table of tables

1 Introduction

According to protocol inclusion (Section 6.2 in the protocol) and protocol randomisation (Section 6.4 in the protocol), 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. The tables in Section 2 and 3 must be used to determine subjects eligibility.

The BMI ≥ 30 kg/m^2 for adults by international cut-off points are tabulated in Section 2.1 [1].

The 95th percentile for males and females of different ages are tabulated in Section 3 [2].

According to protocol exclusion (Section 6.3 in the protocol), subjects with a body weight equal to or below 60 kg must be excluded.

If a BMI corresponding to ≤ 25 kg/m^2 for adults by international cut-off point is reached, subjects should be assigned a maintenance diet, at the discretion of the investigator. See Section 2.2.

2 International BMI cut off points

2.1 Cut off points to determine subject's eligibility

Table 1 International cut off points for BMI for obesity by sex for children between 12 and 17 years old, 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.

Age: Years	BMI 30 kg/m^2 Males	BMI 30 kg/m^2 Females
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

Adapted from Cole et al.[1]

2.2 Cut off points for diet maintenance

Table 2 International cut off points for BMI for obesity by sex for children between 12 and 17 years old, 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.

Age: Years	BMI 30 kg/m^2 Males	BMI 30 kg/m^2 Females
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

Adapted from Cole et al.[1]

3 Determination of a subject's BMI > 95th percentile

In order to determine whether a subject is eligible according to inclusion criterion no.3, the investigator should use Table 2 for females and Table 3 for males. Based on the subject's age, it can be determined if the BMI is above the 95th percentile.

Table 3 BMI-for-age-FEMALES (12-18 years old)

Year: Month	Month	95th percentile (BMI in kg/m^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

Year: Month	Month	95th percentile (BMI in kg/m^2)
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
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

Year: Month	Month	95th percentile (BMI in kg/m^2)
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

Year: Month	Month	95th percentile (BMI in kg/m^2)
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
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

Year: Month	Month	95th percentile (BMI in kg/m^2)
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-MALES (12-18 years old)

Year: Month	Month	95th percentile (BMI in kg/m^2)
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

Year: Month	Month	95th percentile (BMI in kg/m^2)
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
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

Year: Month	Month	95th percentile (BMI in kg/m^2)
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

Year: Month	Month	95th percentile (BMI in kg/m^2)
15:11	191	26.1
16:0	192	26.1
16:1	193	26.2
16:2	194	26.3
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

Year: Month	Month	95th percentile (BMI in kg/m^2)
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

4 References

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

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

Appendix B

Liraglutide
NN8022-4180

Blood pressure ranges for children

Table of Contents

Page

Table of figures

Table of tables

1 Introduction

According to exclusion criterion (Section 6.3 in the protocol), subjects must be excluded from the trial in cases where they have uncontrolled treated or untreated hypertension >99th percentile for age and gender in children, in accordance with "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 in accordance with 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 subject's height percentile according to Figure 1 for females and Figure 2 for males.

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 females and Table 2 for males.

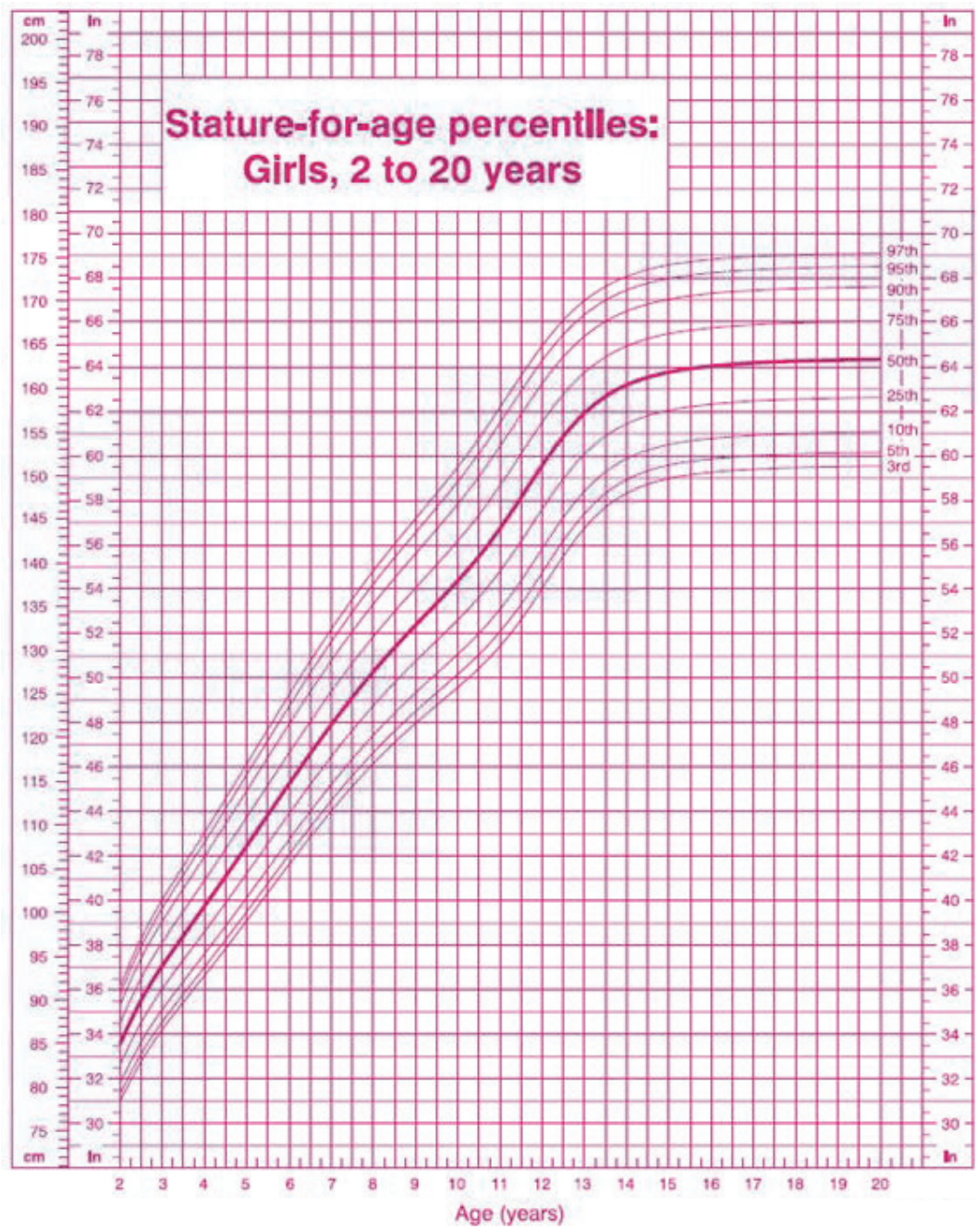

Figure 1 Height for age percentiles in females

Table 1 Blood pressure levels for females 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
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

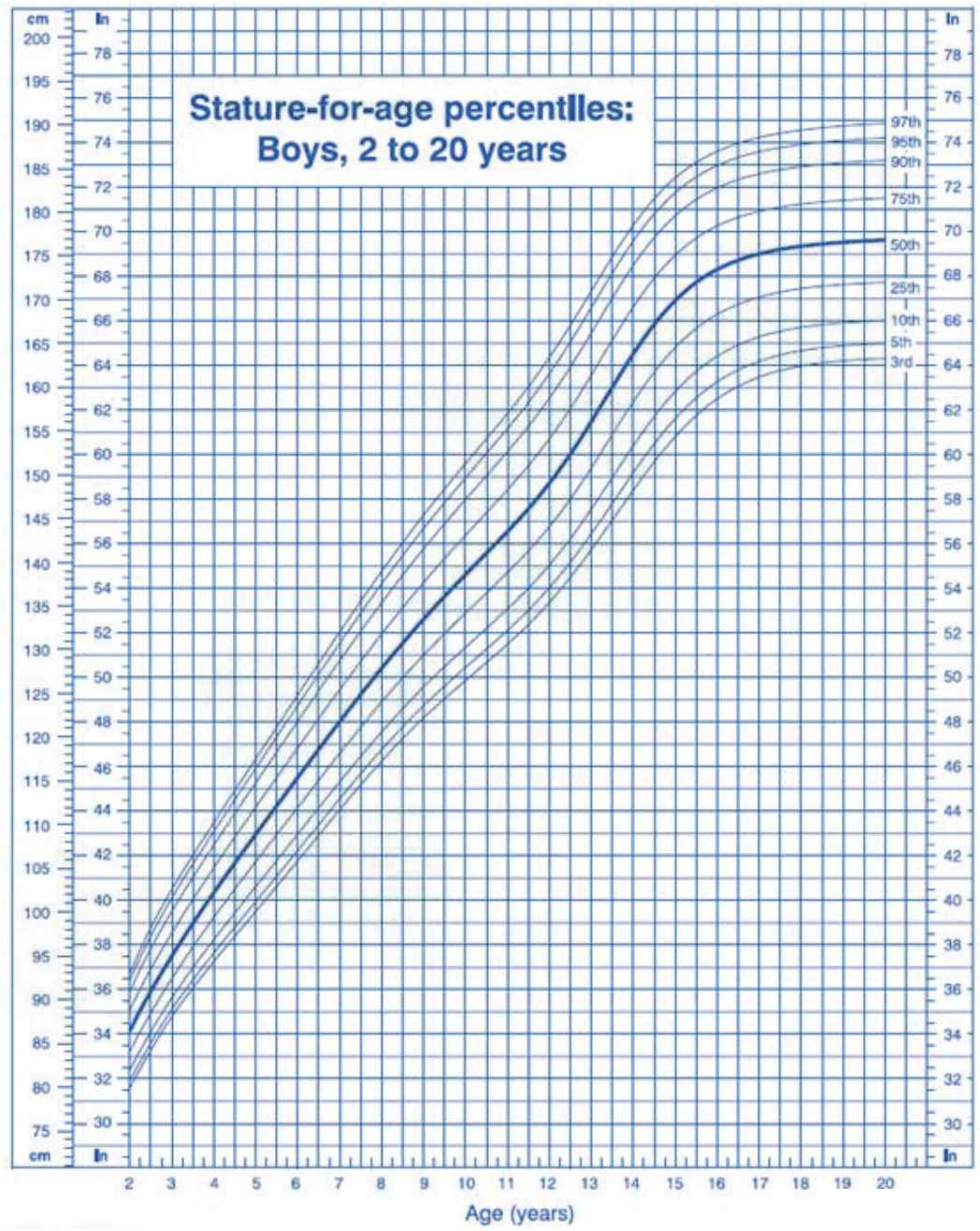

Figure 2 Height for age percentiles in males

Table 2 Blood pressure levels for males 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
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

3 References

1 The fourth report on the: Diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. U.S.Department of Health and Human Services, National Institute of Health National Heart Lung and Blood Institute. 2012.

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
NN8022-4180

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 limit of normal 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 (12 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 post randomisation will be reviewed monthly by the International Medical Director (IMD) for this project or the director's surrogate. Calcitonin levels above upper limit of normal will be flagged by the central laboratory on the laboratory report, and reported to the investigator, the International Trial Manager (ITM), and IMD. 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.

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, final version 1.0
dated 01 June 2016

Trial ID: NN8022-4180

Effect of liraglutide for weight management in pubertal adolescent subjects with obesity

56-week, double-blind, randomised, parallel-group, placebo-controlled multi-national trial followed by a 26-week period off study-drug

Trial phase: 3a

Applicable to Sweden

Amendment originator: [redacted]

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

The present local substantial amendment for Sweden implements a requirement from the Swedish Medical Products Agency (MPA) to specify the definition on adequate contraceptive measures for Swedish trial participants in accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials, Final Version 2014-09-15.

In this protocol amendment:

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

2 Changes

6 Trial Population

6.3 Exclusion criteria

Changes to exclusion criteria number 30:

For Sweden only: ~~Oral (except low-dose gestagen [lynestrenol and norestisteron]), injectable, or implanted hormonal contraceptives, intrauterine device, intrauterine system (for example, progestin-releasing coil), vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate). Use of contraception is not required for female subjects who have not yet made their sexual debut and/or are not sexually active.~~ *Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined (estrogen and progestogen containing) oral/intravaginal/transdermal contraceptives, progestogen-only oral/injectable/implantable contraceptives, intrauterine device (IUD, IUS), sexual abstinence or vasectomised partner.*

Protocol Amendment

no 2
to Protocol, final version 1.0
dated 01 June 2016

Trial ID:NN8022-4180

Effect of liraglutide for weight management in pubertal adolescent subjects with obesity

56-week, double-blind, randomised, parallel-group, placebo-controlled multi-national trial followed by a 26-week period off study-drug

Trial phase: 3a

Applicable to Mexico

Amendment originator:
[redacted]

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

The present local amendment for Mexico implements a requirement from the Research Committee to explicitly mention the 'informed assent' in the inclusion criterion number 1 to align with the text in protocol Sections 8.1.1 and 18.2.

In addition, editorial changes are addressed upon request from the Research Committee.

In this protocol amendment:

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

2 Changes

2.1 Section 1.0 Summary

Trial design:

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to ~~those~~ *subjects* in the European Union. All subjects will undergo counselling in healthy nutrition and physical activity for weight loss and must be prescribed a structured programme from the beginning of the 12-week run-in period and continuing through the 26-week follow-up period off trial drug.

Key inclusion criteria:

- Informed consent *from the legally acceptable representative (LAR) and informed assent from the subject* 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.

- BMI corresponding to ~~≥30 kg/m^2~~ ≥ *30 (kg/m^2)* for adults by international cut-off points and ≥ the 95th percentile for age and sex (for diagnosis of obesity)

Key randomisation criteria:

- BMI corresponding to ~~≥30 kg/m^2~~ ≥ *30 (kg/m^2)* for adults by international cut-off points and ≥ the 95th percentile for age and sex (for diagnosis of obesity).

2.2 Section 5.1 Type of Trial

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to ~~those~~ *subjects* in the European Union. All subjects will undergo counselling in healthy nutrition and physical activity for weight loss and must be prescribed a structured programme from the beginning of the 12-week run-in period and continuing through the 26-week follow-up period off trial drug. The trial design is shown schematically below:

2.3 Section 6.2 Inclusion criteria:

1. Informed consent *from the legally acceptable representative (LAR) and informed assent from the subject* 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.

3. BMI corresponding to ~~≥30 kg/m^2~~ *≥30 (kg/m^2)* for adults by international cut-off points and ≥ the 95th percentile for age and sex (for diagnosis of obesity)

2.4 Section 6.4 Randomisation criteria

3. BMI corresponding to ~~≥30 kg/m^2~~ *≥30 (kg/m^2)* for adults by international cut-off points and ≥ the 95th percentile for age and sex (for diagnosis of obesity)

2.5 Section 8.6.2.1 Counselling in healthy nutrition

If a BMI corresponding to ~~≤ 25 kg/m^2~~ *≤ 25 (kg/m^2)* for adults by international cut-off point[53] is reached, subjects should be assigned a maintenance diet, at the discretion of the investigator. For details, refer to Appendix A.