Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04775082
Sponsor trial ID:	NN8022-4392
Official title of study:	Effect and safety of liraglutide 3.0 mg on weight management in children with obesity aged 6 to <12 years: 56-week, double-blind, randomised, placebo-controlled trial
Document date*:	30 April 2024

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header from Page 2 and 117 is the date of compilation of the documents and not of an update to content.

9.1.1 Protocol and protocol amendments

List of contents

Protocol Version 5.0 ..... Link

Protocol Attachment ..... Link

Protocol

Protocol title:

Effect and safety of liraglutide 3.0 mg on weight management in children with obesity aged 6 to <12 years: 56-week, double-blind, randomised, placebo-controlled trial

Substance: liraglutide

Universal Trial Number: U1111-1247-8226

EU-CT number: 2023-508504-38

Trial phase: 3a

In the following, Novo Nordisk A/S and its affiliates will be stated as “Novo Nordisk”.

This ~~confidential~~ document is the property of Novo Nordisk. ~~No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.~~

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 5.0	30 April 2024	All countries
Protocol version 4.0	19 May 2022	All countries
Protocol version 3.0	05 November 2020	All countries
Protocol version 2.0	02 October 2020	Not submitted in any country
Original protocol version 1.0	30 April 2020	Submitted for FDA review

Protocol version 5.0 (26 April 2024)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union for the countries participating in the Extension phase of the trial.

Overall rationale for preparing protocol, version 5.0:

The overall rationale for amending the protocol is to update the retention period of documentation and EU CT number in the Protocol.

A Clinical Trial Report (CTR) will be prepared for the Main phase of the trial, and an Extension CTR will be prepared for the Extension phase of the trial. The extension phase will have no effect on the timelines for the submission of the Main phase CTR to Health Authorities.

Section # and name	***Description of change***	***Brief rationale***
Cover page	EudraCT number was replaced with EU CT number	To align with EU CT submission in EU CTIS
Section 12, Appendices 3, #11	Retention of clinical trial documentation updated to 25 years	To align with PI-IC forms (template ver 12.0)

Table of Contents

Page

Protocol amendment summary of changes table **2**

Table of Contents **3**

1 Synopsis **6**

2 Flowchart, Main phase **10**

3 Flowchart, Extension phase **13**

4 Introduction **15**
4.1 Trial rationale 15
4.2 Background 16
4.2.1 Liraglutide 16
4.2.2 Trial Population 17
4.3 Benefit-risk assessment 17
4.3.1 Benefits 17
4.3.2 Risks and precautions 18
4.3.3 Conclusion on benefit-risk profile 20

5 Objectives, endpoints and estimands **21**
5.1 Primary, secondary and exploratory objectives 21
5.2 Primary, secondary and exploratory endpoints 22
5.2.1 Primary endpoint 22
5.2.2 Secondary endpoints 22
5.2.2.1 Confirmatory secondary endpoints 22
5.2.2.2 Supportive secondary endpoints 22
5.2.2.3 Exploratory endpoints 22

6 Trial design **24**
6.1 Overall design 24
6.2 Subject and trial completion 25
6.3 End of trial definition 25
6.4 Scientific rationale for trial design 26
6.5 Justification for dose 27

7 Trial population **28**
7.1 Inclusion criteria 28
7.2 Exclusion criteria 28
7.3 Randomisation criteria for Main phase only 30
7.4 Lifestyle restrictions 30
7.4.1 Meals and dietary restrictions 30
7.5 Screen failures 31
7.6 Run-in failures 31

8 Treatments **32**
8.1 Treatments administered 32
8.2 General injection instructions 32
8.3 Initial dose and dose escalation instructions 32
8.4 Dose modification for the open-label treatment period phase 34
8.5 Auxiliary supplies 34
8.6 Medical devices 34
8.7 Diet and physical activity counselling 35
8.8 Dose modification 35
8.8.1 Tolerability at maximum tolerated dose 35

8.9 Method of treatment assignment....36
8.10 Blinding....36
8.11 Preparation/Handling/Storage/Accountability....37
8.12 Treatment compliance....38
8.12.1 Clinical efficacy laboratory assessments....39
8.12.2 Missed doses....39
8.13 Concomitant medication....38
8.14 Treatment after the end of the trial....38

9 Discontinuation of trial treatment and subject discontinuation/withdrawal....39
9.1 Discontinuation of trial treatment....39
9.1.1 Temporary discontinuation of trial treatment....41
9.2 Withdrawal from the trial....41
9.2.1 Replacement of subjects....42
9.3 Lost to follow-up....42

10 Trial assessments and procedures....43
10.1 Efficacy assessments....44
10.1.1 Body measurements....44
10.2 Adverse events....45
10.2.1 Time period and frequency for collecting AE and SAE information....45
10.2.2 Method of detecting AEs and SAEs....48
10.2.3 Follow-up on AEs and SAEs....48
10.2.4 Regulatory reporting requirements for SAEs....48
10.2.5 Cardiovascular and death events....48
10.2.6 Pregnancies and associated adverse events....48
10.2.7 Medical device incidents (including malfunctions)....49
10.2.8 Technical complaints....49
10.3 Treatment of overdose....49
10.4 Safety assessments....50
10.4.1 Mental health evaluation....50
10.4.2 Physical examinations....51
10.4.3 Vital signs....51
10.4.4 Pubertal status....52
10.4.5 Bone age assessment (x-ray)....52
10.4.6 Electrocardiograms....52
10.4.7 Clinical safety laboratory assessments....52
10.4.8 Immunogenicity assessments....52
10.4.9 Severe hypersensitivity....53
10.5 Pharmacokinetics....53
10.6 Pharmacodynamics....54
10.7 Genetics....54
10.8 Biomarkers....54
10.9 Biosamples for future analysis....54
10.10 Subject diaries....55
10.10.1 PK diary....55
10.10.2 Menstrual period diary....55
10.10.3 Diabetes diary....55

11 Statistical considerations....56
11.1 Sample size determination....56
11.2 Definition of analysis sets....58
11.2.1 Main phase....58
11.2.2 Extension phase....59
11.3 Statistical analyses....59
11.3.1 Primary endpoint....60

11.3.2 Secondary endpoints 62
11.3.3 Supportive secondary endpoints 62
11.3.4 Exploratory endpoints 62
11.3.5 Interim analyses 64
11.3.6 Other analyses 64
11.4 Pharmacokinetic and/or pharmacodynamic modelling 64

12 Appendices 66

Appendix 1 Abbreviations and Trademarks 67

Appendix 2 Clinical laboratory tests 69

Appendix 3 Trial governance considerations 74

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting 83

Appendix 5 Contraceptive guidance and collection of pregnancy information 88

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting 91

Appendix 7 Retention of human biosamples 93

Appendix 8 Assessments for subjects with T2D 94

Appendix 9 Hypoglycaemic episodes 97

Appendix 10 Clinical Charts for Body Mass Index by gender and age 99

Appendix 11 Monitoring of calcitonin 102

Appendix 12 Country-specific requirements 105

Appendix 13 Protocol amendment history 108

13 References 109

Protocol attachment I Global list of key staff and relevant departments and suppliers
Protocol attachment II Country list of key staff and relevant departments

1 Synopsis

Rationale:

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.[1-3] Paediatric obesity is associated with a number of complications, including hypertension, type 2 diabetes, early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems.[4] Furthermore, paediatric overweight/obesity is an independent risk factor for obesity in adulthood[5], thus predisposing to future comorbid conditions and reduced life expectancy.[6, 7]

Although lifestyle modification is the recommended first-line treatment, widespread adoption of this treatment method and long-term compliance are problematic[8-10] and treatment intensification may be needed. Currently, orlistat is the only pharmacotherapy with U.S. Food and Drug Administration approval for the management of obesity in the paediatric population and is indicated for those aged ≥12 years[11]. There are no pharmacotherapies approved for weight management in young children below the age of 12 in either the United States or European Union (EU).[12]

Main phase

The NN8022-4392 trial is being conducted to assess the effect and safety of liraglutide 3.0 mg in the paediatric population in order to potentially address the unmet need for treatment of children aged 6 to <12 years with obesity.

Extension phase

Childhood obesity is a chronic, progressive and relapsing disease.[5-9] When the Main phase has LPLV in 2024, no anti-obesity medication with regulatory approval is expected to be available for this age group (ages 6 to <12 years). The open-label treatment period will provide both access to liraglutide 3.0 mg (for eligible subjects) as well as to continued lifestyle intervention, to all subjects. Additionally, the Extension phase includes yearly safety visits for 2 years that will provide a unique opportunity to obtain much needed long-term safety and efficacy data from children treated with anti-obesity medication.

Objectives, endpoints and estimands:

Main phase

Primary objective

To compare the effect of liraglutide 3.0 mg subcutaneous (s.c.) once daily versus liraglutide placebo on weight management in children aged 6 to <12 years with obesity.

"Liraglutide placebo" will hereafter be referred to as "placebo".

Secondary objectives

To compare the effect of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity on:

- Cardiovascular risk factors

- Glucose metabolism

To evaluate the safety and tolerability of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity.

Extension phase

Exploratory objectives

To investigate the long-term efficacy and safety of liraglutide 3.0 mg s.c. once daily in children aged 6 to <12 years (at time of signing of informed consent for Main phase of trial) with obesity.

Main phase

Primary endpoint

Relative change in Body Mass Index (BMI) from baseline (week 0) to week 56 (%)

Extension phase

Exploratory endpoints

Exploratory safety and efficacy endpoints are defined in Section 5.2.2.3.

Main phase

Primary estimand

The estimand will quantify the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised subjects regardless of adherence to treatment or initiation of rescue interventions (such as weight management drugs or bariatric surgery) ("effectiveness"/"treatment policy" estimand). The estimand will cover all effect-related objectives.

Secondary estimand

The estimand will quantify the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any rescue intervention (such as weight management drugs or bariatric surgery) ("efficacy"/"hypothetical" estimand). The estimand will cover the primary objective

Overall design:

Main phase

The Main phase of the trial is a double-blind, randomised, parallel group, placebo-controlled, multi-national clinical trial comparing liraglutide 3.0 mg s.c. once daily with placebo in children, aged 6 to <12 years, with obesity, with or without comorbidities. The Main phase of the trial includes:

- a 2-week screening period
- a 12-week run-in period
- a 56-week treatment period
- a 26-week off-drug follow-up period

Extension phase

The Extension phase of the trial includes:

- a 2-week screening period
- a 56-week open-label treatment period
- a 2-week off-drug follow-up period
- an off-treatment, safety follow-up visit one year after the end of the open-label treatment period
- an off-treatment, safety follow-up visit two years after the end of the open-label treatment period

All subjects will be offered lifestyle intervention from the beginning of the 12-week run-in period of the Main phase to the end of the 2-week off-drug follow-up period of the Extension phase.

Key inclusion criteria

- Informed consent of parent(s) or legally acceptable representative of subject and child assent, as age-appropriate, obtained before any trial-related activities for the Main phase as well as for the Extension phase of the trial. 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, aged 6 to <12 years at the time of signing informed consent
- Tanner stage 1-5 pubertal development at the time of signing informed consent
- BMI ≥95th percentile, on gender and age-specific growth charts (CDC.gov)
- History of failing to lose sufficient weight with lifestyle modification as judged by the investigator

For subjects with type 2 diabetes at screening the following inclusion criterion apply in addition:

- Haemoglobin A1c (HbA1c) ≤10.0% (86 mmol/mol) as measured by central laboratory at

Subjects who do not meet the eligibility criteria to receive liraglutide 3.0 mg during the open-label treatment period will still be eligible to participate in the Extension phase but will receive intervention with diet and physical activity counselling only. Please see Section 7 for details.

Number of subjects:

Main phase

Approximately 103 subjects will be screened to achieve approximately 87 subjects to be included in the run-in period to reach the anticipated 78 subjects randomly assigned to trial product.

Extension phase

All approximately 78 subjects randomised to trial product in the Main phase who also attend the End of Main phase visit (week 82) will be eligible to participate in the Extension phase.

Treatment groups and duration:

Main phase

The total Main phase duration for the individual subject will be approximately 96 weeks. The trial includes a screening period to assess the subject's eligibility followed by a 12-week run-in period with lifestyle intervention before randomisation. Eligible subjects will be randomised in a 2:1 manner to receive either liraglutide 3.0 mg s.c. or placebo s.c. once daily as an adjunct to lifestyle intervention as follows:

- For children with a body weight ≥45 kg at randomisation:

  Dosing will be initiated with liraglutide/placebo 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until a dose of 3.0 mg liraglutide/placebo is reached or an individual maximum tolerated dose (as judged by the investigator) The treatment continues with 52 weeks on maintenance dose until the 'end of treatment' visit followed by a 26 weeks follow-up period

- For children with a body weight <45 kg at randomisation:

  Dosing will be initiated with liraglutide/placebo 0.3 mg daily for one week and increased to 0.6 mg after the first week, thereafter the dose is increased in weekly steps of 0.6 mg until a dose of 3.0 mg liraglutide/placebo is reached or an individual maximum tolerated dose (as judged by the investigator). The treatment continues with 51 weeks on maintenance dose until the 'end of treatment' visit followed by a 26 weeks follow-up period

- Maintenance dose for all children is 3.0 mg once daily or individual maximum tolerated dose.
- Dose escalation will be based on tolerability as judged by the investigator (Section 8.3).

Randomisation will be stratified by gender and Tanner stage (1 vs 2-3 vs 4-5).

Extension phase

The maximum total duration of the open-label treatment period will be 64 weeks. This allows for a 2-week screening period, 4-8 weeks of dose escalation, 48-52 weeks of maintenance treatment, and a 2-week off-drug, follow-up period. Eligible subjects (details are in Section 7) will receive liraglutide 3.0 mg daily (or maximum tolerated dose) in addition to lifestyle intervention. Dosing will be initiated and escalated as in the Main phase of the trial (Section 8.3).

The off-treatment, safety follow-up visits will occur 1 and 2 years after the open-label treatment period.

The following trial products are supplied by Novo Nordisk A/S

- Liraglutide 6.0 mg/mL, 3.0 mL, for s.c. injection with FlexPen®.
- Liraglutide placebo (referred to as placebo), 3.0 mL, for s.c. injection with FlexPen®.

2 Flowchart, Main phase

Main phase	Screening	Run-in						Randomisation	Dose escalation				Maintenance										**End of treatment	Off-drug follow-up				End of main phase
Visit*	V1	V2	P3	V4	P5	V6	P7	V8	V9	V10	V11	V12[a]	V13	P14	V15	P16	V17	P18	V19	P20	V21	P22	V23	V24	P25	V26	P27	V28[j]
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	21	26	31	36	41	46	51	56	58	64	70	76	82
Visit Window (Days)	-7/0	±5	±5	±5	±5	±5	±5	0	±2	±2	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/+7	±7	±7	±7	0/+7
Attend visit fasting (7.4.1)		X						X									X						X	X**				X
Informed consent, child assent and Demography[b] (Appendix 3)	X																											
Inclusion and exclusion criteria (7.1, 7.2)	X	X																										
Randomisation criteria and randomisation 7.3)								X																				
Medical history[c] and Concomitant illness (10.4)	X																											
Concomitant medication (8.13)	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
Childbearing potential[d] (Appendix 5)	X			X				X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[e] (10.2.6), (Appendix 2) (Appendix 5)	X							X	X	X	X	X	X		X		X		X		X		X	X		X		X
Pubertal Status (10.4.4)	X							X									X						X					X
Laboratory assessments (Appendix 2)	X	X						X					X		X		X				X		X	X				X
Body Weight (10.1.1)	X	X		X		X		X	X	X	X	X	X		X		X		X		X		X	X		X		X
Height (10.1.1)	X							X					X		X		X		X		X		X	X		X		X
Waist Circumference (10.1.1)								X															X					X
ECG (10.4.6)	X							X															X					
Vital Signs (10.4.3)	X	X		X		X		X	X	X	X	X	X		X		X		X		X		X	X		X		X
Physical Examination (10.4.2)	X							X									X						X					
Bone age measurement (x-ray) (10.4.5)								X															X					
Biosamples for future analysis[f] (10.9)								X															X					X
Evaluation of glycaemic status[g] (10)								X									X						X					

Main phase	Screening	Run-in						Randomisation	Dose escalation				Maintenance										End of treatment	Off-drug follow-up				End of main phase
Visit*	V1	V2	P3	V4	P5	V6	P7	V8	V9	V10	V11	V12[a]	V13	P14	V15	P16	V17	P18	V19	P20	V21	P22	V23	V24	P25	V26	P27	V28[j]
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	21	26	31	36	41	46	51	56	58	64	70	76	82
Visit Window (Days)	-7/0	±5	±5	±5	±5	±5	±5	±0	±2	±2	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/+7	±7	±7	±7	0/+7
Diet and physical activity counselling[h] (8.7)		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
Mental Health Evaluation 10.4.1)		X		X		X		X	X	X	X	X	X		X		X		X		X		X	X		X		X
Adverse event (10.2), (Appendix 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
Technical complaint (Appendix 6)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Hand out and instruct in PK diary (10.10)												X	X		X				X		X							
Hand out and instruct in menstrual period diary[i] (10.10)						X									X						X					X		
IWRS Session 8.9, 8.11)	X							X				X	X		X		X		X		X		X					
Trial Product Dispensing (8)								X				X			X		X		X		X							
Training in trial product, pen-handling (8.6)								X				X	X		X		X		X		X							
Treatment compliance (8.12)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
The following assessments are only applicable to subjects with type 2 diabetes (T2D) at screening or if diagnosed during the trial																												
Attend visit fasting (7.4.1)		X						X					X				X				X		X	X				X
Fasting self-measured plasma glucose (SMPG) (Appendix 8)								X	X	X	X	X	X		X		X		X		X		X	X		X		X
Hypoglycaemic episodes (Appendix 9)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand out and instruct in BG-meter (Appendix 8)								X																				
Hand out and instruct in diabetes diary (10.10.3, (Appendix 8)								X	X	X	X	X	X		X		X		X		X		X	X		X		

Footnotes:

* Visits marked as phone visits can be replaced by site visits or video calls to ensure flexibility for the subjects

**2-hr fasting (non T2D only)

a) For children with a body weight <45 kg, the investigator must ensure correct dose escalation steps to 3.0 mg or individual maximum tolerated dose via phone, video call and/or an additional visit between V12 and V13

b) Demography consists of date of birth, gender, ethnicity, and race (according to local regulation)

c) Medical history of subjects with T2D must include diabetes history and complications

d) Only for females

e) Only for females that have started their menstrual period (of childbearing potential): Urine pregnancy test should also be performed at any time during the trial if pregnancy is suspected, if a menstrual period is missed, and/or according to local regulations/law. If a female becomes of childbearing potential (has first menstrual period) during the trial, a urine pregnancy test must be performed for that subject at the latest at the next site visit.

f) Only for subjects where the separate informed consent for biosamples for future research has been signed

g) Only subjects without T2D at screening.

h) The counselling can be done independent of the site visits within the visit window and flexibly as a site visit or a phone/video call

i) Only for females that have started their menstrual period

j) Biochemistry and haematology panels only required for subjects continuing in Extension phase

3 Flowchart, Extension phase

Extension phase	End of main trial	Screening visit Extension phase	Dose escalation					Maintenance							End of Treatment Extension Period	Off-drug Follow-up	1-year safety follow-up	2-year safety follow-up (End of Trial)
Visit*	V28	V28A	V29	V30	V31	V32	V33	P34	V35	P36	V37	P38	V39	P40	V41	V42	V43	V44
Timing of Visit (Weeks)	82		84	85	86	87	88	94	100	106	112	119	126	133	140	142	192	244
Visit Window (Days)	0/+7		0	±2	±2	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	0/+7	±7	±7
Attend visit fasting (7.4.1)	X										X				X	X**	X	X
Informed consent of extension, child assent		X																
Inclusion and exclusion criteria (7.1, 7.2)		X																
Re-use from main trial - Medical history[a] and Concomitant illness (10.4)																		
Concomitant medication (8.13)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childbearing potential[b] (Appendix 5)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[c] (10.2.6), (Appendix 2) (Appendix 5)	X		X	X	X	X	X		X		X		X		X	X	X	X
Pubertal Status (10.4.4)	X										X				X		X	X
Laboratory assessments (Appendix 2)	X	X[g]							X[d]		X		X[d]		X	X	X	X
Hand out and instruct in PK diary (10.10)						X	X		X		X		X					
PK samples (Appendix 2)							X		X		X		X		X	X		
Antibodies samples (Appendix 2)	X						X		X		X		X		X	X		
Body Weight (10.1.1)	X		X	X	X	X	X		X		X		X		X	X	X	X
Height (10.1.1)	X		X						X		X		X		X		X	X
Waist Circumference (10.1.1)	X														X		X	X
ECG (10.4.6)		X													X			
Vital Signs (10.4.3)	X		X	X	X	X	X		X		X		X		X	X	X	X
Physical Examination (10.4.2)		X									X				X		X	X
Bone age measurement (x-ray) (10.4.5)															X			

Evaluation of glycaemic status[e] (10)		X									X				X		X	X
Diet and physical activity counselling[f] (8.7)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Mental Health Evaluation 10.4.1)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse event (10.2), (Appendix 4)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaint (Appendix 6)			X	X	X	X	X	X	X	X	X	X	X	X	X			
Hand out and instruct in menstrual period diary[c] (10.10)		X																
Training in trial product, pen-handling (8.2, 8.6)			X	X	X	X	X		X		X		X					
IWRS session (8.9 and 8.11)			X				X		X		X		X		X			
Trial Product Dispensing (8.1)			X				X		X		X		X					
Treatment compliance (8.12)				X	X	X	X	X	X	X	X	X	X	X	X			
The following assessments are only applicable to subjects with type 2 diabetes (T2D) at screening or if diagnosed during the trial																		
Attend visit fasting (7.4.1)	X								X		X		X		X	X	X	X
Fasting self-measured plasma glucose (SMPG) (Appendix 8)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hypoglycaemic episodes (Appendix 9)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Use BG-meter handed out and instructed in main trial (Appendix 8)																		
Hand out and instruct in diabetes diary (10.10.3, (Appendix 8)		X					X		X		X		X		X			

*Visits marked as phone visits can be replaced by site visits or video calls to ensure flexibility for the subjects

**2-hr fasting

a) Medical history of subjects with T2D must include diabetes history and complications

b) Only for females

c) Only for females that have started their menstrual period (of childbearing potential): Urine pregnancy test should also be performed at any time during the trial if pregnancy is suspected, if a menstrual period is missed, and/or according to local regulations/law. If a female becomes of childbearing potential (has first menstrual period) during the trial, a urine pregnancy test must be performed for that subject at the latest at the next site visit.

d) Only for subjects with T2D

e) Only for subjects without T2D at screening.

f) The counselling can be done independent of the site visits within the visit window and flexibly as a site visit or a phone/video call

g) This lab assessment includes additional tests to allow for screening and should be done in addition to the V28 (end of Main phase) lab assessments

4 Introduction

4.1 Trial rationale

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.[1-3] The American Medical Association (2013) as well as a number of leading institutions such as the National Institutes of Health (1998), The Obesity Society (2008), the World Obesity Federation (2017)[13] and the American Association for Clinical Endocrinology (2012) classify obesity as a disease, calling for dedicated efforts in prevention, diagnosis and treatment.[14] Paediatric obesity is associated with a number of complications, including hypertension, type 2 diabetes (T2D), early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems.[4] Furthermore, paediatric overweight/obesity is an independent risk factor for obesity in adulthood[5], thus predisposing to future comorbid conditions and reduced life expectancy.[6, 7] 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.[15-18]

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[8-10] and treatment intensification may be needed. Currently, orlistat is the only pharmacotherapy with U.S. Food and Drug Administration (FDA) approval for the management of obesity in the paediatric population and is indicated for those aged ≥12 years.[11] However, orlistat effects modest weight loss in adolescents and treatment compliance is low due to gastrointestinal adverse events (AEs).[10, 11, 19] Metformin, when used for indications like dysglycaemia and polycystic ovary syndrome (PCOS), has only a modest effect on body weight.[20, 21] No medication is currently approved for the treatment of obesity in individuals <12 years in the European Union. For paediatric subjects with severe obesity, long-term success of lifestyle interventions and pharmacotherapy has been disappointing. For some adolescents with severe obesity surgical treatment may offer an effective alternative.[22, 23] 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.[24] Thus, effective weight loss treatments with optimised safety/tolerability profiles which do not discourage compliance are urgently needed for the paediatric population.

Main phase

The aim of the Main phase of this trial is to assess the effect and safety of liraglutide 3.0 mg on weight management in children aged 6 to <12 years with obesity to potentially address the unmet need of pharmacotherapy. This clinical trial is also being conducted to fulfil the regulatory requirement for paediatric trials from the FDA and the European Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

Extension phase

Childhood obesity is a chronic, progressive and relapsing disease.[5-9] When the Main phase has LPLV in 2024, no anti-obesity medication with regulatory approval is expected to be available for

this age group (ages 6 to <12 years). The open-label treatment period will provide both access to liraglutide 3.0 mg (for eligible subjects) as well as to continued lifestyle intervention, for all subjects. The addition of the extension phase, after the 26-week "off-drug" period of the Main phase, will mimic the likely intermittent nature of anti-obesity treatment in the paediatric population with obesity, in a real-world setting. Additionally, the Extension phase includes yearly safety visits for 2 years that will provide a unique opportunity to obtain much needed long-term safety and efficacy data in children treated with anti-obesity medication.

4.2 Background

4.2.1 Liraglutide

The glucagon-like-peptide-1 receptor agonist (GLP-1 RA), liraglutide, is approved for treatment of T2D (1.2 and 1.8 mg/day as Victoza®) and weight management (3.0 mg as Saxenda®). Through activation of the GLP-1 receptor, liraglutide stimulates insulin secretion in a glucose-dependent manner and reduces appetite and energy intake.[25] In the weight management development program in adults, treatment with liraglutide 3.0 mg, as an adjunct to diet and exercise, was safe and generally well-tolerated and resulted in significantly greater weight loss than diet and exercise alone in subjects with obesity and in subjects with overweight with at least one weight-related co-morbidity.[26, 27] Liraglutide exposure has been shown to increase proportionally with dose. Furthermore, higher exposure is expected in subjects with low body weight compared to subjects with higher body weight.

To date, six randomised, controlled clinical trials with liraglutide have been completed in paediatric subjects. Three of these were clinical pharmacology trials. In trial (NN2211-1800), liraglutide at doses up to 1.8 mg/day was generally well tolerated for 5-6 weeks in paediatric subjects with T2D aged 10 to <18 years.[28] Liraglutide at doses up to 3.0 mg/day was also generally well tolerated, both when used for 5 weeks in adolescents with obesity aged 12 to <18 years (NN8022-3967)[29], and when used for 7 weeks in children with obesity aged 7 to <12 years (NN8022-4181).[12] In a recently completed trial (NN8022-4179), the effect of liraglutide 3.0 mg on weight loss was investigated in children aged 6 and <18 years with Prader-Willi syndrome and obesity. The confirmatory safety and efficacy trial (NN2211-3659) in paediatric subjects investigated the treatment of T2D with liraglutide 1.8 mg/day for 52 weeks in subjects aged 10 to <18 years.[30] Another safety and efficacy trial (NN8022-4180) investigated the treatment of obesity with liraglutide 3.0 mg for 56 weeks in adolescents aged 12 to <18 years.[31] The overall safety profile for liraglutide in paediatric subjects, observed in the six randomised, controlled clinical trials, is consistent with the safety profile for liraglutide observed in trials with adult subjects.

A comprehensive review of results from the non-clinical and clinical studies of liraglutide can be found in the latest edition of the Liraglutide 3.0 mg (Saxenda®) Weight Management investigator's brochure (IB[32]) or any updates hereof.

4.2.2 Trial Population

The trial population consists of children, aged 6 to <12 years, with obesity (BMI ≥95th percentile on CDC's gender and age-specific growth charts).

First line treatment in weight management should always be lifestyle modification through a dietary intervention and increased physical activity. Thus, only children who have tried but failed a dietary weight loss intervention will be included in accordance with the EMA[33] and FDA guidelines. Thereby, these children represent a clinically relevant population, where pharmacotherapy could be considered.

In Main phase of the trial, at least 23 subjects (30% of the 78 randomised subjects) will be either:

- ≤9 years old with Tanner 1 (premature adrenarche permitted)
- ≤9 years old with signs of pubertal development (greater than Tanner 1)
- >9 years of age with Tanner 1 (premature adrenarche permitted)

Of these 23 subjects, a minimum of 15 subjects must be Tanner 1 (premature adrenarche permitted), regardless of age.

Additionally, subjects with Tanner stage 2-5 pubertal development will be enrolled, to reflect the target population and to support trial recruitment.

The inclusion of patients with T2D is accepted, as it is a well-known complication.

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to those in the European Union, to fulfil requirements from EMA/PDCO.

4.3 Benefit-risk assessment

The trial will be conducted in compliance with ICH GCP[34], applicable regulatory requirements and in accordance with the Declaration of Helsinki.[35]

4.3.1 Benefits

Participation in the present trial is restricted to children aged 6 to <12 years (at signing of informed consent), who have obesity and who have a documented history of failing to lose weight with lifestyle modifications. The children will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial. Subjects randomised to active treatment in Main phase and eligible for active treatment in Extension phase 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 and overweight.[36]

It is expected that the children and their parent(s)/legally acceptable representative (LAR) will benefit from participation through close contact with the trial site medical staff and counselling on diet and physical activity by a dietitian or a similarly qualified healthcare professional according to local standards, all of which may result in improved weight management.

4.3.2 Risks and precautions

The section below describes identified and potential risks associated with liraglutide treatment. For classification and further details of the risks, please refer to the current version of the IB[32] or any

updates hereof. The identified/potential risks are based on finding in non-clinical studies, clinical trials and during the post-marketing safety surveillance of post-marketing reports from marketed liraglutide (Victoza® and Saxenda®).

- Gastrointestinal adverse events

  Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical trials with liraglutide were gastrointestinal (GI) AEs. In order to improve gastrointestinal tolerability of liraglutide, a weekly dose-escalation scheme will be used and the trial product dose will be escalated only if the previous dose is tolerated (as judged by the investigator) (Section 6.5 and 8.3).Subjects treated with trial product should be advised of the potential risk of dehydration and take precautions to avoid fluid depletion.

- Hypoglycaemic episodes, mainly in combination with other anti-glycaemic agents

  Overall, the incidence of hypoglycaemia with liraglutide is low. However, a higher incidence and severity was seen in the clinical development programme when liraglutide was combined with other anti-glycaemic agents; therefore, hypoglycaemia, mainly in combination with other anti-glycaemic agents is classified as an important identified risk for all patients. Concomitant treatment with sulfonylurea is not allowed in this study. If insulin treatment is initiated as rescue medication for diabetes in this trial, then titration should be done cautiously under frequent blood glucose monitoring.

- Altered renal function

  During post-marketing surveillance of spontaneous reports from marketed use of liraglutide for T2D (Victoza®), Novo Nordisk A/S identified reports of acute renal failure. These events mainly occurred in relation to dehydration as a result of GI AEs, and the majority were reported in patients with pre-existing renal impairment.

- Allergic reactions

  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. As a precaution, subjects with known or suspected hypersensitivity to liraglutide or related products will not be enrolled in this trial.

- Acute pancreatitis

  Acute pancreatitis has been observed with the use of GLP-1 RA drug class, and there have been a few reported events of pancreatitis in clinical trials with liraglutide in weight management. As a precaution, children with a history of chronic or acute pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued if acute pancreatitis is suspected in accordance with section 9.1.

- Acute gallstone disease

  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 the literature, it is well-known that obesity carries an increased risk of

cholelithiasis and that an association between rapid and or marked weight loss and the development of cholelithiasis is present[59-62]. As a precaution, if cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.

- Other risks

  Patients treated with liraglutide may also experience dehydration, insomnia, dizziness, dysgeusia, tachycardia, urticaria, injection site reactions, asthenia, fatigue, malaise, headache, cutaneous amyloidosis and increased pancreatic enzymes (lipase and amylase).

- Hyperglycaemia due to insulin discontinuation (for subjects with T2D)

  Hyperglycaemia is considered an important potential risk in patients with T2D based on post-marketing experience with liraglutide 1.8 mg used for T2D indication (Victoza®).

- Medullary thyroid cancer (MTC) (based on non-clinical data)

  C-cell tumours induced in mice and rats following dosing of liraglutide are believed to be caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive. The relevance for humans is likely to be low. Data from the intensive monitoring of calcitonin (a biomarker for MTC) in plasma in the liraglutide clinical development programme do not support a liraglutide effect on calcitonin in humans. As a precaution, exclusion and discontinuation criteria related to medical history of multiple endocrine neoplasia type 2 (MEN2) or MTC and elevated plasma levels of calcitonin have been implemented in the trial.

- Neoplasms (including melanoma)

  Patients with obesity or overweight 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. A limited number of reports in the weight management programme identified a numerical imbalance in events of malignant melanoma, breast neoplasms in females and colorectal adenomas in males. Neoplasms are classified as an important potential risk for liraglutide in weight management.

- Pancreatic cancer

  There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by EMA. As a precaution, children with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.

- Growth and pubertal development

  In non-clinical studies, dosing liraglutide from post-natal day 21 to 91 in juvenile rats caused a dose-dependent delay in sexual maturation rate that was most pronounced in females. A delay in sexual maturation is known to occur in humans under caloric restriction/increased energy expenditure.[37] In the paediatric clinical trials investigating liraglutide 1.8 mg and 3.0 mg, no clinically relevant changes or differences between groups

were seen on pubertal progression (Tanner staging), height/growth related parameters (height SDS, height velocity and height velocity SDS) and bone age.[30, 31] Pubertal and growth- related- hormonal levels, biochemical parameters of bone metabolism and radiological assessment of bone age, as well as growth and pubertal development will be monitored in the present trial.

- Risk related to COVID-19

  Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with liraglutide. More detailed information about the known risks for liraglutide may be found in the investigator's brochure (IB)[32] or Summary of Product Characteristics[39].

4.3.3 Conclusion on benefit-risk profile

Necessary precautions have been implemented in the design and planned conduct of the trial in order to mitigate the risks and inconveniences of participation in the trial. The safety profile for liraglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of liraglutide 3.0 mg once-daily in children with obesity with the potential exception of any unforeseen effects on growth and pubertal development. An external independent Data Monitoring Committee (DMC) will be established and will perform review of unblinded safety data at regular intervals throughout the Main phase, and the open-label treatment period, see Appendix 3. The results of the adult and adolescent trials indicate that liraglutide will provide a clinically meaningful weight loss.

In conclusion, the potential risk to the subjects in this trial is considered to be low and to be outweighed by the anticipated benefits of liraglutide on weight loss and cardiometabolic parameters. Additionally, all subjects will potentially benefit from the diet and physical activity counselling which will be provided throughout the Main phase and until the end of the 2-week off-drug follow-up period of the Extension phase.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of liraglutide 3.0 mg (Saxenda®) may be found in the current version of the IB[32] and any updates hereof.

5 Objectives, endpoints and estimands

5.1 Primary, secondary and exploratory objectives

Main Phase

Primary objective

To compare the effect of liraglutide 3.0 mg s.c. once daily versus placebo on weight management in children aged 6 to <12 years with obesity

Secondary objectives

To compare the effect of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity on:

- Cardiovascular risk factors
- Glucose metabolism

To evaluate the safety and tolerability of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity

Extension phase

Exploratory objectives:

To investigate the effect and safety of liraglutide 3.0 mg and lifestyle intervention in:

- Subjects randomised to liraglutide treatment in the Main phase who continue liraglutide treatment in the open-label extension, compared to
- Subjects randomised to placebo treatment in the Main phase who initiate liraglutide treatment in the open-label extension.

To evaluate the long-term (2 years after open-label treatment) effect and safety of liraglutide 3.0 mg in:

- Subjects randomised to liraglutide treatment in the Main phase who continue liraglutide treatment in the open-label extension, compared to
- Subjects randomised to placebo treatment in the Main phase who initiate liraglutide treatment in the open-label extension.

5.2 Primary, secondary and exploratory endpoints

5.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Relative change in BMI	From baseline (week 0) to week 56	Percent

5.2.2 Secondary endpoints

5.2.2.1 Confirmatory secondary endpoints

Effect endpoints		
Relative change in body weight	From baseline (week 0) to week 56	Percent
Subjects achieving ≥5% reduction of BMI	From baseline (week 0) to week 56	Yes/no

5.2.2.2 Supportive secondary endpoints

Endpoint title	**Time frame**	**Unit**
Effect endpoints		
Change in body weight	From baseline (week 0) to week 56	kg
Change in BMI standard deviation score (WHO.int)[6]	From baseline (week 0) to week 56	Unitless
Subjects achieving ≥10% reduction of BMI	From baseline (week 0) to week 56	Yes/no
BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) (Appendix 10)	From baseline (week 0) to week 56	Percent point
Change in waist circumference	From baseline (week 0) to week 56	cm
Change in systolic blood pressure	From baseline (week 0) to week 56	mmHg
Change in diastolic blood pressure	From baseline (week 0) to week 56	mmHg
Change in HbA1c	From baseline (week 0) to week 56	Percent point
Safety endpoints		
Treatment emergent adverse events (TEAEs)	From baseline (week 0) to week 82	Number
Treatment emergent serious adverse events (SAEs)	From baseline (week 0) to week 82	Number

5.2.2.3 Exploratory endpoints

Endpoint title	**Time frame**	**Unit**
Effect endpoints		
Change in homeostasis model assessment (HOMA-B)	From baseline (week 0) to week 56	Percent point
Change in HOMA-IR	From baseline (week 0) to week 56	AU
Body weight reduction ≥5% from baseline	From baseline (week 0) to week 56	Yes/no
Low density lipoprotein (LDL) cholesterol	From baseline (week 0) to week 56	mmol/L
High density lipoprotein (HDL) cholesterol	From baseline (week 0) to week 56	mmol/L
Triglycerides	From baseline (week 0) to week 56	mmol/L

Relative change in BMI	From baseline (week 0) to week 140 From baseline (week 0) to week 244	Percent
Relative change in body weight	From baseline (week 0) to week 140 From baseline (week 0) to week 244	Percent
Change in waist circumference	From baseline (week 0) to week 140 From baseline (week 0) to week 244	cm
BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov)	From baseline (week 0) to week 140 From baseline (week 0) to week 244	Percent point
Safety endpoints		
Treatment emergent adverse events (TEAEs)	From baseline (week 0) to week 142 From baseline (week 0) to week 244	Number
Treatment emergent serious adverse events (SAEs)	From baseline (week 0) to week 142 From baseline (week 0) to week 244	Number
Safety endpoints (for children with T2D only)		
Number of treatment emergent hypoglycaemic episodes (Appendix 9)	From baseline (week 0) to week 142 From baseline (week 0) to week 244	Number

Safety assessments

Anti-liraglutide antibodies, bone age, carcinoembryonic antigen (CEA), hormone levels, bone metabolism markers, pubertal status, and height standard deviation score (SDS) will be assessed as depicted in the flowcharts (Sections 2 and 3).

Estimands for the Main phase

Primary estimand

The estimand will quantify the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised subjects regardless of adherence to treatment or initiation of rescue interventions (such as weight management drugs or bariatric surgery) (“effectiveness”/”treatment policy” estimand). The estimand will cover all effect-related objectives.

Secondary estimand

The estimand will quantify the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any rescue intervention (such as weight management drugs or bariatric surgery) (“efficacy”/”hypothetical” estimand). The estimand will cover the primary objective.

6 Trial design

6.1 Overall design

Main Phase

This is a double-blind, randomised, parallel group, placebo-controlled, multi-national clinical trial (see Figure 6-1) comparing liraglutide 3.0 mg s.c. once daily with placebo in children, aged 6 to <12 years, with obesity with or without comorbidities. The Main phase of the trial includes a 2-week screening, 12-week run-in and a 56-week treatment period with an off-drug follow-up period of 26-weeks.

In the Main phase, subjects who have fulfilled the randomisation criteria (see Section 7.3) will be randomised 2:1 to receive liraglutide 3.0 mg s.c. or placebo s.c. once daily. Randomisation will be stratified by gender and Tanner stage (1 [premature adrenarche included] vs 2-3 vs 4-5).

Extension Phase

The Extension phase consists of an open-label treatment period with a 2-week screening, a 56-week treatment period, and a 2-week off-drug follow-up period, followed by a safety, follow-up phase with yearly visits for 2 years.

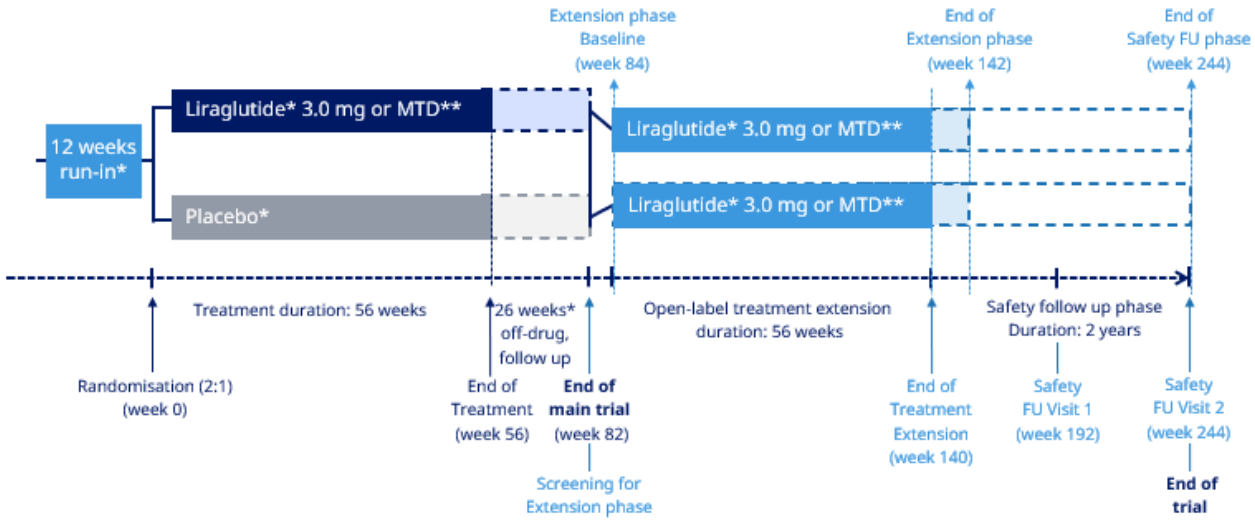
During the safety, follow-up phase subjects will not receive study intervention (i.e. neither intervention with healthy nutrition and physical activity counselling nor active treatment) and will thus be considered off-treatment. After end of the open-label treatment period (week 142), subjects can be treated at the discretion of the investigator (including anti-obesity medication), and participation in other clinical studies is also allowed (Section 8.14)

The updated trial design with the different phases is outlined in Figure 6-1.

All subjects (and parent(s)/LAR) will receive counselling in healthy nutrition and physical activity from run-in (week 12) until end of the 2-week off-drug, follow-up period (week 142), for a total of 154 weeks

Please see the description of the initial dose and dose escalation instructions in Section 8.3 and Table 8-3 for subjects with a body weight <45 kg.

Figure 6-1 A schematic diagram of the trial design



*As an adjunct to a reduced-calorie diet and increased physical activity in children with obesity; Dose initiation from 0.3 mg for children with body weight <45 kg and from 0.6 mg for children with ≥45 kg and will be escalated further.

**MTD, Maximum Tolerated Dose

6.2 Subject and trial completion

Trial period completion for a subject

Trial period completion is defined as when the randomised subject has completed the final scheduled visit ('end of trial' (V44) according to the flowchart). 'Date of trial completion' is the date the subject completed the final scheduled visit.

Treatment period completion for a subject

Main phase

Treatment period completion for the Main phase is defined as when the randomised subject has attended the 'end of treatment' visit (V23) according to the flowchart (Section 2).

Extension phase

Treatment period completion for the open-label treatment period is defined as when the subject has completed the 'end of treatment' visit (V41) according to the Extension phase flowchart (Section 3).

6.3 End of trial definition

The end of the trial is defined as the date of the last visit of the last subject (LPLV) in the trial (V44).

The primary endpoint of the trial is evaluated at week 56 (V23). The primary completion date (PCD) is defined as the date of Visit 23 on which the last subject in the clinical trial has an assessment for the primary endpoint. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed Visit 23.

The CTR will be published with an evaluation of the data from LPLT (V23), and the 26-week off-drug extension follow-up period (V28), of the Main phase.

Following the end of the trial (V44), an extension CTR will be published including data generated during both the open-label treatment period, and the 1- and 2-year safety follow-up visits.

6.4 Scientific rationale for trial design

Main Phase

A double-blinded, randomised, parallel-group, placebo-controlled, multi-national clinical trial design is chosen to minimise bias in the assessment of the effect and safety of liraglutide 3.0 mg once-daily versus placebo.

A 56-week treatment duration is considered sufficient to assess weight loss, safety and tolerability in the paediatric phase 3 weight management development programme in accordance with regulatory guidelines from EMA/PDCO and FDA.

The 26-week duration of the off-study-drug follow-up period is aligned with regulatory recommendations[33] and is considered to be sufficient to assess maintenance of effect and any evidence of rebound, as well as to monitor post-treatment safety.

The trial includes a screening period to assess the subject's eligibility. As lifestyle modification is the recommended first-line treatment for overweight/obesity in the paediatric population, a 12-week run-in period with counselling in diet and physical activity is included in the trial.[8, 9] Only subjects who, after this lifestyle modification attempt, fulfil the definition of obesity and the randomisation criteria will enter the active double-blind trial phase. All subjects will undergo diet and physical activity counselling for weight loss from the beginning of run-in (week 12) and continuing through the entire trial. Subjects will be randomised 2:1 to receive liraglutide 3.0 mg or placebo once daily.

Extension Phase

Lifestyle modification is the recommended first-line treatment of childhood obesity, but childhood obesity is a chronic, progressive and relapsing disease[5-9], thus safe and efficacious treatment with anti-obesity medication is needed for some. Alternating periods of treatment with anti-obesity medication and off-treatment will be similar to a real-world setting, where patients are likely, for a variety of reasons (such as availability of medication through insurance, treatment fatigue, relevant weight loss, etc.), to come on and off of treatment over time. The two-arm trial design in the Extension phase will enable investigation of the effect and safety of initial treatment (Main phase) with liraglutide 3.0 mg and lifestyle intervention versus initial treatment with lifestyle intervention only, followed by (for both arms) 26-weeks of lifestyle intervention only (Main phase) and 56 weeks of open-label treatment with liraglutide 3.0 mg (Extension phase) in children with obesity. This trial design will also provide long-term effect and safety data from the off-treatment, follow up period with yearly safety visits for 2 years after liraglutide 3.0 mg treatment discontinuation.

Blinding to treatment allocation during the Main phase will be maintained until database lock (DBL) of the Main phase. Blinding of the Main phase will therefore not be compromised. All subjects entering the Extension phase, will have been off of study drug for 26 weeks, and will undergo dose escalation.

6.5 Justification for dose

The relatively slow absorption and half-life of approximately 13 hours make liraglutide suitable for once-daily administration, at any time of the day.[38, 39]

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 an adjunct to diet and exercise) was the most efficacious in terms of weight loss and improvements in cardiometabolic and quality of life endpoints. Body weight is an important covariate for exposure, which was confirmed in children aged 7 to <12 years with obesity in the NN8022-4181 pharmacokinetic (PK) trial, where children with a baseline body weight ≥45 kg had exposure within, but at the higher end of the previously-observed range of liraglutide exposure in adults and adolescents. In the NN8022-3967 PK trial in adolescents aged 12 to <18 years with obesity, it was demonstrated that liraglutide could be initiated at a daily dose of 0.6 mg with subsequent weekly dose escalation of 0.6 mg in accordance with the Saxenda® prescribing information to mitigate GI side effects. At present, no data exist on exposure with liraglutide in subjects with a body weight <45 kg. Due to exposure being inversely related to body weight, children with a body weight <45 kg are expected to have a higher exposure compared to children with higher weight. Therefore, a differentiated starting dose will be applied with 0.3 mg and 0.6 mg for children weighing <45 kg and ≥45 kg, respectively, to improve GI tolerability. Based on exposure simulation this approach is expected to result in overlapping peak concentrations in subjects with body weight <45 kg and ≥45 kg during the initial escalation period. Furthermore, the safety profile of liraglutide 3.0 mg has generally been similar irrespective of levels of exposure, once subjects had reached the maintenance dose. The only types of AEs found to be dose-dependent were GI disorders that were generally transient. Therefore, a target maintenance dose of 3.0 mg is considered acceptable for the included children irrespective of their weight at randomisation. An individual maximum tolerated dose is accepted in this trial.

Please refer to Section 8.3 for more details on treatment doses.

7 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

7.1 Inclusion criteria

Subjects are eligible to enter run-in of the Main phase, and to dose escalation of liraglutide 3.0 mg in the open-label treatment period, only if all of the following criteria apply:

1. Informed consent of parent(s) or LAR of subject and child assent, obtained before any trial-related activities for the Main phase as well as for the Extension phase of the trial. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
    a) The parent(s) or LAR of the child must sign and date the Informed Consent Form (according to local requirements)
    b) The child must sign and date the Child Assent Form or provide oral assent (according to local requirements)
2. Male or female, aged 6 to <12 years at the time of signing informed consent for the Main phase
3. Tanner stage 1-5 pubertal development at the time of signing informed consent
4. BMI ≥95th percentile[a]
5. History of failing to lose sufficient weight with lifestyle modification prior to entering the Main phase as judged by the investigator

[a]On gender and age-specific growth charts (CDC.gov) (Appendix 10)

For subjects with T2D at screening the following inclusion criteria apply in addition to criteria 1-5:

6. Subject with T2D treated with either diet and exercise alone or stable treatment with metformin for at least 90 days prior to screening
7. HbA1c ≤10.0% (86 mmol/mol) as measured by central laboratory at screening

7.2 Exclusion criteria

Subjects are excluded from run-in of the Main phase, and from the dose escalation of liraglutide 3.0 mg in the open-label treatment period, if any of the following criteria apply:

Obesity related

1. A self-reported (or by parent(s)/LAR where applicable) change in body weight >5 kg (11 lbs) within 90 days before screening visit (week 12) for the Main phase, irrespective of medical records
2. Treatment with any medication for the indication of obesity within the past 90 days before screening visit (week 12) for the Main phase and screening visit (week 82) for the Extension phase
3. Uncontrolled thyroid disease, in the opinion of the investigator
4. Subjects with secondary causes of obesity (for example hypothalamic, monogenic or endocrine causes)

Mental health

5. History of major depressive disorder within 2 years before screening
6. Diagnosis of other severe psychiatric disorders (e.g., schizophrenia, bipolar disorder)
7. A lifetime history of suicidal attempt
8. Subjects with confirmed diagnosis of bulimia nervosa disorder

General Safety

9. History or presence of pancreatitis (acute or chronic)
10. Calcitonin ≥50 ng/L
11. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
12. Type 1 diabetes
13. Impaired renal function defined as serum-creatinine >UNR for age in children unless renal function is proven normal by further assessments at the discretion of the investigator
14. History of malignant neoplasms within the past 5 years prior to the day of screening
15. Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator
16. Known or suspected abuse of alcohol or recreational drugs
17. Known or suspected hypersensitivity to trial product(s) or related products
18. For Main phase only: Previous participation in this trial. Participation is defined as signed informed consent
19. For Main phase only: Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening*
20. Other subject(s) from the same household participating in any liraglutide trial
21. Female who is of child-bearing potential and not using a highly effective contraceptive method (Appendix 5)
22. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

*Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening

Glycaemia-related

23. Treatment with glucose-lowering agent(s) within 90 days before screening visit (week 12) for the Main phase and screening visit (week 82) for the Extension phase (except for metformin)
24. Treatment with a GLP-1 receptor agonist within 180 days before screening

The criteria will be assessed at the investigator's discretion unless otherwise stated

Subjects not fulfilling the inclusion and/or exclusion criteria at screening visit (week 12) for the Main phase will be considered screen failures, see Section 7.5.

Subjects not fulfilling inclusion criteria or who meet any of the exclusion criteria at the screening visit (week 82) for the Extension phase will not receive active treatment with liraglutide 3.0 mg, but

can continue into the Extension phase and receive lifestyle intervention with diet and physical activity counselling.

7.3 Randomisation criteria for Main phase only

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

1. BMI corresponding to ≥95th percentile[a]
2. Ability to comply with protocol requirements assessed by the investigator based on compliance with procedures and visit schedules in the 12-week run-in period
3. Have been included in accordance with the inclusion and exclusion criteria
4. Have not participated in another clinical trial during the run-in period[b]
5. No history or presence of pancreatitis (acute or chronic)
6. No safety concerns as judged by the investigator

[a]On gender and age-specific growth charts (CDC.gov) (Appendix 10)
[b]Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial product

Subjects not fulfilling the randomisation criteria for the Main phase will be considered run-in failures, see Section 7.6.

Subjects not randomised in the Main phase of the trial will not be able to participate in the Extension phase.

7.4 Lifestyle restrictions

To ensure alignment regarding performance of assessments across subjects and trial sites, the below restrictions apply.

7.4.1 Meals and dietary restrictions

- The subjects must attend several visits fasting according to the flowchart
- Fasting is defined as at least 8 hours before the visit, without food, trial product or liquids, except for water. Where specified in the Flowcharts (V24 and V42), non-T2D subjects only need to fast for 2 hours prior to the visit.
- Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained
- If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting procedures done

7.5 Screen failures

Screen failures during Main phase are defined as subjects who consent to participate in the Main phase of the trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes demography,

screen failure details, eligibility criteria, and any serious adverse event (SAE). A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in the Main phase of the trial may not be rescreened. Re-sampling is not allowed if the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost samples), re-sampling is allowed for the affected parameters.

If a subject is in screening for the Extension phase, and decides not to continue into the open-label treatment period, then the subject will not be a 'screen failure'. The investigator will need to do an 'end of trial' IWRS session for this subject (more details are in Section 9.1).

7.6 Run-in failures

Run-in failures are defined as subjects who fulfilled the in/exclusion criteria and entered run-in but are not eligible for randomisation according to the randomisation criteria.

A screen failure session must be made in the interactive web response system (IWRS).

8 Treatments

8.1 Treatments administered

- Handling of trial product should be done in accordance with the direction for use (DFU).
- All trial products listed in Table 8-1 are considered investigational medicinal products (IMPs).
- Trial product must only be used, if it appears clear and colourless.

Table 8-1 Trial products provided by Novo Nordisk A/S

Trial product name	Dosage form	Route of administration	Dosing instructions	Delivery device
Liraglutide 6.0 mg/mL[a]	Solution for injection	Subcutaneous injection (s.c.)	Once daily	3 mL FlexPen®
Liraglutide placebo[b] (referred to as placebo)				

[a]During Main phase and Extension phase of the trial

[b]During Main phase of the trial

8.2 General injection instructions

- All subjects and subject's parent(s)/LAR must be instructed in handling of the device and the trial product. This should include training in injection site and injection technique. At all subsequent visits, subjects and/or subject's parent(s)/LAR should be retrained at the investigator's discretion.
- Subjects and subject's parent(s)/LAR must be instructed to follow the DFU when handling the pre-filled pen.
- The injections can be administered 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.
- Injection sites should always be rotated within the same region in order to reduce the risk of cutaneous amyloidosis (see section 4.3.2).

8.3 Initial dose and dose escalation instructions

- The first dose of trial product must be injected at the site, post blood sampling, on the day of randomisation and documented in the subject's medical record.
- All subjects should aim at reaching the recommended target dose of 3.0 mg liraglutide once daily or the corresponding volume of placebo. The trial product dose will be escalated only if the current dose is tolerated.
- For children with a body weight ≥45 kg at randomisation, dosing will be initiated with liraglutide/placebo 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until a dose of 3.0 mg liraglutide/placebo or the individual maximum tolerated dose (MTD) is reached (see Figure 6-1).
- For children with a body weight <45 kg at randomisation, dosing will be initiated with liraglutide/placebo 0.3 mg daily for one week and increased to 0.6 mg after the first week,

thereafter the dose is increased in weekly steps of 0.6 mg until a dose of 3.0 mg liraglutide/placebo or the individual MTD is reached

- If a subject has tolerability issues during dose escalation (as judged by the investigator), it is allowed to lower to the previous dose level or to remain on the current dose level for a maximum of 2 weeks. This extended time of one additional week is allowed at each dose level, i.e. the complete dose escalation process may take up to 8 (≥45 kg) or 10 (<45 kg) weeks in total (see example in Table 8-2).
- To mitigate and manage gastrointestinal symptoms the investigator can advise subjects to eat more slowly, eat smaller meals, and stop eating when feeling full.
- After a maximum of 2 weeks on a dose level and after at least one (re-)escalation has been attempted (at the discretion of the investigator), the subject should remain on the current dose level throughout the trial until 'end of treatment', if the individual MTD is reached as judged by the investigator.
- If a subject treated with the individual weight-based starting dose experiences unacceptable intolerance as judged by the investigator, the subject must be discontinued from trial product.
- It is recommended that the investigator consults Novo Nordisk in case of persistent deviation from the planned escalation regimen.

A dose reminder card will be handed out to the subjects at each site visit during the escalation period. This is to remind the subjects of the dose to be taken until next site visit and provide a conversion of the dose to value shown in the dose counter. Once the target dose has been reached, the dose reminder card is only handed out as needed.

Table 8-2 Dose escalation instructions based on tolerability as judged by the investigator

Tolerability	Action	Additional instructions	Dose escalation period limit
Dose level is tolerated by subject	Escalate to next dose level		The dose escalation process may take up to 8-10 weeks in total
If the subject has tolerability issues	Remain on dose level for a maximum of 2 weeks	The subject must still follow the visit schedule (V9-V12 and V29-V33). For the remaining dose escalation step(s) after V12 (Main phase) and after V33 (open-label treatment period), it is at the discretion of the investigator to be in frequent contact (e.g., by phone/video call) with the subject to ensure correct dose settings. Contacts regarding dose escalation must be documented in the subject's medical record.	
	Remain on dose level if the individual MTD has been reached (after ≥ 1 unsuccessful attempt to (re-) escalate)		

	Reduce to previously tolerated dose level	In cases where a subject experiences tolerability issues at the current dose, the trial product dose may be lowered to previously tolerated dose as needed (section 8.8.1). The reason for lowering the trial product dose must be documented in the subject's medical record.	

8.4 Dose modification for the open-label treatment period phase

Safety and tolerability should be evaluated broadly throughout the trial (e.g., growth and development, including mental health) and dose modification should be considered accordingly, preferably by lowering to a previous dose level. Likewise, if a subject with a BMI below the 85th percentile on CDC's growth charts continues to lose weight, and there is a health concern, the investigator should consider reducing the dose of the trial product. The investigator may contact Novo Nordisk for guidance.

Table 8-3 Dose escalation and maintenance of liraglutide/placebo

Relevant dose in mg	Value shown in dose counter of FlexPen®
0.3 mg (only for children with body weight <45 kg)	5
0.6 mg	10
1.2 mg	20
1.8 mg	30
2.4 mg	40
3.0 mg	50

8.5 Auxiliary supplies

See Table 8-4 for auxiliary supplies to be provided in accordance with the trial materials manual (TMM):

Table 8-4 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for the device with a maximum needle length of 6 mm. Only needles provided and/or approved by Novo Nordisk must be used for administration of trial product.
Direction for use (DFU)	Direction for use for the FlexPen® Not included in the dispensing unit and to be handed out separately.
Blood glucose (BG) meters	For subjects with T2D at screening or if diagnosed during the trial: BG meter will be provided by Novo Nordisk.

8.6 Medical devices

Information about the FlexPen® may be found in the IB[32] and any updates hereof.

Information about the use of liraglutide 6.0 mg/mL, 3.0 mL with FlexPen® and liraglutide placebo, 3.0 mL with FlexPen® can be found in the DFU.

Training in the FlexPen®

The investigator must document that DFU are given to the subjects and their parent(s)/LAR verbally and in writing at the first dispensing visit. Training must be repeated during the trial at regular intervals in order to ensure correct use of the medical device.

Training is the responsibility of the investigator or a delegate.

8.7 Diet and physical activity counselling

All subjects (and parent(s)/LAR, as applicable) must receive individualised counselling in healthy nutrition with the goal of obtaining a weight loss. The focus of the counselling in healthy nutrition must be to educate on healthier food choices.

The counselling should also contain instructions and advice on physical activity. The focus of the counselling in physical activity is to encourage and reinforce a goal of 60 minutes of moderate to high intensity physical activity per day.[40]

The counselling is initiated at run-in (V2, week -12) and continues through the main phase (V28, week 82), and for participating subjects, through the open-label treatment period (V42, week 142). The counselling must be done by a certified dietitian or a similarly qualified health care professional according to local standard. The counselling can be done independently of the site visits within the visit window and flexibly as site visits, phone or video calls.

Activity trackers can be provided by Novo Nordisk in order to support the physical activity of the subjects and any data obtained from the devices will not be collected by Novo Nordisk. The use of these trackers is optional.

If the participant's BMI falls below the 85th percentile, and there is a health concern related to continued weight loss, the subject should be counselled on a eucaloric diet, at the discretion of the investigator.

8.8 Dose modification

8.8.1 Tolerability at maximum tolerated dose

In case a subject experiences tolerability issues at the target dose (3.0 mg once daily) or at the individual MTD during the trial, as judged by the investigator, the trial product dose may be lowered to the next, lower dose level as needed, shown in Table 8-5.

Please refer to Section 8.3 and 8.4 for details on Dose modifications.

Table 8-5 Dose lowering steps

Children with a body weight ≥45 kg	Children with a body weight <45 kg
From 3.0 mg to 2.4 mg	From 3.0 mg to 2.4 mg

From 2.4 mg to 1.8 mg	From 2.4 mg to 1.8 mg
From 1.8 mg to 1.2 mg	From 1.8 mg to 1.2 mg
From 1.2 mg to 0.6 mg	From 1.2 mg to 0.6 mg
	From 0.6 mg to 0.3 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 can return to MTD again.

If doses are completely missed, refer to Section 8.12.1 for actions.

8.9 Method of treatment assignment

Main phase

All subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarised in the Main phase flowchart.

Randomisation will be stratified according to the following Tanner stages of pubertal development:

- Tanner stage 1 pre-pubertal (premature adrenarche permitted)
- Tanner stage 2-3
- Tanner stage 4-5

Extension phase

All subjects eligible for treatment with liraglutide 3.0 mg s.c during the open-label treatment period will be dispensed liraglutide 3.0 mg at the trial visits summarised in the Extension phase flowchart.

8.10 Blinding

Main Phase

The Main phase of the trial is double-blinded. The active drug and placebo drug are visually identical for the following trial products:

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

The IWRS is used for blind-breaking. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation.

Whenever the blind is broken, the person breaking the blind must print the "code break confirmation" notification generated by the IWRS, record the reason and sign and date the document.

Database lock (DBL) will occur after the last subject has completed the Main phase of the trial. When the blind is broken at DBL of the Main phase (V28, week 82), 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 blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

Extension Phase

The open-label treatment period is un-blinded. All subjects eligible for treatment with liraglutide 3.0 mg will receive liraglutide 6.0 mg/mL, 3.0 mL, s.c. injection with FlexPen®.

8.11 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product.

Trial Product storage, in-use conditions and in-use time will be available on the label and in the TMM.

- 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 screening and randomisation
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. 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 or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject and their parent(s)/LAR in what to return at the next visit.
- Drug accountability should be performed on a pen level and must be documented in the IWRS according to the flowchart.
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.

- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- Destruction of trial products must be documented in the IWRS.
- All returned, un-used, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the trial site.

8.12 Treatment compliance

Throughout the trial, the investigator will remind the subjects and their parent(s)/LAR to follow the trial procedures and requirements to ensure subject compliance.

When subjects with support from their parent(s)/LAR self-administer trial product(s) at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, apart from occasionally missed doses, the site must enter into a dialogue with the subjects and their parent(s)/LAR, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. If ≥3 consecutive doses have been missed, this should be described in the subject's medical records and entered into the CRF.

Trial product compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned trial product, visual inspection of pens
- Review of PK diaries (see Section 10.10.1)
- Questioning of subjects

Treatment start and stop dates will be recorded in the CRF.

8.12.1 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 must be conducted in accordance with the flowchart and the laboratory manual.

8.12.2 Missed doses

In case of a missed dose:

- 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 3 or more consecutive days have elapsed since the last dose:

- The subject should be encouraged to recommence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria, see Section 9.1.

- The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical expert.
- The subject should be encouraged to contact the site in case of missed doses, to ensure guidance to recommence the treatment and recording of the missed doses.

8.13 Concomitant medication

Any medication or vaccine (including over-the-counter or prescription medicines), other than the trial product that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates
- Dose and route of administration only for the weight-related co-morbidities (diabetes, hypertension and dyslipidaemia)

During the trial, subjects should not initiate any weight-lowering medication which is not part of the trial procedures. If such treatment is initiated, the subject should be instructed to stop the weight-lowering medication.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 10.2.

8.14 Treatment after the end of the trial

After the open-label treatment period (week 142), and the end of the trial (week 244), the subject should be treated at the discretion of the investigator in accordance with standard of care.

9 Discontinuation of trial treatment and subject discontinuation/withdrawal

Treatment of a subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have the subjects, who discontinue trial product continue in the trial according to schedule. Subjects and their parent(s)/LAR must be educated about the continued scientific importance of their data, even if they discontinue trial product. Only subjects who withdraw consent will be considered as withdrawn from the trial.

9.1 Discontinuation of trial treatment

Discontinuation of treatment can be decided either by the investigator, the subject and/or their parent(s)/LAR.

Main phase

- Subjects who discontinue trial product should continue with the scheduled visits and assessments in the Main phase flowchart to ensure continued counselling and data collection
- If the subject and/or their parent(s)/LAR do not wish to attend the scheduled clinic visits, efforts should be made to have the visits converted to phone or video calls. However, all efforts should be made to have the subject attend at least the Main phase 'end of treatment' visit (V23, week 56), and the 'end of main phase' visit (V28, week 82).
- If the subject, and/or their parent(s)/LAR, refuse to attend the Main phase 'end of treatment' visit and/or 'end of trial' visit as described above, information about the attempts to follow-up with the subject must be documented in the subject's medical record.

The subject must be discontinued from trial product, if any of the following applies:

1. Safety concern as judged by the investigator
2. Calcitonin ≥50 ng/L (Appendix 11)
3. Suspicion of acute pancreatitis[a]
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product[b]
5. Diagnosis of type 1 diabetes

For female subjects only:

6. Pregnancy

[a]If acute pancreatitis is suspected, appropriate actions should be initiated, including local measurement of amylase and lipase and local imaging assessment (see Appendix 4 for reporting).
Subjects meeting discontinuation criterion no. 3 are allowed to resume the trial product, if the Atlanta criteria[41] are not fulfilled and thus, the suspicion of pancreatitis is not confirmed. The trial product may be restarted for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

[b]Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial product.

Subjects meeting discontinuation of trial product criterion no. 1 and 6 are allowed to resume the trial product, if the criteria are no longer met (see Section 9.1.1).

The primary reason for discontinuation of trial product must be specified in the source data at the time of discontinuation. A Main phase treatment discontinuation session must be made in the IWRS. If subject is not allowed to resume trial product, then the reason for discontinuation will be recorded in the Main phase 'end of treatment' form in the CRF, and final drug accountability must be performed.

Extension phase

- If the subject discontinues trial product treatment after V28A (week 82), but prior to V41 (week 140), effort should be made to have the subject attend a clinic visit, no sooner than 2 weeks after discontinuing treatment. At this premature discontinuation visit, final PK and antibody samples will be taken.
- Subjects who discontinue trial product should continue with the scheduled visits and assessments in the Extension phase flowchart to ensure continued counselling and data collection, **however no additional PK and antibody samples should be taken unless the subject resumes trial product treatment** (see Section 9.1.1)
- If the subject and/or their parent(s)/LAR do not wish to attend the scheduled clinic visits, efforts should be made to have the visits converted to phone or video calls.
- Effort should be made to have the subject attend the Extension phase 'end of treatment' visit (V41, week 140), and the safety-follow-up visits (V43 at week 192, and V44 and week 244).
- If the subject, and/or their parent(s)/LAR, refuse to attend V41, V42, V43 and/or V44, information about the attempts to follow-up with the subject should be documented in the subject's medical record.

The subject must be discontinued from trial product, but may continue in the open-label treatment period only on lifestyle management, if any of the following applies:

1. Safety concern as judged by the investigator
2. Calcitonin ≥50 ng/L (Appendix 11)
3. Suspicion of acute pancreatitis[a]
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product[b]
5. Diagnosis of type 1 diabetes

For female subjects only:

6. Pregnancy

[a]If acute pancreatitis is suspected, appropriate actions should be initiated, including local measurement of amylase and lipase and local imaging assessment (see Appendix 4 for reporting). Subjects meeting discontinuation criterion no. 3 are allowed to resume the trial product, if the Atlanta criteria[41] are not fulfilled and thus, the suspicion of pancreatitis is not confirmed. The trial product may be restarted for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

[b]Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial product.

Subjects meeting discontinuation of trial product criterion no. 1 and 6 are allowed to resume the trial product, if the criteria are no longer met (see Section 9.1.1).

The primary reason for discontinuation of trial product must be specified in the source data at the time of discontinuation. An Extension phase treatment discontinuation session must be made in the IWRS. If the subject is not allowed to resume trial product, then the reason for discontinuation will be recorded in the Extension phase 'end of treatment' form in the CRF, and final drug accountability must be performed.

9.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product and is allowed to resume, the subject should follow the guide for missed doses (Section 8.12.1).

If a treatment discontinuation session previously has been made in IWRS to indicate discontinuation of trial product, a new treatment session must be made in the IWRS to resume trial product.

9.2 Withdrawal from the trial

A subject may withdraw consent at any time at his/her own request, or at the request of the subject's parent(s) or the subject's LAR. Only subjects who withdraw consent will be considered as withdrawn from the trial.

If a subject withdraws consent during the trial, the investigator must ask the subject/subject's parent(s)/LAR if he/she is willing to have an assessment performed, according to the relevant 'end of treatment' visit: Main phase (V23, week 56), Extension phase (V41, week 140). Main phase 'end of treatment' **or** the Extension phase 'end of treatment' forms must be completed by the investigator. Additionally, the 'end of trial' form must be completed by the investigator. As a minimum, height and weight for BMI determination and safety assessments should be performed if the subject agrees. See the flowcharts and Appendix 2 for data to be collected. Final drug accountability must be performed even if the subject is not able to come to the trial site. Either a Main phase, or Extension phase, treatment discontinuation session must be made in the IWRS.

If a subject withdraws from the trial, he/she or the subject's parent(s)/LAR may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

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

9.2.1 Replacement of subjects

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

9.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject and/or their parent(s)/LAR fails to return to the trial site for a required visit:

- The site must attempt to contact the subject and/or their parent(s)/LAR and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject and/or their parent(s)/LAR (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject and/or their parent(s)/LAR continue to be unreachable until 'last subject last visit' at site, he/she will be considered to have withdrawn from the trial with a primary reason of ‘lost to follow-up'.

10 Trial assessments and procedures

- Trial procedures and their timing (including visit number and weeks) are summarised in the flowcharts for the Main phase and the Extension phase (Sections 2 and 3)
- Informed consent and informed assent (per local requirements) must be obtained before any trial related activity, see Appendix 3 and Appendix 7.
- Screening activities are registered in IWRS which will trigger the CRF form.
- All screening evaluations must be completed for the Main phase of the trial and for the Extension phase and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects or their parent(s)/LAR will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- To ensure flexibility for the subjects, phone visits may be replaced by site visits or video calls.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments. The suggested order of the assessments:

  1. ECG and vital signs
  2. Blood samples
  3. Other assessments

- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, ECG and diary recordings.
- Subjects and/or their parent(s)/LAR must receive training in how to collect dosing information prior to PK sampling in a designated diary (during the Main phase and Extension phase).
- Only the subject and/or their parent(s)/LAR can make entries and corrections in the diaries, unless the section is specified for site staff.
- Review of completed diaries, ECG, laboratory reports etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- Main phase: Approximately 115.5 mL of blood will be collected from subjects without T2D and approximately 128.5 mL of blood will be collected from subjects with T2D during the main phase of the trial
- Extension phase:
  - 1-year open-label treatment period: Approximately, 55.5 mL of blood will be collected from subjects without T2D and approximately 88 mL of blood will be collected from subjects with T2D during this period

- 1- and 2-year safety follow-up visits: Approximately 27 mL of blood will be collected from subjects without T2D and approximately 40 mL of blood will be collected from subjects with T2D

- Blood collection should be performed in accordance with the guidelines in EU Directive 2001/20/EC[42] unless stricter local requirements apply. According to EU Directive 2001/20/EC it is recommended not to draw more than 3% of the total blood volume in a 4-week period and 1% of the total blood volume at any single occasion. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg body weight. If a subject weighs less than the 1% threshold (mL/kg) of total blood volume to be collected at a given visit, a prioritisation of blood samples will be made on a case-by-case basis.
- For subjects who have consented to have biosamples for future analysis collected, an additional 1 mL of blood will be collected at V8 and at V23 followed by 2.5 mL for genetic analysis at V28.
- Repeat samples may be taken for technical issues and additional samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.
  According to the flowcharts, the investigator will periodically evaluate the glycaemic status of subjects without T2D. This evaluation will be based on all available relevant information e.g. medical records, concomitant medication, BG parameters (HbA1c, fasting plasma glucose (FPG)) and AEs. The subject's glycaemic status will be categorised as normo-glycaemia, prediabetes or diagnosed with T2D according to the American Diabetes Association's (ADA) definitions.[43]

10.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowcharts.
Additional assessments must be performed for subjects with T2D at screening or if diagnosed during the trial, according to the flowcharts and Appendix 8.

10.1.1 Body measurements

Body measurements should be taken as instructed in Table 10-1, and preferably be measured by the investigator or the same qualified delegate throughout the duration of the trial. This is especially important for the measurements of body weight and height at 'randomisation' (V8), Main phase 'end of treatment' (V23), 'end of Main phase' (V28), at the end of the open-label treatment period (V41), and at the 1- and 2-year off-treatment, safety follow-up visits (V43 and V44).

Table 10-1 Body measurements and instructions

Measurement	Measurement instructions	Equipment and equipment instructions	Unit
Body weight	Measured at all site visits without shoes, with an empty bladder and only wearing light clothing	Digital scale with graduation increments of 0.1 kg/0.1 lb The same scale should be used throughout the trial The scale must be calibrated yearly as a minimum	Kilograms or pounds (one decimal)

Height	Measured without shoes as two individual measurements performed by a single observer using identical technique The subject should be repositioned between the two measurements	Harpenden or another wall mounted stadiometer with graduated increments to the nearest 0.1 cm (1 mm). The same stadiometer should be used throughout the trial	Centimetres (one decimal)
Waist circumference (defined as abdominal circumference located midway between the lower rib margin and the iliac crest)	Measures must be obtained in standing position with a non-stretchable measuring tape 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	Non-stretchable measuring tape The same measuring tape should be used throughout the trial The measuring tape will be provided by Novo Nordisk to ensure standardisation	Nearest 0.5 centimetre

BMI will be calculated in the CRF every time the weight and height are measured.

10.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4, along with a description of AEs requiring additional data collection.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

10.2.1 Time period and frequency for collecting AE and SAE information

All AEs must be collected from the first trial-related activity after obtaining informed consent and assent and until the end of the open-label treatment period (V42) at the time points specified in both the Main phase and Extension phase flowcharts.

At both the 1- and 2-year off-treatment follow-up visits (V43 and V44, respectively; Figure 6-1 and Section 3), only those AEs and SAEs which are assessed to be causally related to trial product (liraglutide) by the investigator must be collected. In addition, any events that fulfil the criteria for AEs requiring additional data collection (Table 10-2) must also be collected and reported regardless of causality.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 4. All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

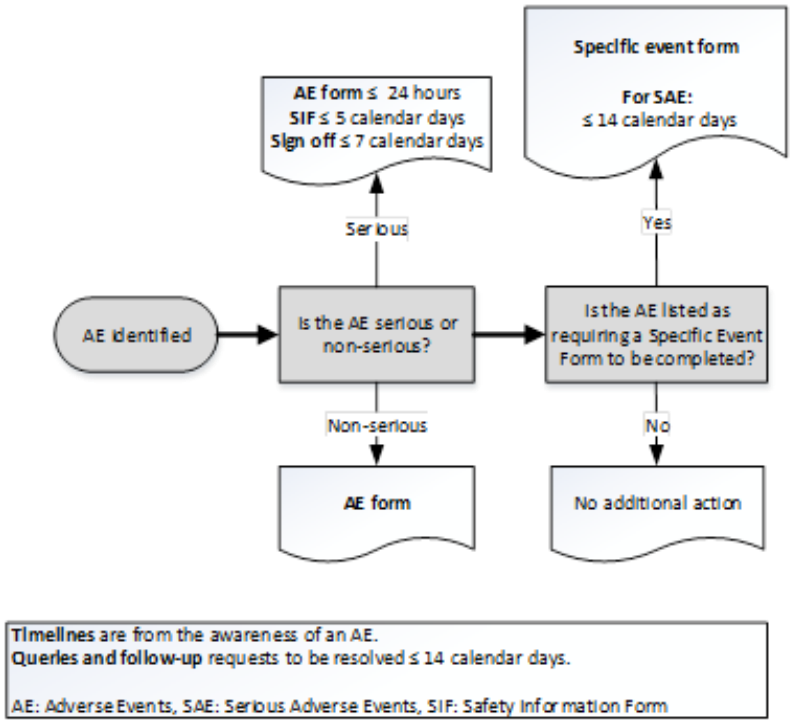
The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Timelines for reporting of AEs are listed in Figure 10-1.

Some AEs require additional data collection via a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant specific events are listed in Table 10-2 and the reporting timelines in Figure 10-1.

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines for adverse events

Main phase and Extension phase (until Visit 42)



Extension phase (visit 43 and 44)

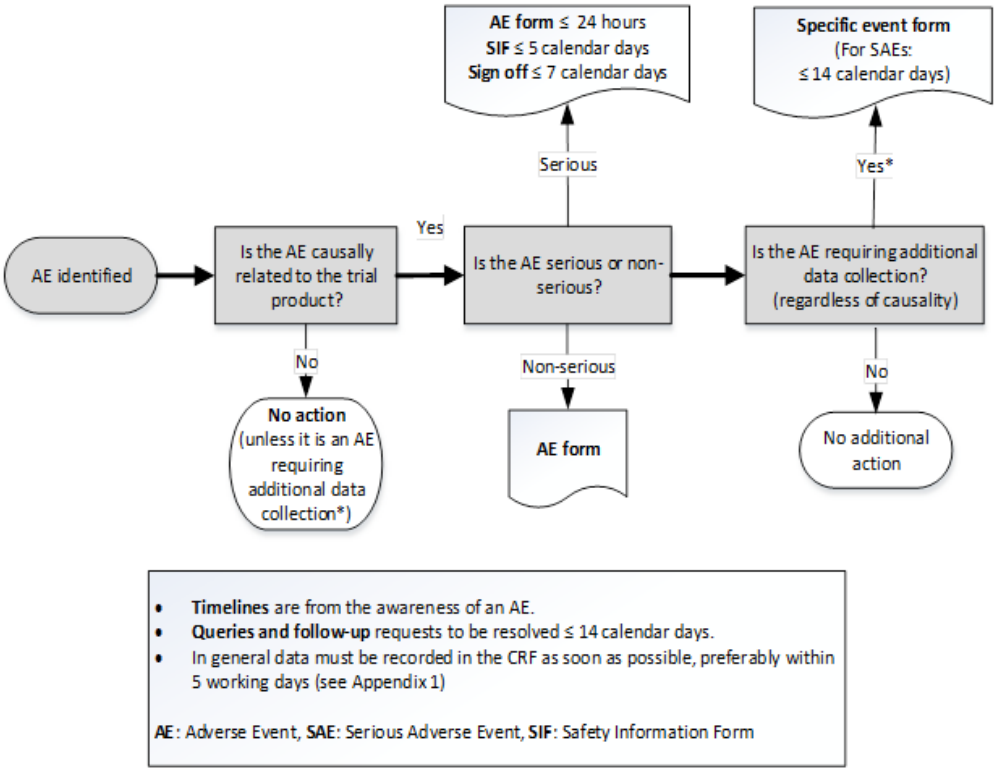


Table 10-2 AEs requiring additional data collection (via specific event form)

Event type
Acute gallbladder disease
Acute pancreatitis
Malignant neoplasm
Hepatic events
Medication error
Misuse and abuse

A detailed description of the events mentioned in the above table can be found in Appendix 4

10.2.2 Method of detecting AEs and SAEs

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

10.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the subject is lost to follow-up as described in Section 9.3. Further information on follow-up and final outcome of events is given in Appendix 4.

10.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs), from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.2.5 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in Section 10.2.1.

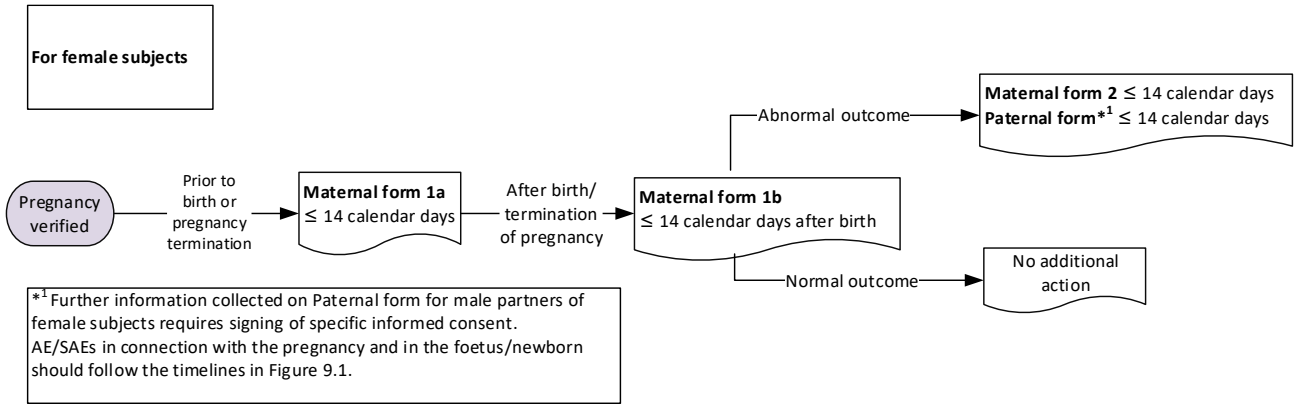
10.2.6 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected after first exposure to trial product and until the end of trial.

If a female subject becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Figure 10-2 and Appendix 5.

Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy



10.2.7 Medical device incidents (including malfunctions)

Section not applicable for this trial. Refer to technical complaints in Section 10.2.8.

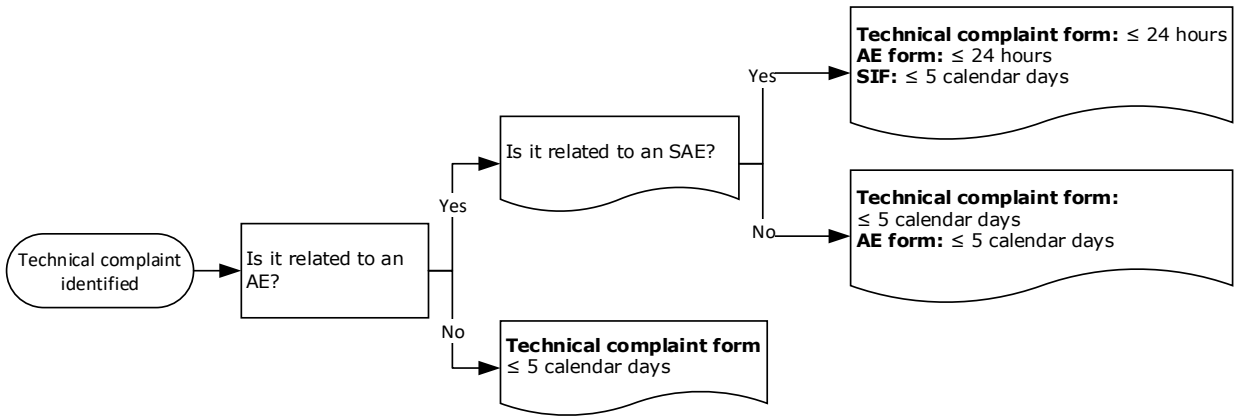
10.2.8 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.

The definitions and reporting process for technical complaints can be found in Appendix 6.

Timelines for reporting technical complaints are listed in Figure 10-3.

Figure 10-3 Decision tree for determining the forms to complete with associated timelines for technical complaints



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

10.3 Treatment of overdose

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

In the event of overdose, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms. The subject should be observed for clinical signs of dehydration and blood glucose should be monitored.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse (Appendix 4). For reporting timelines see Section 10.2.1 and Figure 10-1.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE.

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.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

For more information on overdose, also consult the current version of the IB[32] and any updates hereof.

10.4 Safety assessments

A **concomitant illness** is any illness (including COVID-19) that is present at the start of the trial (i.e., at the first visit) or found as a result of a screening procedure.

Medical history is a medical event that the subject experienced prior to the timepoint from which AEs are collected. Any information of weight history, co-morbidities and history of psychiatric disorder must be recorded, otherwise only relevant and significant medical history (including COVID-19) should be recorded as judged by the investigator.

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/Concomitant Illness form.

Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from screening (V1) must be reported as an AE (see Section 10.2).

10.4.1 Mental health evaluation

The mental health evaluation will be made by the investigator at each visit to the clinic after screening.

Thus, the investigator must ask the subject as well as the subject's parent(s)/LAR whether the subject has experienced any clinically relevant mood changes since the last clinic visit.

Further, the investigator must ask the subject's parent(s)/LAR whether the subject has experienced any clinically relevant changes in behaviour or changes in school performance since the clinic visit.

The outcome of these evaluations must be thoroughly documented in the subject's medical records and recorded in the CRF.

If any clinically relevant changes in mood, behaviour and/or school performance reveal a concern for the subject's mental well-being, as judged by the investigator, the C-SSRS* (Columbia Suicidality Severity Rating Scale) parental card version[44] can be administered, as per investigator's discretion and/or the child may be referred to a mental health professional (MHP).

When referred to a MHP, the investigator should explain to the subject and the subject's parent(s)/LAR, why the referral and psychiatric evaluation by a MHP is needed. If the subject's parent(s)/LAR refuses the referral, it should be documented in the subject's medical records and assessed if it is safe for the subject to continue on trial product.

If referral is not deemed relevant this and the reason why, must be documented in the subject's medical records.

If the subject is diagnosed with a psychiatric disorder which can be adequately treated with psychotherapy and/or pharmacotherapeutic treatment, then the subject, at the discretion of the investigator (and in agreement with the MHP), may continue in the trial on trial product.

For any clinically relevant changes in mood, behaviour and/or school performance, it should be evaluated whether the criteria for adverse event reporting is fulfilled upon investigator's discretion.

*The C-SSRS parental card version is a short questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire can be used at the investigator's discretion as an interview tool. The questionnaire will be available in a linguistically validated translated version. When answering the questions on the C-SSRS parental card version after screening (V1), the subject and the subject's parent(s)/LAR should be instructed to answer the questions having the period since the last clinic visit in mind. If the child answers 'yes' to any question on the questionnaire the child must be evaluated as soon as possible by a MHP.

10.4.2 Physical examinations

- A physical examination will include assessments of the general appearance, thyroid gland, abdomen, central and peripheral nervous systems as well as the cardiovascular and respiratory systems.
- Body measurements (Section 10.1.1) will also be measured and recorded as specified in the flowchart.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

10.4.3 Vital signs

- The method for measuring systolic and diastolic blood pressure and pulse needs to follow the standard clinical practice at site, but as a minimum meet the following:

  Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones).
  Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

10.4.4 Pubertal status

- Pubertal development must be assessed by the Tanner staging in accordance with stages 1-5[45]. The assessments must be conducted by site staff trained in pubertal assessments, and preferably by the same qualified staff member at each visit. For males, the assessment of testicular volume by orchidometer 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 CRF 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 10.2 and Appendix 4.
- Tanner staging is not required once the subject reaches the Tanner stage 5, as judged by the investigator.

10.4.5 Bone age assessment (x-ray)

- An x-ray of left hand and wrist will be performed at randomisation (V8), at the Main phase 'end of treatment' (V23), and at the end of the open-label treatment period (week 140) for all subjects to evaluate their bone age. An x-ray will not be performed at V23 for subjects for whom the bone age evaluation at randomisation indicates that the epiphyses are fused, or at V41 if epiphyses are fused at V23 (or at randomisation).
- The x-ray imaging data will be submitted to a supplier selected for central medical imaging services and will be analysed in a blinded manner 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.

10.4.6 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the flowchart using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals. The investigator should make an overall interpretation of the ECG.

10.4.7 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the flowchart in Section 2.

10.4.8 Immunogenicity assessments

- 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 Appendix 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. All samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day.

- Samples are analysed by the special laboratory for anti-liraglutide antibody formation including cross reactivity to endogenous GLP-1.
- Anti-liraglutide antibody positive follow-up samples will be analysed for in vitro neutralising effect towards liraglutide. In addition, follow-up samples which are also positive for cross-reactivity to endogenous GLP-1 will be analysed for in vitro neutralising effect towards endogenous GLP-1. The results of the analysis will only be disclosed after completion of the CTR if required by local regulation.

10.4.9 Severe hypersensitivity

In case of suspicion of an acute severe systemic hypersensitivity reaction to the trial product, the subject must for safety concerns be discontinued from trial product but should remain in the trial.

In the event of an acute severe systemic hypersensitivity reaction possibly or probably related to trial product, the following sample should be taken 3-4 hours after the reaction, if possible:

- Tryptase

Furthermore, a follow-up blood sample should be taken as soon as possible and no later than 1-2 weeks after the reaction. A second sample should be taken 3-4 weeks after the reaction.

For both samples, the following assessments will be performed:

- Anti-liraglutide IgE antibodies
- Anti-liraglutide antibodies
- Tryptase

If deemed relevant by Novo Nordisk other relevant exploratory tests may be performed, e.g. basophil activation, complement tests, prick tests and/or intra-dermal tests.

The analyses will be performed by a laboratory assigned by Novo Nordisk.

10.5 Pharmacokinetics

- Blood samples for measuring plasma concentration of liraglutide will be drawn for all randomised subjects on visits specified in Appendix 2
- Subject must be instructed to withhold their trial product dose in the morning of the clinic visit until blood sampling has been performed
- Doses taken prior to the PK sample must be recorded in the CRF
- The exact timing of obtaining the PK sample must be recorded on the laboratory form
- The subjects and/or their parent(s)/LAR must be instructed to complete the PK dosing diary for liraglutide PK assessment

Samples will be used to evaluate the PK of liraglutide and may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial.

See details regarding PK samples in relation to discontinuation in Section 9.1.

Subject confidentiality will be maintained.

10.6 Pharmacodynamics

Not applicable for this trial.

10.7 Genetics

Not applicable for this trial.

10.8 Biomarkers

Collection of samples for biomarker research is part of this trial to support the safety objectives. The following samples are required and will be collected from all subjects in the trial as specified in the laboratory manual and Appendix 2.

Biomarkers:

- Carcinoembryonic antigen serum
- Serum insulin-like growth factor 1

10.9 Biosamples for future analysis

Collection of biosamples for future analysis (stored in a biobank) is a component of this trial. The samples will allow future analyses of biomarkers, both genetic and circulating when new knowledge or improved measurement technologies may have become available. Refer to Appendix 7 for further details.

Participation is optional and the subject's parent(s)/LAR will be asked to sign a separate informed consent in order to let their child participate in the biobank component. If the parent(s)/LAR do not wish to let their child participate in the biobank component, their child may still participate in the trial. For the biobank, blood samples will be collected according to Appendix 2 and stored for future use.

Genetic analyses may include analysis of candidate genes or genetic markers throughout the genome with the purpose of understanding and predicting response to liraglutide as well as to understand obesity or other related diseases. For subjects who have consented to give samples for genetic analysis, an additional 2.5 mL blood sample will be collected at the end of the Main phase (V28).

Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entity with the purpose of understanding and predicting response to liraglutide as well as understanding obesity or other related diseases.

These samples need to be frozen and should be sent in batches to the central laboratory. Results will not be part of the CTR. The biobank samples may be stored up to 15 years after end of trial at a central storage facility (see Appendix 7).

10.10 Subject diaries

Subjects will be provided with a paper diary to be completed at home. Only the subject and/or their parent(s)/LAR can make entries and corrections in the diaries, unless the section is specified for site staff. Subjects and their parent(s)/LAR will be instructed by the investigator on when and how to

complete the diary. It is important to explain to the subjects and/or their parent(s)/LAR 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 and/or the parent(s)/LAR 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 diaries must be transcribed into the CRF.

10.10.1 PK diary

Trial product dosing diary pages should be completed by the subjects and/or their parent(s)/LAR before a visit including a blood sampling for liraglutide plasma concentration (see Section 10.5).

The last three doses of trial product should be recorded in the diary before a visit with PK sampling stating:

1. Dose
2. Date
3. Exact time for dosing

10.10.2 Menstrual period diary

For female subjects of childbearing potential, the following should be recorded:

- First date of last menstrual period before the site visit of V8 (randomisation), V17, V23 (Main phase 'end of treatment'),V28 ('end of main trial'), V37, and V41 (Extension phase 'end of treatment'). If a subject experiences a first menstrual period during the trial, the subject and/or parent(s)/LAR should be instructed to contact the site for contraception guidance (Appendix 5) and diary initiation.

10.10.3 Diabetes diary

Subjects with T2D at screening or if diagnosed during the trial will be provided with a diabetes diary on self-measured plasma glucose (SMPG) measurements and hypoglycaemic episodes. Refer to Appendix 8.

11 Statistical considerations

Main phase

Taxonomy of week 56 assessments

For each subject a given assessment at week 56 may be available or missing and Table 11-1 describes the taxonomy for this. Note, this is done per assessment and per subject; subjects may be

a different type for different assessments (a subject may have "available on randomised treatment (AT)" for body weight but "missing on randomised treatment (MT)" for waist circumference).

Table 11-1 Taxonomy for subjects based on week 56 assessments

Assessment at week 56	Subjects on randomised treatment at week 56	Type description	Type Abbreviation
Available	Yes	**Available on randomised treatment**: Subjects who complete the trial on randomised treatment with an assessment at week 56: Includes those that stop and restart trial product.	AT
	No	**Available but discontinued:** Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 56. These are also called retrieved subjects	AD
Missing	Yes	**Missing on randomised treatment**: Subjects who complete the trial on randomised treatment without an assessment at week 56: Includes those that stop and restart trial product.	MT
	No	**Missing and discontinued**: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 56. These are also called non-retrieved subjects	MD

11.1 Sample size determination

As no long-term clinical trial of liraglutide 3.0 mg on weight management in children has yet been completed, the estimate of effect is based on observations from adult trials. For the power calculation it is assumed that the effect of liraglutide 3.0 mg on weight management in children will be similar to the effect observed in adults despite dosing flexibility. This assumption is based on the fact that body weight is the primary determinant for exposure; although the individual maximum tolerated dose may be lower in a proportion of the subjects with lower weight, the exposure is expected to be within the same range. The anticipated treatment difference for change in BMI (%) as -4.5% and -5.0% were investigated (based on phase III 56-week trials 1839, 1922 and 1923; 3,037 subjects in pooled analysis). The range of standard deviations assessed (SD) is based on the two more recent trials NN8022-4272 and NN8022-4274, where retention was optimized.

In agreement with EMA/PDCO, the minimum number of randomised subjects should be 78. In a fixed sample size design with a total of 78 subjects, the power calculation is performed using the following scenarios with SD of 4%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0% and 7.5%.

The effect of withdrawals on the analysis is accounted for as a reduction of the anticipated treatment difference and an increase of the SD. Missing values are handled by assuming that withdrawn subjects respond as if treated with placebo for the entire trial. The assumed withdrawal percentage for this paediatric trial is 20%.

Power calculation for different investigated scenarios of treatment difference and SD is shown in Table 11-2.

Table 11-2 Summary of power calculation for fixed sample size

Sample Size	Power (%)	SD						
	Treatment difference	4	5	**5.5**	6	6.5	7	7.5
78	-4.5	94.10%	81.80%	74.60%	67.50%	60.80%	54.80%	49.40%
	-5	97.20%	88.60%	**82.50%**	76.00%	69.60%	63.40%	57.70%

(Total sample size of 78 subjects and withdrawal rate of 20% and a=0.05; two-sided)

A treatment difference of -5.0% (SD=5.5), which is believed to be a realistic scenario, can be detected with at least 80% power and significance level of 0.05 (two-sided) with a randomisation ratio of 2:1 for a fixed sample size of 78 subjects

Multiplicity Adjustment

1. Relative change in BMI from baseline (week 0) to week 56
2. Relative change in body weight from baseline (week 0) to week 56
3. Subjects achieving ≥5% reduction of BMI from baseline (week 0) to week 56

The primary endpoint followed by the two confirmatory secondary endpoints will be evaluated using a hierarchical testing procedure starting with the treatment difference between the relative change in BMI. In the case of a significant treatment difference the test procedure proceeds to test the treatment difference between the relative change in body weight followed by the treatment difference between the subjects achieving ≥5% reduction of BMI. This test procedure will protect the family-wise type 1 error in the strong sense on a 5% level of significance.

The test hierarchy is given in Table 11-3 with marginal power and effective power. The effective power is calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively.

Table 11-3 Summary of power calculation for fixed sample size for confirmatory secondary endpoints

Endpoints	Sample Size	Power(%)	SD						
		Treatment difference	4	5	5.5	6	6.5	7	7.5
Relative change in	**78**	-5.6	99.0	94.0	89.60	84.30	78.6	72.80	67.10

body weight		-5	97.20	88.60	82.50	76.00	69.60	63.40	57.70
		-5.3	98.3	91.6	86.4	80.5	74.3	68.2	62.5
5% reduction in BMI	**78**	**Treatment proportions**							
		Lira; Placebo 60.7%; 24.4%	88.1%						

Table 11-4 Marginal power and effective power for each endpoint in the hierarchical testing procedure given a fixed sample size of 78 randomised subjects

Endpoints	Treatment difference	Marginal power %	Effective power %
Relative change in BMI	**-5**	**82.5**	**82.5**
Relative change in bodyweight	**-5.3**	**86.4**	**71.3**
5% reduction in BMI	**36.3**	**88.1**	**62.8**

11.2 Definition of analysis sets

11.2.1 Main phase

Two analysis sets are defined in accordance with the ICH E9.

The full analysis set (FAS) includes all randomised subjects according to the intention-to-treat principle, i.e., subjects are included according to planned treatment.

The safety analysis set (SAS) includes all randomised subjects exposed to at least one dose of randomised treatment and subjects are included according to actual treatment.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided.

Two observation periods are defined for each subject:

- In-trial: The in-trial period is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.
- On-treatment (with trial product): A time-point is considered as 'on-treatment' if 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) first follow-up visit (V24 for subjects with trial product discontinued), or c) last study visit (subjects withdrawn without follow-up visit).

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

11.2.2 Extension phase

Analysis set for Extension phase is defined as follows.

Full analysis set: All subjects exposed to at least 1 dose of trial product.

Two observation periods are defined for each subject:

- Extension in-trial: The extension in-trial period is defined as the uninterrupted time interval from date of the start of the Extension phase to date of last contact with trial site.
- Extension on-treatment (with trial product): A time-point is considered as 'on-treatment' for the Extension phase if defined as events with onset date between the first day of trial product administration in the Extension phase and whatever comes first: a) 14 days after the last day on trial product, b) first follow-up visit (V42 for subjects with trial product discontinued), or c) last study visit (subjects withdrawn without follow-up visit).

The Extension phase in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

11.3 Statistical analyses

A complete description of the statistical analyses will be provided in statistical analysis plan (SAP) for this trial. First version of SAP will be prepared before first subject first visit and finalised SAP will be prepared before database lock.

Effect endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

Results from statistical analyses will generally be accompanied by two-sided 95% confidence intervals and corresponding p-values. Superiority of confirmatory endpoints will be claimed if p-values are less than 5% and the estimated treatment contrasts favour liraglutide 3.0 mg.

Handling of missing baseline data

If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment was made at screening, the screening value will be used as the baseline value.

Taxonomy for subjects based on week 56 assessments being available (Available on randomised treatment [AT] or Available but discontinued [AD]) or missing (missing on randomised treatment [MT] or missing but discontinued [MD]) will be explained in detail in the SAP.

11.3.1 Primary endpoint

Definition of primary endpoint: % change in BMI

Change from baseline (week 0) to week 56 in BMI (%) is defined as

$$\% \text{ change in BMI} = \frac{(\text{BMI at week 56} - \text{BMI at baseline})}{\text{BMI at baseline}} \times 100.$$

Analyses addressing the primary estimand

The analysis model for % change in BMI is a linear regression (ANCOVA) assuming unequal variances between the treatment arms of % change in BMI on randomised treatment and stratification group (gender *Tanner stage group) as factors and baseline BMI (kg/m^2) as covariate. The estimated treatment difference between liraglutide 3.0 mg once-daily and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

BMI will be calculated in the CRF every time the weight and height are measured. BMI SDS and height SDS will be calculated using the methods outlined in WHO 2007.[46, 47]

All subjects in the FAS are included in this analysis.

The superiority tests of liraglutide 3.0 mg vs. placebo will be carried out as follows.

Let μliraglutide and μplacebo denote the true mean of % change in BMI for s.c. liraglutide 3.0 mg once-daily and placebo group, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{liraglutide} \geq \mu_{placebo} \; vs$$
$$H_A: \mu_{liraglutide} < \mu_{placebo}.$$

The null hypothesis will be rejected, and superiority claimed, if the upper limit of the estimated two-sided 95% CI is below 0.

Handling of missing week 56 values for the primary estimand

All available data at week 56 (AT and AD) are used and missing values (MT and MD) at week 56 will be imputed. Two approaches for imputation will be applied. First, a description of the primary imputation approach to address the primary estimand for the primary endpoint is given followed by a description of the sensitivity analysis. The sensitivity analysis investigates how assumptions on BMI development after discontinuation of randomised treatment impact the estimated treatment contrasts between liraglutide 3.0 mg once-daily and placebo.

Primary imputation approach for the primary estimand

The primary imputation approach for the primary estimand is multiple imputation approach as described by McEvoy where missing BMI measurement at week 56 for non-retrieved dropouts (MD) are imputed by sampling from values obtained from retrieved drop-outs (AD) in each randomised treatment arm. This will be done according to the timing (monthly) of last available observation (of BMI measurement) on randomised treatment (LAO-OT). Missing BMI measurements at week 56 for subjects on drug treatment (MT) are imputed by sampling from subjects on randomised treatment (AT) in the relevant randomised treatment arm.

More detailed description of multiple imputation approach will be provided in SAP.

Sensitivity analysis

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

- The approach for multiple imputations of missing values of BMI (kg/m2) at week 56 (type MT+MD) for both the liraglutide 3.0 mg and placebo group is by sampling all available assessments at respective landmark visits in the placebo group (type AT+AD). This approach is also known as jump to reference and makes the assumptions that subjects instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to diet and exercise. The multiple imputation approach is done as that of primary endpoint.

- The sensitivity analysis will be done by doing the multiple imputation approach using wash-out method where, missing BMI measurement at week 56 for subjects on liraglutide arm will be imputed with observed baseline data from liraglutide placebo group. No intermediate values from liraglutide arm will be used in the imputation for the missing measurements of the liraglutide group. For subjects on liraglutide placebo arm, intermediate observed values from placebo completers will be used while imputing missing values at week 56. This approach assumes that the subjects after discontinuation have a wash out (return to baseline) of any potential treatment effect.

- The sensitivity analysis for the primary endpoint assuming equal variances between the treatment arms will be done by doing imputation method similar to the one described for primary imputation approach for the primary estimand.

More detailed description of sensitivity analysis will be provided in SAP.

Analyses addressing the secondary estimand

The secondary estimand for % change in BMI will be assessed using a mixed model for repeated measurements (MMRM). The MMRM will use post-baseline assessments only from subjects who are taking the randomised treatment until planned end of treatment or until first discontinuation of randomised treatment. This means that assessments at week 56 for retrieved drop-outs (type AD) will be discarded. The MMRM will be fitted using % change in BMI and the same factor and covariate as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

11.3.2 Secondary endpoints

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

11.3.3 Supportive secondary endpoints

Supportive secondary endpoints listed in Section 5 will be analysed as follows.

Analyses addressing the primary estimand from baseline (week 0) to week 56

The effect-related supportive secondary endpoints will be analysed using the same imputation approach as used for the primary endpoint and to address the primary estimand. The imputation model is the same as for the primary endpoint with BMI replaced by assessments of the endpoint to be analysed.

The statistical model for continuous endpoints will be analysed using ANCOVA with factor and covariate used as for the primary endpoint % change in BMI with baseline BMI assessment replaced by the baseline assessment of the endpoint.

The statistical model for the responder endpoints relating to BMI will be analysed using logistic regression with factor and covariates used as for primary endpoint with baseline BMI assessment replaced by the baseline assessment of the endpoint.

Analyses addressing the secondary estimand

The supportive secondary endpoints which relate to the primary objective will be analysed to address the secondary estimand using the same MMRM for efficacy described for the primary endpoint.

12.3.4 Analysis of safety endpoints from baseline (week 0) to week 82

AEs will be defined as “treatment-emergent” (TEAE), if the onset of the event occurs in the on-treatment period (see definition in Section 11.2.1). TEAEs and SAEs will be summarised by descriptive statistics, such as frequencies and percentages. No formal statistical inference will be carried out based on the number of TEAEs and SAEs.

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.

11.3.4 Exploratory endpoints

Exploratory endpoints are listed in Section 5 and will be analysed as follows.

Main phase

Analyses addressing the primary estimand

The effect-related exploratory endpoints will be analysed using the same imputation approach as used for the primary endpoint and to address the primary estimand. The imputation model is the same as for the primary endpoint with BMI replaced by assessments of the endpoint to be analysed.

The statistical model for continuous endpoints will be analysed using ANCOVA with factor and covariate used as for the primary endpoint % change in BMI with baseline BMI assessment replaced by the baseline assessment of the endpoint.

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.

The statistical model for responder endpoints relating to body weight will be analysed using logistic regression with factor and covariates used as for primary endpoint with baseline BMI assessment replaced by the baseline assessment of the endpoint.

In addition, LDL cholesterol, Triglycerides, HOMA-B and HOMA-IR will be analysed separately using an analysis similar to primary endpoint using a multiplicative model will be used, i.e. all the values will be log-transformed prior to analysis.

Analysis of safety endpoints

Hypoglycaemic episodes (for T2D subjects only)

The hypoglycaemic episodes will be summarised descriptively by severity and treatment in terms of the number and percentage of subjects with at least one event and the total number of events. In the same way as for AEs, there will be separate summaries for the “in trial”, “on treatment” and “on treatment without rescue medication” periods. Hypoglycaemic episodes in the screening period will be presented in listings

Extension phase

Analyses addressing the exploratory endpoints

Exploratory endpoints for the Extension phase listed in Section 5.2.2.3 will be analysed as follows.

The exploratory endpoints and assessments at scheduled timepoints will be summarised descriptively by treatment group (Section 5.1) based on the FAS, using the extension on-treatment observation period, and the extension in-trial observation period. Descriptive statistics (mean, Standard Deviation (SD), median, and range for continuous variables and proportion for categorical variables) will be used. No formal statistical inference will be carried out based on the numbers obtained.

Analyses of safety endpoints

AEs will be defined as “treatment-emergent” (TEAE) if the onset of the event occurs in the on-treatment period (see definition in Section 11.2.2). TEAEs and SAEs will be summarised descriptively by treatment group (Section 5.1), based on FAS using the extension on-treatment observation period and the extension in-trial observation period. Descriptive statistics such as frequencies and percentages will be used. No formal statistical inference will be carried out based on the number of TEAEs and SAEs.

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.

Hypoglycaemic episodes (for T2D subjects only)

The hypoglycaemic episodes will be summarised for the open label treatment period just as for the Main phase (Section 11.3.4).

11.3.5 Interim analyses

No interim analyses are planned for this trial.

11.3.6 Other analyses

All collected data that were not defined as endpoints will be summarised by descriptive statistics and more details will be provided in SAP.

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, respectively. Subjects who are positive for antibodies at any time will also be summarised.

In addition, a comparison of the change in 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 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.

11.4 Pharmacokinetic and/or pharmacodynamic modelling

Liraglutide concentrations from samples drawn at site visits will be used to describe the liraglutide exposure and to investigate the effects of covariates on the pharmacokinetics. Data from pre-defined historical trials (i.e., adolescent and 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 Pharmacometrics, 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 database 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). Average concentration and 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 (child/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

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

12 Appendices

Appendix 1 Abbreviations and Trademarks

AD	Available but discontinued
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	Available on randomised treatment
BG	blood glucose
BMI	Body mass index
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Preventi
CEA	carcinoembryonic antigen
COVID	coronavirus disease
CRF	case report form
C-SSRS	Columbia Suicidality Severity Rating Scale
CTR	clinical trial report
DMC	data monitoring committee
DPP	dipeptidyl peptidase
DRE	disease related event
DUN	dispensing unit number
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like-peptide-1 receptor agonist
HbA1c	glycated haemoglobin
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee

IMP	investigational medicinal product
IRB	institutional review board
ISPAD	International Society for Pediatric and Adolescent Diabetes
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LAO-OT	last available observation during the on-treatment
LAR	legally acceptable representative
LDL	low-density lipoprotein
MD	Missing and discontinued
MEN2	multiple endocrine neoplasia type 2
MHP	Mental health professional
MMRM	mixed model for repeated measurements
MT	Missing on randomised treatment
MTC	medullar thyroid carcinoma
MTD	maximum tolerated dose
PCD	primary completion date
PDCO	European Paediatric Committee
PG	plasma glucose
PYE	patient years of exposure
PYO	patient years of observation
SAE	serious adverse event
SAP	statistical analysis plan
SDS	standard deviation score
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TEAE	“treatment-emergent” AE (TEAE)
TMM	trial materials manual
ULN	upper limit of normal
WOCBP	woman of childbearing potential

Appendix 2 Clinical laboratory tests

- Laboratory samples specified in the protocol should be sent to the central laboratory for analysis
- The tests detailed in Table 12-1, Table 12-2, Table 12-4, and Table 12-5 will be performed by the central laboratory
- The tests detailed in Table 12-3 and Table 12-6 will be performed by a special laboratory
- All samples should be shipped to the central laboratory for analysis or further distribution
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should 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
- The central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab standard operating procedures. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.
- The investigator must review all laboratory results for concomitant illnesses and AEs
- Laboratory samples will be destroyed no later than at finalisation of the CTR except antibody samples which will be stored until marketing authorisation or destroyed at the latest 15 years from end of trial
- Human biosamples for future analysis will be stored as described in Appendix 7
- For haematology samples (differential count) where the test result is not normal, a part of the sample may be kept for up to two years or according to local regulations
- The use of topical anaesthetics (e.g. numbing cream) for blood sampling should be according to local practice

Table 12-1 Protocol-required efficacy laboratory assessments (Main phase)

Laboratory assessments	Parameters
Glucose metabolism (V2, V8, V17, V23, V28)	• Fasting plasma glucose[1] • Fasting serum insulin • HbA1c (to be taken at V1, not V2) • Homeostasis model assessment (HOMA-B and HOMA-IR)
Glucose metabolism (for subjects with T2D) (V2, V8, V13, V17, V21, V23, V28)	• Fasting plasma glucose[1] • Fasting serum insulin • HbA1c (to be taken at V1, not V2) • Homeostasis model assessment (HOMA-B and HOMA-IR)
Lipids (V8, V17, V23, V28)	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very low density lipoprotein cholesterol (VLDL) • Triglycerides
NOTES: [1]A FPG result ≤3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Appendix 4).	

Table 12-2 Protocol-required safety laboratory assessments (Main phase)

Laboratory assessments	Parameters
Haematology (V1, V8, V17, V23)	• Haemoglobin • Haematocrit • Thrombocytes • Erythrocytes • Leucocytes • Eosinophils • Neutrophils • Basophils • Lymphocytes • Monocytes
Biochemistry[1] (V1, V8, V17, V23)	• Creatinine • Creatine kinase • Urea (BUN) • Albumin • Bilirubin (total) • Alanine aminotransferase (ALT)[2] • Aspartate aminotransferase (AST)[2] • Alkaline phosphatase (ALP) • Sodium • Potassium • Calcium total • Calcium (albumin corrected) • Gamma-glutamyltransferase (GGT) • Calcitonin • Amylase • Lipase
Hormones (V8, V17, V23, V28)	• Thyroid stimulating hormone (TSH) (also taken at V1) • Free thyroxine (free T4) (also taken at V1) • Dehydroepiandrosterone sulfate (DHEAS) • Luteinising hormone (LH) • Follicle stimulating hormone (FSH) • Estradiol (females) • Testosterone (males) • Sex hormone binding globulin (SHBG) (males) • Prolactin • ACTH • Cortisol
Bone metabolism (V8, V23, V28)	• Type 1 collagen C-telopeptide (CTx1) • Alkaline phosphatase (bone)
Pregnancy Testing (V1, V8, V9, V10, V11, V12, V13, V15, V17, V19, V21, V23, V24, V26, V28)	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP), see Appendix 5 for further information
Biomarkers (V8, V17, V23)	• Carcinoembryonic antigen (CEA) serum • Serum insulin-like growth factor 1
Other tests	• Tryptase in case of acute severe systemic hypersensitivity, see Section 10.4.9 • Biosamples for future analysis (V8, V23, V28), see Section 10.9

Laboratory assessments	Parameters
Notes: [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 4 (Hy's Law) and Section 9.1 [2]If ALT or AST >3 upper normal limit (UNL) additional relevant blood samples should be taken by local laboratory (except at screening visit). Repeat testing of the abnormal lab assessments should be performed for the subject until abnormalities return to normal or baseline state.	

Table 12-3 Protocol-required special laboratory parameters (Main phase)

Laboratory assessments	Parameters
Antibodies (V8, V13, V15, V17, V21, V23, V24, V28)	• Anti-liraglutide antibodies (also unscheduled[1]) • Antibodies cross-reacting native GLP-1[2] --- • Liraglutide antibodies (neutralising effect) (V24 and V28 only)[3] • Antibodies neutralising native GLP-1 (V24 and V28 only)[4] • Anti-liraglutide IgE antibodies (unscheduled[1])
PK (V13, V15, V17, V21, V23, V24)	• Liraglutide PK
NOTES: [1]unexpected anti-liraglutide antibodies are analysed in case of suspicion of trial drug induced acute severe systemic hypersensitivity, see Section 10.4.9 and Appendix 4. [2]measured in confirmed anti-liraglutide antibody positive samples from any visit [3]measured in visit 24 and visit 28 samples confirmed positive for anti-liraglutide antibodies [4]measured in visit 24 and visit 28 samples confirmed positive for cross reactivity to native GLP-1.	

Table 12-4 Protocol-required efficacy laboratory assessments (Extension phase)

Laboratory assessments	Parameters
Glucose metabolism (V37, V41, V43, V44)	• Fasting plasma glucose[1] • Fasting serum insulin • HbA1c • Homeostasis model assessment (HOMA-B and HOMA-IR)
Glucose metabolism (for subjects with T2D) (V35, V37, V39, V41, V42,V43, V44)	• Fasting plasma glucose[1] • Fasting serum insulin • HbA1c • Homeostasis model assessment (HOMA-B and HOMA-IR)
Lipids (V37, V41, V43, V44)	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very low density lipoprotein cholesterol (VLDL) • Triglycerides
NOTES: [1]A FPG result ≤3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Appendix 4).	

Table 12-5 Protocol-required safety laboratory assessments (Extension phase)

Laboratory assessments	Parameters
Haematology (**V28A**, V37, V41)	• Haemoglobin • Haematocrit • Thrombocytes • Erythrocytes • Leucocytes • Eosinophils • Neutrophils • Basophils • Lymphocytes • Monocytes
Biochemistry[1] (**V28A**, V37, V41, V43, V44)	• Creatinine • Creatine kinase • Urea (BUN) • Albumin • Bilirubin (total) • Alanine aminotransferase (ALT)[2] • Aspartate aminotransferase (AST)[2] • Alkaline phosphatase (ALP) • Sodium • Potassium • Calcium total • Calcium (albumin corrected) • Gamma-glutamyltransferase (GGT) • Calcitonin • Amylase • Lipase
Hormones (V37, V41, 43, 44)	• Thyroid stimulating hormone (TSH) Free thyroxine (free T4) • Luteinising hormone (LH) • Follicle stimulating hormone (FSH) • Estradiol (females) • Testosterone (males) • Sex hormone binding globulin (SHBG) (males)
Bone metabolism (V37, V41)	• Type 1 collagen C-telopeptide (CTx1) • Alkaline phosphatase (bone)
Pregnancy Testing (V29, V30, V31, V32, V33, V35, V37, V39, V41, V42, V43, V44)	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP), see Appendix 5 for further information
Other tests	• Tryptase in case of acute severe systemic hypersensitivity, see Section 10.4.9
NOTES: [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 4 (Hy's Law) and Section 9.1 [2]If ALT or AST >3 upper normal limit (UNL) additional relevant blood samples should be taken by local laboratory (except at screening visit). Repeat testing of the abnormal lab assessments should be performed for the subject until abnormalities return to normal or baseline state.	

Table 12-6 Protocol-required special laboratory parameters (Extension phase)

Laboratory assessments	Parameters
Antibodies[1] (V28, V33, V35, V37, V39, V41, V42)	• Anti-liraglutide antibodies (also unscheduled[2]) • Antibodies cross-reacting native GLP-1[3] --- • Liraglutide antibodies (neutralising effect) (V42)[4] • Antibodies neutralising native GLP-1 (V42)[5] • Anti-liraglutide IgE antibodies (unscheduled[2])
PK (V33, V35, V37, V39, V41, V42)	• Liraglutide PK

NOTES:

[1]If a subject discontinues treatment after V28, but prior to V41, the subject should attend a clinic visit no sooner than 2 weeks after discontinuing treatment. At this premature discontinuation visit, the subjects final PK and antibody samples will be taken. No further PK and antibody samples should be taken unless the subject resumes trial product treatment (See Section 9.1).

[2]Unexpected anti-liraglutide antibodies are analysed in case of suspicion of trial drug induced acute severe systemic hypersensitivity, see Section 10.4.9 and Appendix 4.

[3]Measured in confirmed anti-liraglutide antibody positive samples from any visit

[4]Measured in visit 24, visit 28 and visit 42 (extension) samples confirmed positive for anti-liraglutide antibodies

[5]Measured in visit 24, visit 28 and visit 42 (extension) samples confirmed positive for cross reactivity to native GLP-1.

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[49] and applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[50]
- Applicable laws and regulations
- The protocol, informed consent form, child assent form, IB (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received

The investigator will be responsible for:

- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CTR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

2) Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.

For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and their parent(s)/LAR and answer all questions regarding the trial
- The investigator must give the subject and their parent(s)/LAR verbal and written information according to his/her capacity to understand, always taking into consideration the subject's presumed willingness to participate in the trial

- The investigator must ensure the subject and their parent(s)/LAR ample time to come to a decision whether or not to participate in the trial
- Subjects and their parent(s)/LAR must be informed that their participation is voluntary
- Subjects and their parent(s)/LAR must be informed about their privacy rights
- Subjects and their parent(s)/LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[50], Declaration of Helsinki[49] and the IRB/IEC or trial site
- The medical record must include a statement that written informed consent/child assent were obtained before any trial related activity and the date when the written consent/assent were obtained. The authorised person obtaining the informed consent/assent must also sign and date the informed consent/assent forms before any trial related activity.
- The responsibility of seeking informed consent and assent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements
- Subjects and/or their parent(s)/LAR must be re-consented to the most current version of the informed consent/assent form(s) during their participation in the trial
- A copy of the informed consent/assent form(s) must be provided to the subject or the subject's parent(s)/LAR
- During the trial, the investigator should reassess the assent of a child in recognition of their advancing age, evolving maturity and competency

4) Information to subjects during trial

The site will be offered a communication package for the subject and their parent(s)/LAR during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects and/or their parent(s)/LAR. The written information will be translated and adjusted to local requirements and distributed to the subject and/or their parent(s)/LAR at the discretion of the investigator. The subject and their parent(s)/LAR may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject and/or their parent(s)/LAR may receive other written information during the trial.

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

The initiatives for subject retention must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

5) Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or

leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.

- The subject and the parent(s)/LAR must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject and their parent(s)/LAR
- The subject and the parent(s)/LAR must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal liraglutide safety committee. 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.

Data monitoring committee

The 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 done 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.

7) Publication policy

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 investigators 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 CTR for this trial.

One (or two) investigator(s) will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator(s)) on behalf of all participating investigators.

Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed 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. 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 Main phase of the trial and at the End of 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. 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.

Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by Committee of Medical Journal Editors.[51]

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

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

For a multicentre 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. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

Investigator access to data and review of results

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

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

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[52], the Food and Drug Administration Amendment Act (FDAAA)[53], European Commission Requirements[54-56] and other relevant recommendations or regulations. If a subject request to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint and is for this trial Last Subject First Treatment (LSFT) + 56 weeks corresponding to visit 'end of treatment' visit 23. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed 'end of treatment' visit 23. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- 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 CRF is revoked or the CRF is temporarily unavailable:
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)
    - AE 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 when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

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

Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data 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).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.
- 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 CRF.

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay 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 CRF or via listings from the trial database.

10) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- The original of the completed diaries must not be removed from the trial site, unless they form part of the CRF, and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must

be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

- It must be possible to verify subject's medical history in source documents such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 25 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

12) Trial and site closure

Novo Nordisk reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or 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.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of subjects by the investigator
- discontinuation of further trial product development

13) 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 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 that 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).

14) Indemnity statement

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

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

Novo Nordisk may pay additional costs incurred in relation to assessments relevant for following the safety of the subject. Investigator must contact Novo Nordisk on a case by case basis for whether the costs will be covered

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP • An AE can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected • Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected • Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent • A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
• Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history • Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE • Medical or surgical procedures not preceded by an AE or worsening of a known condition

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' 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 were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE. Note: ▪ Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs

▪ Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical event: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion. • The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable: ▪ Suspicion of transmission of infectious agents via the IMP ▪ Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law)

Description of AEs requiring additional data collection (via specific event form)

AEs requiring additional data collection

Event type	Description
Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features, according to the Atlanta criteria[41] below 1. abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) 2. serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal 3. characteristic findings of acute pancreatitis on imaging
Malignant neoplasm	Malignant neoplasm by histopathology or other substantial clinical evidence
Hepatic events	Hepatic event defined as: - Disorders of the liver including cholestatic conditions and liver related signs and symptoms - ALT or AST >3x UNL and total bilirubin >2x UNL* - ALT or AST >3x UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) *Please note that in case of a hepatic event defined as ALT or AST >3x UNL and total bilirubin >2x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

	Medication error	A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the subject, such as: • Administration of wrong drug • Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug • Wrong route of administration, such as intramuscular instead of subcutaneous • Accidental administration of more than 3.0 mg/day or a higher dose than intended during dose escalation, however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur
	Misuse and abuse**	• Situations where the IMP is intentionally and inappropriately used (e.g. overdose to maximise effect) • Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)

**Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycaemia or other), this must be reported on an additional AE form.

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- 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. For sign-off of SAE related forms refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

Note: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:

- 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 IMP.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.

The investigator should use the investigator's brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

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

The investigator may change his/her opinion of causality in light of follow-up information and update the causality assessment in the CRF.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

- The investigator will select the most appropriate outcome:
- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **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 sequelae 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.
- Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **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 a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals. If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology. New or updated information will be recorded in the CRF.

SAE reporting via electronic CRF
• Relevant forms (AE and safety information form) must be completed in the CRF. • For reporting and sign-off timelines, see box below. • If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days then the site will use the safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available, see 10.2.1. • After the trial is completed at a given site, the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF
• Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier. • For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 10-1) • AE form within 24 hours. • Safety information form within 5 calendar days. • Both forms must be signed within 7 calendar days after first knowledge by the investigator. • The specific event form for AEs requiring additional data collection within 14 calendar days. • Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 5 Contraceptive guidance and collection of pregnancy information

It must be recorded in the CRF whether female subjects are of childbearing potential (have had first menstrual period).

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.
If fertility is unclear (e.g. amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

The childbearing potential of female subjects must be evaluated as specified in the flowchart (Section 2) until the female subject becomes of childbearing potential.

Contraception guidance

Male subjects

No contraception measures are required for male subjects as the risk of teratogenicity/fetotoxicity caused by transfer of liraglutide in seminal fluid is unlikely.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in the table below:

Table 12-7 Highly effective contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
Highly effective methods[b,c] that have low user dependency *(Failure rate of <1% per year when used consistently and correctly)*: 1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] 2. Intrauterine device (IUD) 3. Intrauterine hormone-releasing system (IUS)[b] 4. Bilateral tubal occlusion **Highly effective methods[b,c] that are user dependent** *(Failure rate of <1% per year when used consistently and correctly)*: 5. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal • injectable 6. Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from

heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
NOTES a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Contraception should be utilised during the treatment period and for at least 7 days (corresponding to time needed to eliminate trial product) after the last dose of trial product. This period should be extended by 30 days in case of genotoxicity.

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive urine pregnancy test at screening (V1) and randomisation (V8). A girl is considered WOCBP *if* she has had her first menstrual period prior to Visit 1.
- For WOCBP urine pregnancy testing must be performed at every site visit during the treatment and follow-up periods.
- Additional pregnancy testing should be performed during the treatment period, if required locally.
- *If* a girl becomes of childbearing potential (has first menstrual period) during the trial a urine pregnancy test must be performed as soon as possible or at the latest at the next site visit.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding ‘gestational’, ‘pregnancy related’ or a similar term when reporting the AE/SAE.

- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the trial will discontinue trial product.

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

Technical complaint definition
• 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:

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

Time period for detecting technical complaints
All technical complaints, which occur from the time of receipt of the product at trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form.

Reporting of technical complaints to Novo Nordisk
Contact details (fax, e-mail and address) for Customer Complaint Center, please refer to Attachment I Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within the timelines specified Figure 10-3 If the CRF is unavailable or when reporting a technical complaint on a trial product that is not yet allocated to subject, 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 CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at trial site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

Appendix 7 Retention of human biosamples

Antibody samples

- Antibody samples may be retained for potential later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons
- Only Novo Nordisk staff and personnel from the specialised laboratory will have access to the stored specimens
- The samples will be stored at the specialised laboratory or Novo Nordisk 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
- Samples might be transferred to other countries, if not prohibited by local regulations
- The subject's identity will remain confidential and the 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. The analyses will not have any medical consequences for the subjects or their relatives.
- Subjects and their parent(s)/LAR can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body

Biosamples for future analysis

- In countries where applicable, the trial will involve collection of human biosamples to be stored in a central archive for future use
- The subject's parent(s)/LAR must sign and date a separate informed consent form before their child's biosamples are collected to be stored for future analysis
- The material to be collected:

  i) Plasma (1 mL for analysis of circulating biomarkers) at randomisation (V8) and Main phase 'end of treatment' (V23)
  ii) Whole blood (2.5 mL for genetic analysis) at End of Main phase (V28).

- As new biomarkers related to the disease and/or safety, efficacy or mechanism of action of liraglutide may evolve during the conduct of the trial, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial
- The biosamples will be stored at a central laboratory for 6 months and at a central storage facility contracted by Novo Nordisk for up to 15 years after end of trial. Only Novo Nordisk and storage facility employees will be able to access the stored biosamples. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of trial.

The subject's parent(s)/LAR may request their child's stored biosamples to be destroyed by withdrawing the designated informed consent.

Appendix 8 Assessments for subjects with T2D

Assessments relevant for subjects with T2D at screening or if diagnosed during the trial are described in this appendix.

Medical history of the subjects with T2D must include diabetes history and complications. If the subject is diagnosed with T2D during the trial this must be recorded as an AE.

If the subject is on metformin the dose must be recorded in concomitant medication form.

Diaries on SMPG measurements and hypoglycaemic episodes will be handed out from randomisation (V8) or when diagnosed with T2D. Subjects and their parent(s)/LAR must be instructed in how to transfer the results of the SMPG values into the diary handed out by Novo Nordisk.

At each visit the diaries must be reviewed by investigator or delegate and the results transcribed into the CRF.

Self-measured plasma glucose (SMPG)

Subjects will be provided with a BG meter including auxiliaries as well as instructions for use at randomisation or if diagnosed with T2D during the trial. The subjects and their parent(s)/LAR will be instructed in how to use the device and the instruction should be repeated at regular intervals. Investigator should ensure throughout the trial that the subject and the subject's parent(s)/LAR are able to correctly measure BG at any time.

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

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

SMPG measurements should be taken fasting (at least 8 hours overnight before the visit), and prior to taking any diabetes medication. SMPG should be taken either on the day of the clinic visit or on the day before, according to the flowchart. In case of suspicion of a hypoglycaemic event a SMPG should also be taken. Subjects and their parent(s)/LAR should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time, value and fasting state. All data from the diary must be transcribed into the CRF during or following the contact. If obtained via phone or video call and a discrepancy is later detected, the values in the CRF must be corrected.

Occasional review by the investigator of the BG meter values stored in the memory of the BG meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the trial database.

Rescue criteria

If the confirmatory HbA1c exceeds the values described below then the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and according to the recommendations below. To allow for observation of the expected effect of trial product, rescue criteria will be applied from week 8 (V13) to week 56 (V23) and should be considered at all visits between. Rescue criteria should also be applied during the Extension phase from week 84 (V29) to week 140 (V41). Below rescue criteria applies to all subjects regardless if on active treatment or not.

- subjects with a central HbA1c value above 8.5% (69 mmol/mol), who have experienced deterioration in glycaemic control, as expressed by an increase in HbA1c equal to or above 1% from randomisation (or lowest level post-randomisation) that is confirmed within 30 days by the central laboratory*
- subjects with persistent poor glycaemic control, as expressed by a stable HbA1c value above 8.5% (69 mmol/mol) that is confirmed at the next planned visit and by the central laboratory and considered unacceptably high according to investigator's assessment*

* *with no intercurrent illness or explanation including non-compliance according to Investigator's assessment.*

Rescue medication

Glycaemic rescue medication should be implemented according to the rescue criteria mentioned above and at the discretion of the investigator in case of persistent hyperglycaemia.

The following guidelines should be used:

Rescue medication according to ADA/International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines[57, 58] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication should preferably be weight-neutral.

If deemed necessary at the discretion of the investigator, insulin rescue therapy can be initiated, if so it should be according to ADA/ISPAD guidelines[59] and as short duration as possible.

Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judge that it jeopardises safety. Rescue medication should be documented in medical records and reported as concomitant medication.

Rescue medication will not be supplied by Novo Nordisk but reimbursed as long as subject is participating in the trial, if required according to local regulations.

Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

The following Disease-Related Event (DRE) is common in subjects with T2D and can be serious/life threatening:

- Hypoglycaemic episodes

Definitions, classification and reporting requirements are described in Appendix 9.

Non-serious hypoglycaemia must be reported in the CRF on a hypoglycaemic episode form only.

If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above, an AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes.

Appendix 9 Hypoglycaemic episodes

Table 12-8 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	*Glycaemic criteria*	*Description*
Hypoglycaemia alert value (level 1)	*< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)*	*Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy*
Clinically significant hypoglycaemia (level 2)	*< 3.0 mmol/L (54 mg/dL)*	*Sufficiently low to indicate serious, clinically important hypoglycaemia*
Severe hypoglycaemia (level 3)	*No specific glucose threshold*	*[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery*
Notes: The Novo Nordisk terms are adapted from IHSG[60, 61], ADA[43], ISPAD[59]type 1 diabetes outcomes program[60], ATTD[62]. Severe hypoglycaemia as defined by Seaquist[63]and ISPAD[59].		

[1]Severe hypoglycaemia is defined as an event associated with severe cognitive impairment (including coma and convulsions) requiring external assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions[59].

Nocturnal hypoglycaemia

Nocturnal hypoglycaemic episodes: episodes occurring between 23:00 and 07:00 both inclusive.

Reporting of hypoglycaemic episodes

Reporting of hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the diary/CRF when a hypoglycaemic episode is suspected.

Hypoglycaemic episodes should be reported according to the instructions below. When a subject experiences a hypoglycaemic episode, the subject and/or the subject's parent(s)/LAR should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc.) as described in the diary. The investigator should ensure correct reporting of the hypoglycaemic episode and report the hypoglycaemic episode to the CRF. In case a subject or the subject's parent(s)/LAR is not able to fill in the diary (e.g. in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form in the CRF.

If the hypoglycaemic episode fulfils the criteria for an SAE, then in addition to the above, an AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines[63].

Repeated PG measurements and/or symptoms will by default be considered as one hypoglycaemic episode until a succeeding PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported as only one hypoglycaemic episode. In case of several low PG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the PG value for the hypoglycaemic episode, but the start time of the episode will remain as the time for the first low PG value and/or symptom. The remaining values will be kept as source data.

If the severity of a hypoglycaemic episode changes, only one hypoglycaemic episode will be reported, reflecting the most severe degree of hypoglycaemia.

Regarding the question: "To feel better, did you need help to get a sugary drink, food, or medicine?" the investigator must instruct the subjects to answer "Yes", if the episode was an event that required assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration[63].

Additional information (e.g. description of symptoms, alleviation of symptoms, seizure or coma) in relation to severe hypoglycaemic episodes must be recorded in the hypoglycaemic episode CRF.

Diary review

At each contact the investigator must review the diary data for correct reporting of PG values and hypoglycaemic episodes. In case of incomplete or incorrect data in the diary, the subject and/or the subject's parent(s)/LAR must be questioned whether there have been any severe hypoglycaemic episodes since the last visit and report accordingly.

For low PG values for hypoglycaemic episodes with incomplete reporting information:

1. If a hypoglycaemic episode form in the diary is not completed by the subject and/or the subject's parent(s)/LAR within 7 calendar days of the PG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode CRF with as much information as possible. If the subject did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias[64, 65].

Re-training of subjects

The subject and the subject's parent(s)/LAR must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low PG values not reported as hypoglycaemic episodes. The training should be documented by the investigator in source documents.

Appendix 10 Clinical Charts for Body Mass Index by gender and age

Age calculated from CDC.gov: https://www.cdc.gov/growthcharts/percentile_data_files.htm

In Table 12-9 BMI cut-off points are listed for the entire month; for example, 7:1 (age : months) represent 7 years and 1 month up to but not including 7 years and 2 months of age.

According to the protocol inclusion criterion (Section 7.1) and the protocol randomisation criterion (Section 7.3), subjects must have a BMI corresponding to ≥95th percentile on gender and age-specific growth charts (CDC.gov). Table 12-9 must be used to determine subjects' eligibility.

If the child's BMI falls below the 85th percentile (overweight), and there is a health concern related to continued weight loss, the child should be counselled on a eucaloric diet (see Section 8.7) and/or dose modification should be considered (see Section 8.4 and 8.8), at the discretion of the investigator.

Table 12-9 Cut-off points for BMI (Weight in kg/Height in m^2) for Overweight (BMI ≥85th percentile), obesity (≥95th percentile) by gender for children from 6 and < 14 years of age

Age	Overweight BMI ≥ 85th percentile		Obesity BMI ≥ 95th percentile	
Year : Month	Males	Females	Males	Females
06:00	17.01	17.10	18.41	18.84
06:01	17.04	17.14	18.47	18.90
06:02	17.07	17.17	18.52	18.96
06:03	17.09	17.21	18.58	19.03
06:04	17.12	17.25	18.64	19.09
06:05	17.15	17.29	18.70	19.16
06:06	17.18	17.34	18.76	19.23
06:07	17.22	17.38	18.82	19.30
06:08	17.25	17.43	18.88	19.37
06:09	17.29	17.48	18.95	19.45
06:10	17.32	17.52	19.01	19.52
06:11	17.36	17.57	19.08	19.60
07:00	17.40	17.63	19.15	19.68
07:01	17.44	17.68	19.22	19.76
07:02	17.48	17.73	19.29	19.84
07:03	17.53	17.79	19.37	19.92
07:04	17.57	17.84	19.44	20.00
07:05	17.61	17.90	19.52	20.08
07:06	17.66	17.95	19.59	20.17
07:07	17.71	18.01	19.67	20.25
07:08	17.76	18.07	19.75	20.34
07:09	17.80	18.13	19.83	20.43
07:10	17.85	18.19	19.91	20.52

Age	Overweight BMI ≥ 85th percentile		Obesity BMI ≥ 95th percentile	
Year : Month	Males	Females	Males	Females
07:11	17.90	18.25	19.99	20.61
08:00	17.96	18.32	20.07	20.70
08:01	18.01	18.38	20.15	20.79
08:02	18.06	18.44	20.23	20.88
08:03	18.12	18.51	20.32	20.97
08:04	18.17	18.57	20.40	21.06
08:05	18.23	18.64	20.48	21.15
08:06	18.28	18.71	20.57	21.25
08:07	18.34	18.77	20.65	21.34
08:08	18.40	18.84	20.74	21.44
08:09	18.45	18.91	20.83	21.53
08:10	18.51	18.98	20.91	21.63
08:11	18.57	19.05	21.00	21.72
09:00	18.63	19.12	21.09	21.82
09:01	18.69	19.19	21.18	21.91
09:02	18.75	19.26	21.26	22.01
09:03	18.82	19.33	21.35	22.11
09:04	18.88	19.40	21.44	22.20
09:05	18.94	19.47	21.53	22.30
09:06	19,00	19.55	21.62	22.40
09:07	19.07	19.62	21.71	22.50
09:08	19.13	19.69	21.80	22.59
09:09	19.20	19.76	21.89	22.69
09:10	19.26	19.84	21.98	22.79
09:11	19.32	19.91	22.06	22.89
10:00	19.39	19.98	22.15	22.98
10:01	19.46	20.06	22.24	23.08
10:02	19.52	20.13	22.33	23.18
10:03	19.59	20.20	22.42	23.27
10:04	19.66	20.28	22.51	23.37
10:05	19.72	20.35	22.60	23.47
10:06	19.79	20.43	22.69	23.57
10:07	19.86	20.50	22.78	23.66
10:08	19.92	20.57	22.86	23.76
10:09	19.99	20.65	22.95	23.85
10:10	20.06	20.72	23.04	23.95
10:11	20.13	20.80	23.13	24.05
11:00	20.20	20.87	23.21	24.14
11:01	20.27	20.94	23.30	24.24
11:02	20.33	21.02	23.39	24.33
11:03	20.40	21.09	23.47	24.43
11:04	20.47	21.16	23.56	24.52

Age	Overweight BMI ≥ 85th percentile		Obesity BMI ≥ 95th percentile	
Year : Month	Males	Females	Males	Females
11:05	20.54	21.24	23.64	24.61
11:06	20.61	21.31	23.73	24.71
11:07	20.68	21.38	23.81	24.80
11:08	20.75	21.45	23.90	24.89
11:09	20.82	21.53	23.98	24.98
11:10	20.89	21.60	24.06	25.07
11:11	20.95	21.67	24.15	25.17
12:00	21.02	21.74	24.23	25.26
12:01	21.09	21.81	24.31	25.35
12:02	21.16	21.88	24.39	25.43
12:03	21.23	21.96	24.47	25.52
12:04	21.30	22.03	24.55	25.61
12:05	21.37	22.10	24.63	25.70
12:06	21.44	22.17	24.71	25.79
12:07	21.51	22.23	24.79	25.87
12:08	21.58	22.30	24.87	25.96
12:09	21.65	22.37	24.95	26.05
12:10	21.71	22.44	25.03	26.13
12:11	21.78	22.51	25.10	26.22
13:00	21.85	22.58	25.18	26.30
13:01	21.92	22.64	25.25	26.38
13:02	21.99	22.71	25.33	26.46
13:03	22.06	22.77	25.40	26.55
13:04	22.12	22.84	25.48	26.63
13:05	22.19	22.90	25.55	26.71
13:06	22.26	22.97	25.62	26.79
13:07	22.33	23.03	25.69	26.87
13:08	22.39	23.10	25.77	26.95
13:09	22.46	23.16	25.84	27.03
13:10	22.53	23.22	25.91	27.10
13:11	22.60	23.29	25.98	27.18

Appendix 11 Monitoring of calcitonin

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[66], 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 (6 to <12 years) will have calcitonin levels indistinguishable from adults.[67]

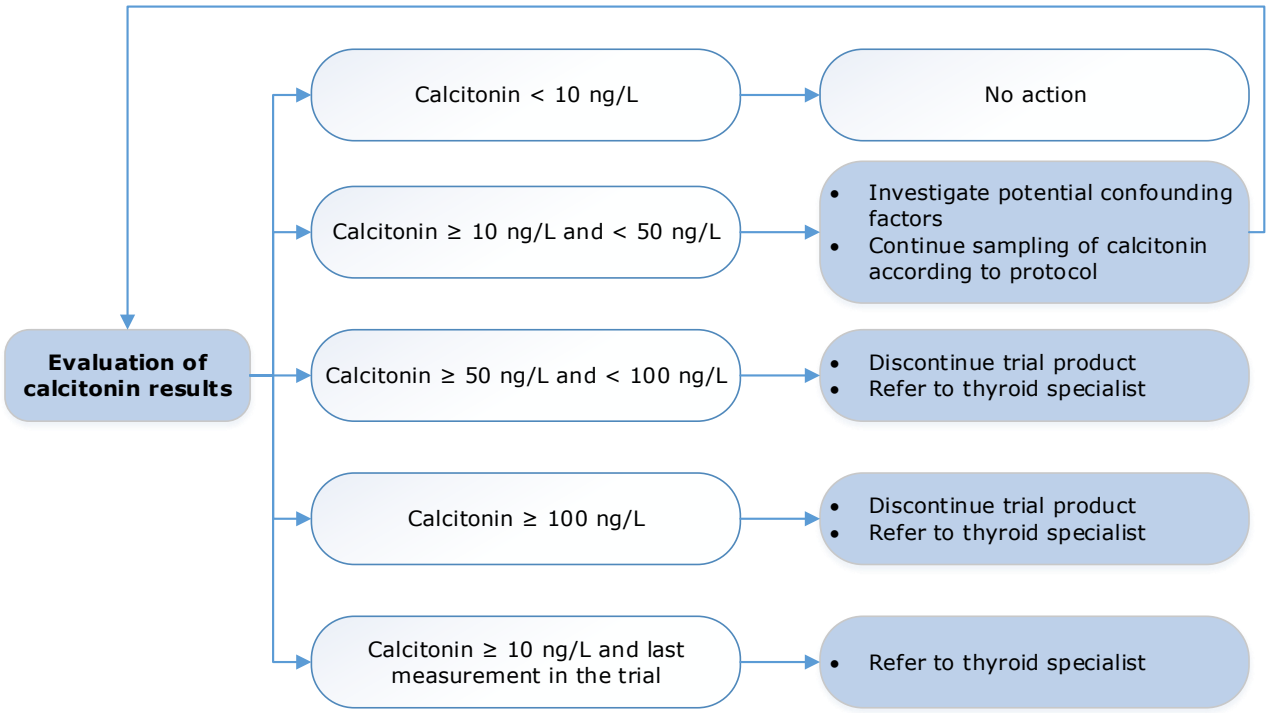
There are several known factors affecting calcitonin levels, namely renal dysfunction, smoking, several drug classes (proton pump inhibitors, beta-blockers, insulin secretagogues). Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e., with various 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.

Calcitonin monitoring

Subjects with a personal or family (family is defined as a first degree relative) history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2) or with a screening calcitonin ≥50 ng/L at visit 1 must be excluded from the trial.

In case a subject has a calcitonin value ≥10 ng/L, the algorithm outlined in Figure 12-1 and described below should be followed. The algorithm applies for all calcitonin values in the trial.

Figure 12-1 Flowchart of calcitonin monitoring



Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a paediatric endocrinologist or thyroid specialist for further evaluation and the trial product must be discontinued (Section 9.1.1). The subject should remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease[66]. All of these patients were diagnosed with MTC, resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- fine needle aspiration of any nodules >1 cm
- potentially, surgery with neck dissection

In case a subject is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 and perform a genetic test for RET proto-oncogene mutation.

Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) should be referred to a paediatric endocrinologist or thyroid specialist for further evaluation. The subject should remain in the trial but must discontinue from trial product.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease[66]. Two of these subjects were diagnosed with MTC and two were diagnosed with C cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available, and if there are no contraindications, a pentagastrin stimulation test should be done. For subjects with positive pentagastrin stimulation test, surgery should be considered
- if pentagastrin stimulation test is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information about the need for surgery

Calcitonin ≥ 10 and < 50 ng/L

Action: The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol.

If the subject is a screen failure, or if the value is from the last sample taken in the trial, the subject should be referred to a paediatric endocrinologist or thyroid specialist for further evaluation.

Background: Calcitonin values from 20-50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease[66]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values between 10-20 ng/L, Costante et al.[66] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin value of 33 ng/L and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin >10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions.[68, 69]

Appendix 12 Country-specific requirements

For Belgium:

Section 7.2 Exclusion criteria and Appendix 5 Contraceptive guidance and collection of pregnancy information

Use of methods of birth control
E.g. 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 IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

Appendix 3 Section 14 Indemnity statement

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.

For Israel:

Section 10.9 Biosamples for future analysis
No subjects from Israel will participate in the optional biobank part of the trial, and no genetic testing will be performed

For Malaysia:

Section 10.9 Biosamples for future analysis
No subjects from Malaysia will participate in the optional biobank part of the trial, and no genetic testing will be performed.

For Mexico:

Section 8 Discontinuation of trial treatment and subject discontinuation/withdrawal
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.

Appendix 3 Section 1 Regulatory and ethical considerations
In the case of Mexico, 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:

a) Investigation follow-up

b) 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;
c) Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;
d) To present in a timely manner the information required by the Health Authority.

Appendix 3 Section 14 Indemnity statement

a) 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.
b) 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 study medication and/or a study procedure that otherwise would not have been part of his/her regular medical 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 study by his own will or by a decision from the investigator.
c) 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.

For Portugal:

Section 7.2 Exclusion criteria and Appendix 5 Contraceptive guidance and collection of pregnancy information

Contraception requirements based on the Recommendations related to contraception and pregnancy testing in clinical trials from CTFG guideline:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

After evaluation of the risk of human teratogenicity/fetotoxicity of the trial product, the level of contraception methods should be decided according to these recommendations.

For Russia:

Appendix 3 Section 1 Regulatory and ethical considerations

The trial should be conducted in compliance with the protocol and Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016 "Approval of rules of good clinical practice and legal requirements of Russian Federation regulating circulation of medicines".

For USA:

Appendix 3 Section 11 Retention of clinical trial documentation

In the United States, 21 CFR 312.62(c) and 21 CFR 812.140(d) require 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

For Switzerland:

Demography: participant's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth in the CRF.

Indemnity Statement: The study will be conducted in compliance with the Therapeutic Products Act (HMG/TPA) of 15 December 2000, the Human Research Act (HFG/HRA) of 30 September 2011 and the Clinical Trial Ordinance (KlinV/ClinO) of 20 September 2013.

Appendix 13 Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 4.0 (19 May 2022)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union for the countries participating in the Extension phase of the trial.

Overall rationale for preparing protocol, version 4.0:

Section # and name	*Description of change*	*Brief rationale*
Sections 1-10 and Appendices 2, 5 and 10	Addition of an Extension phase flowchart and descriptions of the Extension phase of the trial, in all relevant sections.	To provide treatment to all eligible subjects in an open-label treatment period, and to provide lifestyle intervention to all subjects entering the Extension phase. The Extension will provide additional safety and efficacy data.
Section 11.9, Appendices 2, 7	Update of the visit details for the additional collection of biosamples for genetic analysis	To collect additional biosamples for possible genetic analysis
Section 5.5.2 and Section 9.2	Update about the general injection instruction	To provide the instructions about the rotation of injection site to avoid risk of amyloid accumulation
N/A	Minor clarifications and corrections of text	To improve readability of the text

Overall rationale for preparing protocol, version 3.0:

Section # and name	**Description of change**	**Brief rationale**
Section 6.2 Exclusion criteria and section 8.1 Discontinuation of trial treatment	Footnote added allowing co-participation in COVID-19 trials investigating COVID-19 vaccination, treatment and COVID-19 postinfectious conditions	Company position to allow co-participation in COVID-19 trials where deemed safe for the trial subjects
Throughout the protocol	Minor administrative changes	Minor corrections and improved wording

Overall rationale for preparing protocol, version 2.0:

Section # and name	**Description of change**	**Brief rationale**
Section 9 Trial assessments and procedures	Blood volumes added	Requirement
Section 10.3 Statistical analyses	ANCOVA analysis will be performed that assumes unequal variances as the primary analysis and a sensitivity analysis will be performed that assumes equal variances for the same. A multiple imputation approach using wash-out method was added as a sensitivity analysis for assessing	Based on FDA review recommendations

	robustness of the conclusion from the primary analyses.	
Appendix 2, Table 11-1	Fasting Serum Insulin added Type 1 collagen N-telopeptide replaced with Type 1 collagen C-telopeptide	Requirement
Appendix 12, Country Specific Requirements	Complete section inserted	Requirement
Throughout the protocol	Minor administrative changes	Minor corrections and improved wording

13 References

1. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes. 2006;1(1):11-25.
2. Gupta N, Goel K, Shah P, Misra A. Childhood obesity in developing countries: epidemiology, determinants, and prevention. Endocr Rev. 2012;33(1):48-70.
3. Nguyen DM, El-Serag HB. The epidemiology of obesity. Gastroenterol Clin North Am. 2010;39(1):1-7.
4. Lakshman R, Elks CE, Ong KK. Childhood obesity. Circulation. 2012;126(14):1770-9.
5. Luttikhuis HO, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children - art. no. CD001872. Cochrane Database of Systematic Reviews. 2009(1):NIL-NIL.
6. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.
7. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.
8. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet. 2010;375(9727):1737-48.
9. Kohn M, Rees JM, Brill S, Fonseca H, Jacobson M, Katzman DK, et al. Preventing and treating adolescent obesity: a position paper of the Society for Adolescent Medicine. J Adolesc Health. 2006;38(6):784-7.
10. Miller JL, Silverstein JH. Management approaches for pediatric obesity. Nat Clin Pract Endocrinol Metab. 2007;3(12):810-8.
11. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report. Pediatrics. 2007;120:S164-S92.
12. Mastrandrea LD, Witten L, Carlsson Petri KC, Hale PM, Hedman HK, Riesenberg RA. Liraglutide effects in a paediatric (7-11 y) population with obesity: A randomized, double-blind, placebo-controlled, short-term trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics. Pediatr Obes. 2019:e12495.
13. Bray GA, Kim KK, Wilding JPH, Federation WO. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18(7):715-23.
14. The American Society for Metabolic and Bariatric Surgery, The Obesity Society, The American Society of Bariatric Physicians and the American Association of Clinical Endocrinologists. Obesity is a Disease: Leading Obesity Groups Agree (Joint Press Release). 19 June 2013.
15. Kolsgaard ML, Joner G, Brunborg C, Anderssen SA, Tonstad S, Andersen LF. Reduction in BMI z-score and improvement in cardiometabolic risk factors in obese children and adolescents. The Oslo Adiposity Intervention Study - a hospital/public health nurse combined treatment. BMC Pediatr. 2011;11:47.
16. Ford AL, Hunt LP, Cooper A, Shield JP. What reduction in BMI SDS is required in obese adolescents to improve body composition and cardiometabolic health? Arch Dis Child. 2010;95(4):256-61.
17. Reinehr T, Kleber M, Toschke AM. Lifestyle intervention in obese children is associated with a decrease of the metabolic syndrome prevalence. Atherosclerosis. 2009;207(1):174-80.

18. Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of Weight Management Interventions in Children: A Targeted Systematic Review for the USPSTF. Pediatrics. 2010;125(2):E396-E418.
19. Viner RM, Hsia Y, Tomsic T, Wong IC. Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis. Obes Rev. 2010;11(8):593-602.
20. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, Sebring NG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. Diabetes. 2011;60(2):477-85.
21. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(3):709-57.
22. Kumar S, Kelly AS. Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clin Proc. 2017;92(2):251-65.
23. Durkin N, Desai AP. What Is the Evidence for Paediatric/Adolescent Bariatric Surgery? Curr Obes Rep. 2017;6(3):278-85.
24. Crocker MK, Yanovski JA. Pediatric obesity: etiology and treatment. Endocrinol Metab Clin North Am. 2009;38(3):525-48.
25. van C J, Sloth B, Jensen C, Flint A, Blaak EE, Saris W. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite, and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond). 2013;38((6)):784-93.
26. Astrup A, Rossner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009;374(9701):1606-16.
27. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013;37(11):1443-51.
28. Klein DJ, Battelino T, Chatterjee DJ, Jacobsen LV, Hale PM, Arslanian S. Liraglutide's Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Pediatric Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial (Diabetes Technol Ther. 2014; 16(10): 679-687).
29. Danne T, Biester T, Kapitzke K, Jacobsen SH, Jacobsen LV, Petri KC, et al. Liraglutide in an Adolescent Population with Obesity: A Randomized, Double-Blind, Placebo-Controlled 5-Week Trial to Assess Safety, Tolerability, and Pharmacokinetics of Liraglutide in Adolescents Aged 12-17 Years. J Pediatr. 2017;181:146-53.e3.
30. Tamborlane WV, Barrientos-Pérez M, Fainberg U, Frimer-Larsen H, Hafez M, Hale PM, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. N Engl J Med. 2019.
31. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, et al. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. N Engl J Med. 2020.
32. Novo Nordisk A/S. Investigator's Brochure, Liraglutide 3.0 mg (Saxenda), NN8022, (edition 12). 27 Feb 2020.
33. European Medicines Agency. Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev. 1) : Addendum on weight control in children. 2008.
34. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1), Step 4. 10 June 1996.

35. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
36. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11-22.
37. Rogol AD, Clark PA, Roemmich JN. Growth and pubertal development in children and adolescents: effects of diet and physical activity. Am J Clin Nutr. 2000;72(2 Suppl):521S-8S.
38. Victoza (liraglutide), US Prescribing Information. 6/2013 2013.
39. Victoza (liraglutide), EU Summary of Product Characteristics. 4/30/2014 2014.
40. World Health Organization. Fact sheets on Physical activity. 2018.
41. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.
42. The European Commission. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population - Recommendations of the adhoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008.
43. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2017;40 (Suppl. 1):S1-S135.
44. The Columbia Lighthouse Project. Columbia Community Card for Parents 2020 [cited 2020 24 Apr].
45. Tanner JM. Normal growth and techniques of growth assessment. Clin Endocrinol Metab. 1986;15(3):411-51.
46. World Health Organization. Growth reference data for 5-19 years. 2016 [cited 2016 03 June].
47. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85(9):660-7.
48. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.
49. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
50. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Step 4 version. 09 Nov 2016.
51. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.
52. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.
53. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007 as amended by the Final Rule "Clinical Trials Registration and Results Information Submission". 21 September 2016.
54. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal

products for human use, article 11. Official Journal of the European Communities. 01 May 2001.

55. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.
56. The European Parliament and the Council of the European Council. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, article 41. Official Journal of the European Communities. 27 Dec 2006.
57. Association AD. 12. Children and Adolescents:. Diabetes Care. 2018;41(Suppl 1):S126-S36.
58. International Diabetes Federation. Global IDF/ISPAD guideline for Diabetes in Childhood and Adolescence. 2011.
59. Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2018;19 Suppl 27:178-92.
60. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40(12):1622-30.
61. Group IHS. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.
62. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40.
63. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.
64. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Avaliable from: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. 2009.
65. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin. 2009;25(4):929-42.
66. 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):450-5.
67. Basuyau JP, Mallet E, Leroy M, Brunelle P. Reference intervals for serum calcitonin in men, women, and children. Clin Chem. 2004;50(10):1828-30.

68. Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C, et al. Sporadic hypercalcitoninemia: clinical and therapeutic consequences. Endocr Relat Cancer. 2009;16(1):243-53.
69. Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M, et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer. 2007;14(2):393-403.

9.1.1 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.