

Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02963922
Sponsor trial ID:	NN8022-4272
Official title of study:	Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2 diabetes mellitus treated with basal insulin
Document date:	18 February 2019

16.1.1 Protocol and protocol amendments

List of contents

Protocol	Link
Appendix A - Monitoring of calcitonin.....	Link
Attachment I and II.....	Link
Protocol amendment 1 - Global	Link
Protocol amendment 2 - Global	Link
Protocol amendment 3 - Global	Link

*Redacted protocol
Includes redaction of personal identifiable information only.*

Protocol
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

14 September 2016
4.0
Final
1 of 123

Novo Nordisk

Protocol

Trial ID: NN8022-4272

SCALE™ Insulin

Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2 diabetes mellitus treated with basal insulin

Trial phase: 3b

Protocol originator



~~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 No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk.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.~~

Table of Contents

Table of Contents	2
Table of Figures	6
Table of Tables	6
List of abbreviations	7
1 Summary	11
2 Flow chart	15
3 Background information and rationale for the trial	21
3.1 Background information.....	21
3.2 Rationale for the trial.....	21
4 Objectives and endpoints	22
4.1 Objectives.....	22
4.2 Endpoints.....	22
4.2.1 Primary endpoints.....	22
4.2.2 Secondary endpoints.....	22
4.2.2.1 Confirmatory secondary endpoints.....	22
4.2.2.2 Supportive secondary endpoints.....	23
5 Trial design	25
5.1 Type of trial.....	25
5.2 Rationale for trial design.....	26
5.3 Treatment of subjects.....	27
5.3.1 Investigational medicinal product.....	27
5.3.2 Non-investigational medicinal products.....	28
5.3.2.1 Oral antidiabetic medication.....	28
5.3.2.2 Treatment with insulin throughout the trial.....	28
5.3.3 Counselling (intensive behaviour therapy).....	31
5.4 Treatment after discontinuation of trial product.....	32
5.5 Rationale for treatment.....	32
6 Trial population	34
6.1 Number of subjects.....	34
6.2 Inclusion criteria.....	34
6.3 Exclusion criteria.....	34
6.4 Randomisation criterion.....	36
6.5 Criteria for premature discontinuation of trial product.....	36
6.6 Withdrawal from trial.....	37
6.7 Subject replacement.....	37
6.8 Rationale for trial population.....	37
7 Milestones	39
8 Methods and assessments	40
8.1 Visit procedures.....	40
8.2 Subject-related information/assessments.....	42
8.2.1 Demography.....	42

8.2.2	Diabetes history and diabetes complications	42
8.2.3	Hypoglycaemia unawareness.....	43
8.2.4	Concomitant illness and medical history	43
8.2.5	Concomitant medication	44
8.2.6	Childbearing potential.....	44
8.2.7	Tobacco use	45
8.2.8	Amount of alcohol consumed	45
8.2.9	Weight history, including weight-related comorbidities.....	45
8.2.10	Barriers and motivation interview	45
8.2.11	7-day food diary in screening period	45
8.3	Efficacy assessments.....	45
8.3.1	Body weight.....	46
8.3.2	Height	46
8.3.3	Waist circumference	46
8.3.4	HbA _{1c}	46
8.3.5	Fasting plasma glucose	46
8.3.6	Vital signs (blood pressure)	47
8.3.7	Self-measured plasma glucose	47
8.3.8	7-point SMPG profile	47
8.3.9	Insulin dose.....	48
8.3.10	Clinical outcome assessments.....	48
8.4	Safety assessments.....	50
8.4.1	Physical examination	50
8.4.2	Eye examination	50
8.4.3	Adverse events.....	50
8.4.3.1	Medication error.....	51
8.4.3.2	Adverse events requiring additional data collection	51
8.4.4	Hypoglycaemic episodes	53
8.4.5	Vital signs (pulse).....	55
8.4.6	Electrocardiogram.....	55
8.4.7	Patient health questionnaire-9.....	56
8.4.8	Columbia suicidal severity rating scale	56
8.4.9	Breast and colon neoplasm follow up.....	56
8.5	Laboratory assessments	56
8.5.1	Laboratory assessments for efficacy	57
8.5.2	Laboratory assessments for safety	57
8.6	Other assessments	59
8.6.1	Trial product usage	59
8.6.2	Food record and tracking of physical activity.....	59
8.6.3	Diabetes diary	59
8.6.4	Training in the PDS290 pen-injector	60
8.6.5	Inquire about mood.....	60
8.7	Subject compliance	61
8.8	Additional safety assessments.....	61
8.8.1	Suspicion of acute pancreatitis.....	61
8.8.2	Suspicion of acute gallstone disease	62
8.8.3	Neoplasm	62
8.8.4	Hepatic event (suspicion of drug-induced liver injury)	62
8.8.5	Depression, suicidal ideation/behaviour	63

9	Trial supplies	65
9.1	Trial products	65
9.2	Labelling and directions for use	65
9.3	Storage	66
9.4	Drug accountability and destruction	66
9.5	Auxiliary supplies	67
10	Interactive web response system	68
11	Randomisation procedure and breaking of blinded codes	69
11.1	Breaking of blinded codes	69
12	Adverse events, and technical complaints and pregnancies	70
12.1	Definitions	70
12.1.1	Adverse event	70
12.1.2	Serious adverse event	71
12.1.3	Non-serious adverse event	72
12.1.4	Medication errors	72
12.1.5	Adverse events requiring additional data collection	73
12.1.6	Technical complaints	73
12.2	Reporting of adverse events	73
12.3	Follow-up of adverse events	76
12.4	Technical complaints and technical complaint samples	77
12.4.1	Reporting of technical complaints	77
12.4.2	Collection, storage and shipment of technical complaint samples	77
12.5	Pregnancies	78
12.5.1	Pregnancies in female subjects	78
12.6	Precautions and/or overdose	79
12.7	Committees related to safety	80
12.7.1	Novo Nordisk safety committee	80
13	Case report forms	81
13.1	Corrections to case report forms	81
13.2	Case report form flow	82
14	Monitoring procedures	83
15	Data management	84
16	Computerised systems	85
17	Statistical considerations	86
17.1	Sample size calculation	88
17.2	Definition of analysis sets	89
17.3	Primary endpoints	90
17.3.1	Analytical methods addressing the effectiveness estimand for the primary endpoints	90
17.3.1.1	Statistical model for the primary endpoint % weight change	90
17.3.1.2	Statistical model for the primary endpoint 5% responders	91
17.3.2	Handling of missing values for the effectiveness estimand	91
17.3.2.1	Handling of missing values at baseline	91
17.3.2.2	Handling of missing values at week 56	91
17.3.3	Analysis method addressing the efficacy estimand for the primary endpoints	93

17.3.4	Subgroup analyses for primary endpoints.....	94
17.4	Secondary endpoints	96
17.4.1	Confirmatory secondary endpoints	96
17.4.1.1	Description of the testing procedure to address the effectiveness estimand for primary and confirmatory secondary endpoints	97
17.4.2	Supportive secondary endpoints	99
17.4.2.1	Efficacy endpoints.....	99
17.4.2.2	Safety endpoints	99
18	Ethics	105
18.1	Benefit-risk assessment of the trial	105
18.2	Informed consent	108
18.3	Data handling.....	109
18.4	Information to subjects during trial.....	109
18.5	Premature termination of the trial and/or trial site.....	109
19	Protocol compliance	110
19.1	Protocol deviations	110
19.2	Prevention of missing data.....	110
19.3	Protocol compliance for Mexico.....	110
20	Audits and inspections	112
21	Critical documents	113
22	Responsibilities	114
23	Reports and publications.....	115
23.1	Communication of results	115
23.1.1	Authorship	116
23.1.2	Site-specific publication(s) by investigator(s)	116
23.2	Investigator access to data and review of results	116
24	Retention of clinical trial documentation.....	117
25	Institutional Review Boards/Independent Ethics Committees and regulatory authorities.....	118
26	Indemnity statement	119
27	References	120

Appendix A Monitoring of Calcitonin

Attachment I Global list of key staff and relevant departments and suppliers

Attachment II Country list of key staff and relevant departments, if applicable for the individual country

Table of Figures

	Page
Figure 5–1 Trial design	25
Figure 12–1 Reporting of AEs	75
Figure 17–1 Illustration of imputation approaches	95
Figure 17–2 Novo Nordisk classification of hypoglycaemia	101
Figure 17–3 ADA classification of hypoglycaemia	102

Table of Tables

	Page
Table 5–1 Dose escalation and treatment period	27
Table 5–2 Increase of basal insulin dose	29
Table 5–3 Decrease of basal insulin dose	29
Table 5–4 Bolus insulin adjustment	30
Table 8–1 Time points for 7-point SMPG profile	48
Table 9–1 Trial products	65
Table 9–2 Storage conditions	66
Table 17–1 Taxonomy of week 56 assessments being available or missing	87
Table 17–2 General specifications for sample size and power calculation	88
Table 17–3 Assumptions, marginal power and effective power for each confirmatory endpoint in the hierarchical testing procedure given an anticipated number of 400 randomised subjects	89
Table 17–4 Factors and covariates for the analysis of the primary endpoints	90
Table 17–5 Overview of handling of missing values	96
Table 17–6 Hierarchical order and type of statistical model to address the effectiveness estimand for primary and confirmatory secondary endpoints	98

List of abbreviations

AD	available drop-out
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransaminase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT	available on treatment
BMI	body mass index
CCDS	Company Core Data Sheet
CLAE	clinical laboratory adverse event
COA	clinical outcome assessment
CRF	case report form
C-SSRS	Columbia suicide severity rating scale
CTR	clinical trial report
DILI	drug-induced liver injury
DPP-IV-i	dipeptidyl peptidase-4 inhibitor
DUN	dispensing unit number
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FFA	free fatty acids
FSFV	first subject first visit
FPG	fasting plasma glucose
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist

HbA _{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high-density lipoprotein
hs-CRP	High sensitivity C-reactive protein
IBT	intensive behaviour therapy
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalised ratio
IRB	institutional review board
ITT	intention-to-treat
IWQoL-Lite for CT	Impact of Weight on Quality of Life-Lite for Clinical Trials Version
IWRS	interactive web response system
LAO	last available observation
LAO-OT	last available observation (of body weight) on randomised treatment
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LSFV	last subject first visit
LSLV	last subject last visit
MCS	mental component summary
MCID	Minimal Clinically Important Difference
MD	missing drop-out
MedDRA	Medical Dictionary for Drug Regulatory Activities
MEN2	multiple endocrine neoplasia type 2
MHP	Mental health professional
MI	Multiple Imputation
MMRM	mixed model for repeated measurements

MT	missing on treatment
MTC	medullary thyroid carcinoma
NPH	Neutral Protamine Hagedorn
NIMP	non-investigational medicinal products
NYHA	New York Heart Association
OAD	oral anti-diabetic (medication)
OR	odds ratio
PCS	physical component summary
PGI-C	Patients' global impression of change
PGI-S	Patients' global impression of status
PHQ-9	Patient Health Questionnaire-9
PYE	patient years of exposure
PYO	patient years of observation
SAE	serious adverse event
SAP	statistical analysis plan
sBP	systolic blood pressure
s.c.	subcutaneous(ly)
SD	standard deviations
SDV	source data verification
SGLT2i	sodium-glucose cotransporter-2 inhibitors
SIF	safety information form
SF-36	short form-36 version 2.0 acute
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TBL	total bilirubin
TC	total cholesterol
TG	triglycerides

TMM	Trial Materials Manual
TSH	thyroid stimulating hormone
UNL	upper normal limit
UNR	upper normal range
UTN	Universal Trial Number
VLDL	very low density lipoprotein
wANCOVA	weighted analysis of covariance
WC	waist circumference
WRSS	weight related sign and symptom measure

1 Summary

Objectives and endpoints

Primary objective

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on weight loss effectiveness in subjects with overweight or obesity and type 2 diabetes mellitus (T2DM) treated with a basal insulin and up to 2 oral antidiabetic (OAD) medications (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea).

Primary endpoints

- Change in body weight (%) from baseline to week 56
- Proportion of subjects losing at least 5% of baseline body weight at week 56

Secondary objectives

To establish the effects of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on relevant efficacy endpoints in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea)

To establish the safety and tolerability of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea)

Key secondary endpoints

- Proportion of subjects losing more than 10% of baseline body weight at week 56

Change from baseline to week 56 in:

- Waist circumference
- Systolic blood pressure
- HbA_{1c}
- Fasting plasma glucose
- Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical functioning score
- IWQoL-Lite for CT, mental/emotional functioning score

Trial design

This is a 56-week randomised, double-blind, multi-national, multi-centre, placebo-controlled and two-armed trial in subjects with overweight or obesity and T2DM treated with basal insulin and up to two OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea).

Subjects will be randomised in a 1:1 manner to receive either liraglutide 3.0 mg or placebo, as an adjunct to reduced-calorie diet and increased physical activity delivered as part of a comprehensive lifestyle intervention program (in this document referred to as Intensive Behaviour Therapy [IBT]). Subjects treated with sulphonylurea will be stratified between the two arms.

It is recommended that the dose of basal insulin is reduced by 15-20 % for all subjects with HbA_{1c} ≤ 8 % (at the investigator's discretion) at randomisation, followed by weekly adjustment of insulin dose with the aim to achieve same pre-breakfast meal target plasma glucose as well as similar glycaemic control in the two treatment arms. Insulin dose should not be reduced for subjects with HbA_{1c} > 8% to avoid unacceptable deterioration in glycaemic control.

Trial population

The planned number of subjects to be randomised is 400.

Key inclusion criteria

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Diagnosed with type 2 diabetes mellitus
3. Treatment with up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea),
4. Stable treatment with basal insulin according to its label (no requirement of minimum or maximum dose) for at least 90 days prior to screening, as judged by the investigator
5. HbA_{1c} 6.0-10.0% (both inclusive)
6. BMI ≥ 27 kg/m²
7. Age ≥ 18 years at the time of signing informed consent

Key exclusion criteria

1. Diagnosis of type 1 diabetes
2. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8 (see Section [8.2.3](#))
3. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator
4. Unable or unwilling to perform self-monitoring of plasma glucose according to the protocol and to keep a diabetes diary
5. Treatment with any hypoglycaemic medications other than OADs and basal insulin within the past 90 days prior to screening

6. Treatment with a DPP-IV inhibitor within the past 90 days prior to screening
7. Recent history of cardiovascular disease (myocardial infarction or stroke within the past 6 months), severe congestive heart failure (NYHA class III, IV), or second degree or greater heart block
8. Personal or family history of Medullary Thyroid Carcinoma (MTC) or Multiple Endocrine Neoplasia type 2 (MEN2)
9. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice)
For Germany: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner
10. Use in past 90 days of medications known to induce significant weight loss (e.g., prescription weight loss medications) or weight gain (e.g., chronic use of oral steroids, second generation antipsychotics)
11. History of pancreatitis (acute or chronic)
12. History of major depressive disorder within the past 2 years
13. Any lifetime history of a suicide attempt
14. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg).
15. History of malignancy (except for non-melanoma skin cancer) within the past 5 years

Assessments

Efficacy

- Weight
- Waist circumference
- Clinical outcome assessments (IWQoL-Lite for CT, Short Form 36 v2.0 acute)
- Glycaemic parameters (HbA_{1c}, fasting plasma glucose and self-measured plasma glucose)
- Blood pressure

Safety

- Adverse events
- Hypoglycaemic episodes
- Pulse
- ECG
- Biochemistry and haematology

Protocol
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

~~CONFIDENTIAL~~

Date: 14 September 2016
Version: 4.0
Status: Final
Page: 14 of 123

Novo Nordisk

Trial products

The following products will be delivered by Novo Nordisk A/S Denmark:

- Liraglutide 6 mg/mL, solution for injection, 3.0 ml PDS290 pen-injector
- Liraglutide placebo, solution for injection, 3.0 ml PDS290 pen-injector

	Screening	Randomisation	Dose Escalation		Maintenance period																	End-of-treatment	Follow-up ¹¹				
			3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			22	23	24	25
On site visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		
Weeks in relation to visit 2	-1	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	
Visit window, days	-7		±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
History of psychiatric disorders 8.2.4	x																										
Concomitant medication 8.2.5	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Tobacco use 8.2.7	x																										
Amount of alcohol consumed 8.2.8	x																										
Counselling ¹ 5.3.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
EFFICACY																											
Height 8.3.2	x																										
Body weight 8.3.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Waist circumference 8.3.3	x	x		x		x	x	x		x		x		x		x		x		x		x		x		x	
HbA _{1c} 8.3.4	x	x					x				x					x				x						x	
Fasting plasma glucose 8.3.5		x					x				x					x				x						x	
Self-measured plasma glucose (once-daily) ² 8.3.7		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	
7-point SMPG profile 8.3.8		x					x				x					x				x						x	
Vital signs (blood pressure) 8.3.4	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	
Lipids 8.5.1		x																								x	
Impact of Weight on Quality of Life-Lite for Clinical Trials Version 8.3.10		x				x		x		x		x								x						x	

	Screening	Randomisation	Dose Escalation		Maintenance period																	End-of-treatment	Follow-up ¹¹				
			3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			22	23	24	25
On site visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		
Weeks in relation to visit 2	-1	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	
Visit window, days	-7		±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Dispense and instruct in blood glucose (BG) meter use	x																										
Dispense BG meter auxiliaries	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	
Insulin dose adjustment ¹⁰ 5.3.2.2		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Collect, review and transcribe subject diary into eCRF 8.6.2 and 8.6.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Collect questionnaires	x	x				x		x		x		x					x			x					x		

¹Counselling is the intensive behaviour therapy (IBT)

²Based on self-measured plasma glucose (SMPG) records. In the first 5 weeks, the basal insulin dose should not exceed entry dose, and bolus insulin should not be initiated

³Only if not available within last 90 days before screening

⁴For women of childbearing potential: A negative pregnancy test (s-HCG) is required for inclusion

⁵A urine pregnancy test must be performed at any time during the trial if there is a suspicion of pregnancy or if a menstrual period is missed, or as required by local law

⁶Breast neoplasm follow up form is to be filled in by only female subjects

⁷Estimated Glomerular Filtration Rate (eGFR) is calculated at each visit with biochemistry. hs-CRP is only measured at Visit 2 and Visit 24.

⁸At screening a food diary is dispensed, which the subject should fill in for minimum 5 days before randomisation visit in order to meet the randomisation criterion. At all other visits paper diaries will be provided to the subject, if this is his/her preferred method for recording daily dietary intake

Protocol
Trial ID: NN8022-4272

UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

Date: 14 September 2016
Version: 4.0

Status:
Page:

Final
20 of 123 | **Novo Nordisk**

⁹Subject is not allowed to eat or drink at least eight hours overnight before attending a fasting visit (water consumption is allowed)

¹⁰Insulin dose should be decreased by 15- 20% at randomisation if $HbA_{1c} \leq 8\%$. For insulin adjustments after trial product is terminated, please refer to Section [5.4](#)

¹¹The follow up visit should be performed 30 days after the end of treatment as a minimum

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

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

3.1 Background information

Many patients with type 2 diabetes mellitus (T2DM) treated with oral antidiabetic medications (OADs) eventually require insulin to manage the progressive deterioration in glycaemic control³. However, weight gain commonly occurs with escalating insulin therapy, reducing patient satisfaction and treatment adherence⁴.

The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide is approved for the treatment of T2DM (1.2 mg and 1.8 mg) Victoza® and weight management (3.0 mg) Saxenda®. Through activation of the GLP-1 receptor, it stimulates insulin secretion in a glucose-dependent manner and reduces appetite and energy intake. Results from the SCALE™ Diabetes trial demonstrated that liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, is effective for weight loss in subjects with overweight or obesity and T2DM treated with 0-3 OADs (metformin, glitazone, sulphonylurea), and associated with improved glycaemic control, reduction in the use of hypoglycaemic medications, and risk of hypoglycaemia comparable to what is seen with lower doses of liraglutide⁵.

3.2 Rationale for the trial

Previous results suggest that liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity might also be beneficial for patients with overweight or obesity and T2DM treated with basal insulin. Through its mechanisms of action, it is presumed to facilitate adherence to behaviour change, and by reducing body weight, improve physical functioning, such that increased physical activity is easier in those who cannot exercise initially⁶. Moreover, the anticipated lower insulin requirement with liraglutide vs. placebo is expected to further amplify weight loss and reduce exercise-related hypoglycaemia, both of which are barriers to effective and sustainable weight management.

There is currently no data to support use of liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, for weight management in patients with T2DM treated with insulin⁷⁻⁹. However, the combination of basal insulin and liraglutide 1.8 mg is approved for maintaining glycaemic control in patients with T2DM^{10,11}.

For an assessment of benefits and risks of the trial, see Section [18.1](#)

4 Objectives and endpoints

4.1 Objectives

Primary objective

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on weight loss effectiveness in subjects with overweight or obesity and type 2 diabetes mellitus (T2DM) treated with a basal insulin and up to 2 oral antidiabetic (OAD) medications (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea).

Secondary objectives

- To establish the effects of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on relevant efficacy endpoints in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea)
- To establish the safety and tolerability of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea)

4.2 Endpoints

4.2.1 Primary endpoints

Co-primary endpoints addressing the primary objective:

- Change in body weight (%) from baseline to week 56
- Proportion of subjects losing at least 5% of baseline body weight at week 56

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints addressing the secondary efficacy objective:

- Proportion of subjects losing more than 10% of baseline body weight at week 56

Change from baseline to week 56 in:

- Waist circumference
- Systolic blood pressure
- HbA_{1c}
- Fasting plasma glucose
- IWQoL-Lite for CT, physical functioning score
- IWQoL-Lite for CT, mental/emotional function score

Only primary and confirmatory secondary endpoints have been selected for disclosure (e.g. clinicaltrials.gov and EudraCT).

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline to week 56 in:

- Total daily basal insulin dose (% of pre-trial dose in U)
- Total daily basal insulin dose (U/kg)
- Total daily insulin dose (U)
- Total daily insulin dose (U/kg)
- 7-point self-measure plasma glucose (SMPG) profile, mean daytime glucose value
- Diastolic blood pressure
- Lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides [TG], free fatty acids [FFA])
- Short Form-36 v2.0 acute (SF-36) (physical component summary (PCS), mental component summary (MCS) and subdomains)
- Weight related sign and symptom (WRSS) measure, total score

Proportion of subjects with the following at week 56:

- HbA_{1c} <7% and weight loss ≥5%
- HbA_{1c} <7%, weight loss ≥5% and no documented symptomatic hypoglycaemia
- ≥ 2 T-score points increase from baseline in SF-36 PCS
- ≥ 3 T-score points increase from baseline in SF-36 MCS

Supportive secondary safety endpoints

- Adverse events from randomisation until and including the follow-up visit
- Hypoglycaemic episodes until and including the follow-up visit

Change from baseline to week 56 in:

- Physical examination

Protocol
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

~~CONFIDENTIAL~~

Date:	14 September 2016	Novo Nordisk
Version:	4.0	
Status:	Final	
Page:	24 of 123	

- Resting pulse
- ECG
- Laboratory measurements

5 Trial design

5.1 Type of trial

This is a 56-week randomised, double-blind, multi-national, multi-centre, placebo-controlled and two-armed trial in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea).

Subjects will be randomised in a 1:1 manner to receive either liraglutide 3.0 mg or placebo, as an adjunct to reduced-calorie diet and increased physical activity delivered as part of a comprehensive lifestyle intervention program (in this document referred to as IBT) (see [Figure 5-1](#) and Section [5.3.3](#)). Subjects treated with sulphonylurea will be stratified between the two arms.

It is recommended that the dose of basal insulin is reduced for all subjects by 15-20 % for subjects with $HbA_{1c} \leq 8\%$ (at the investigator's discretion) at randomisation, followed by weekly adjustment of insulin dose with the aim to achieve same pre-breakfast meal target plasma glucose as described in Section [5.3.2.2](#), as well as similar glycaemic control in the two treatment arms. Insulin dose should not be reduced for subjects with $HbA_{1c} > 8\%$ at randomisation to avoid unacceptable deterioration in glycaemic control.

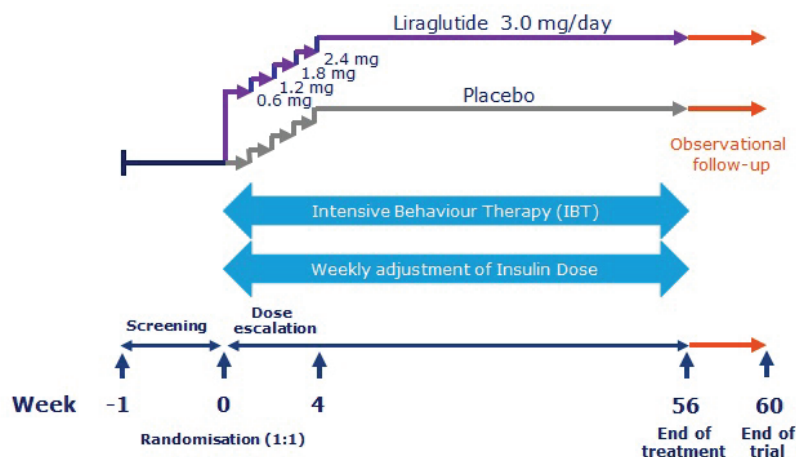


Figure 5-1 Trial design

Adjustment of insulin dose may be initiated one week after randomisation; however, in the first five weeks after randomisation, the basal insulin dose should not exceed the pre-trial dose and bolus insulin should not be initiated, unless deemed necessary by investigator to control unacceptable hyperglycaemia (see Section [5.3.2.2](#)).

5.2 Rationale for trial design

A randomised controlled and double-blinded trial design is chosen to minimise bias in the assessment of the effect and safety of liraglutide 3.0 mg vs placebo, both as an adjunct to IBT.

Subjects discontinuing randomised treatment prematurely are encouraged to stay in the trial and continue IBT, in alignment with current clinical recommendations¹² and to minimise missing data. However, if a discontinued subject do not wish to attend the IBT visits, the investigator should still encourage the subject to come back for V24.

Weekly dose escalation of the trial drug (see Section [5.3.1](#)) is included in accordance with the Saxenda[®] prescribing information⁷⁻⁹. Based on the weight loss time course in SCALE Diabetes[™] (subjects on 0-3 OADs), a trial duration of 56 weeks is considered sufficient to measure the majority of the weight loss curve¹³.

A 30 day follow-up period for safety is included after the 56 weeks treatment period, in accordance with FDA guidance¹⁴.

In accordance with clinical guidelines^{12, 15, 16, 17} IBT consisting of frequent structured counselling, reduced-calorie diet and increased physical activity is an integrated part of the trial design.

Reduction of insulin dose at randomisation is recommended to avoid unnecessary hypoglycaemia associated with the trial's interventions: 1. the lifestyle intervention which, through weight loss, will improve insulin sensitivity and consequently insulin requirements and/or 2. initiation of liraglutide 3.0 mg (Saxenda[®]), which has direct glucose-lowering effects. Conversely, insulin dose will be adjusted weekly starting one week after randomisation to avoid unnecessary hyperglycaemia associated with the initial reduction of insulin dose. This will primarily affect subjects in the placebo group, where lifestyle changes and weight loss are the main sources of improved glycaemic control. The dose of sulphonylurea may be reduced by 50% at investigator's discretion in patients using this OAD since hypoglycaemic events are more frequent when combining liraglutide with sulphonylurea than with other OADs. Furthermore, subjects treated with sulphonylurea will be stratified between the two arms.

Weekly adjustment will also increase the likelihood of achieving similar glycaemic control in the two treatment arms. This is important since improvement/deterioration of glycaemic control directly impact insulin requirements and indirectly, through changes in insulin dose, body weight changes. For information on dose adjustment algorithm, see Section [5.3.2.2](#).

5.3 Treatment of subjects

5.3.1 Investigational medicinal product

The investigational medicinal product (IMP) is injected subcutaneously (s.c.) once daily for 56 weeks. Dose escalation of trial product will take place during the first 4 weeks after randomisation (see [Table 5-1](#)).

Table 5-1 Dose escalation and treatment period

IMP	Dose	Duration
Liraglutide/placebo	0.6 mg	1 week
Liraglutide/placebo	1.2 mg	1 week
Liraglutide/placebo	1.8 mg	1 week
Liraglutide/placebo	2.4 mg	1 week
Liraglutide/placebo	3.0 mg	52 weeks
Follow up period	0 mg	4 weeks

If the subject does not tolerate an increased dose during the dose escalation window, the investigator can delay the dose escalation by maintaining the subject at the current dosage step for one additional week. Such a delay is allowed only once during dose escalation (i.e. maximum allowed time for complete dose escalation to 3.0 mg is 5 weeks). After reaching the maintenance dose (3.0 mg), the dose and dosing frequency should not be changed.

If a single dose is missed, the once-daily regimen should be resumed as prescribed at the next scheduled dose. If more than 3 consecutive days have elapsed since the last dose, subject should re-initiate dose escalation, (e.g. restart the dosing at 0.6 mg and follow the dose escalation schedule again). This is done to reduce the occurrence of gastrointestinal symptoms associated with re-initiation of treatment.

NB: Additional or increased dose should not be taken to make up for missed doses.

Trial product can be taken at any time of day, irrespective of timing of meals. Trial product can be injected s.c. in the abdomen, thigh, or upper arm. The injection site and timing can be changed without dose adjustment.

NB: Trial product must not be administered intravenously or intramuscularly.

If a subject cannot tolerate the 3.0 mg dose, or if any of the other treatment discontinuation criteria are met, then treatment with trial product must be discontinued. For treatment discontinuation reasons, please refer to Section [6.5](#). In case this happens, it is acceptable to restart trial product (at the discretion of investigator and according to the local clinical practice); the dose must be escalated according to the algorithm above, and date of restart and rationale must be documented in the CRF.

5.3.2 Non-investigational medicinal products

Non-investigational medicinal products (NIMP) comprise the following: OADs and insulin.

5.3.2.1 Oral antidiabetic medication

Any approved and marketed metformin, glitazone, SGLT-2 inhibitor or sulphonylurea product or combination products are allowed. Subjects treated with dipeptidyl peptidase-IV (DPP-IV) inhibitors are excluded from participating in the trial since DPP-IV inhibitors and GLP-1 receptor agonists should not be combined.

To mitigate sulphonylurea induced hypoglycaemia, subjects treated with sulphonylurea may be at randomisation be asked to reduce the sulphonylurea dose by 50% at investigator's discretion. The type and dose of other OADs must be kept constant throughout the trial, unless unacceptable hypoglycaemia occurs and cannot be managed by reduction of the basal insulin dose.

In case the type of OAD becomes unavailable during the course of the trial, it is allowed per the discretion of the investigator to shift to an alternative treatment within the same class.

5.3.2.2 Treatment with insulin throughout the trial

Any approved and marketed basal insulin (NPH insulin or insulin analogue) is allowed, at any dose, if used according to its prescribing information at screening. Once-daily or twice-daily dosing is allowed, according to dosing schedule at baseline.

To reduce the risk of hypoglycaemia associated with liraglutide 3.0 mg and lifestyle intervention, it is recommended that the dose of basal insulin is reduced by 15-20 % for subjects with HbA_{1c} ≤ 8 % (at investigator's discretion) at randomisation. Furthermore, the basal dose should not exceed the pre-trial insulin dose in the first five weeks of liraglutide escalation, unless deemed necessary by investigator to treat unacceptable hyperglycaemia.

During the trial, subjects will be required to perform self-measured plasma glucose (SMPG) on 3 consecutive days, each week prior to basal insulin adjustment and enter the values into the subject diabetes diary. In the weeks where no site visits are planned, subjects will adjust their insulin dose themselves, according to the algorithm described below ([Table 5-2](#), [Table 5-3](#), and [Table 5-4](#)). These algorithms are provided to the subject in the diary and is part of the diabetes diary training. In the weeks where phone- or face-to-face contact is conducted, investigator will review previous self-adjustments, and perform adjustment for the current week.

The insulin dose adjustments recorded in the diabetes diary, must be entered in the electronic case report form (eCRF).

Insulin dose adjustments

The aim of this trial is to demonstrate safety and effect of liraglutide 3.0 mg in subjects with T2DM treated with basal insulin. To this end, reaching similar levels of glycaemic control is important, regardless of background medication. Therefore, trial subjects are encouraged, as appropriate, to adjust insulin doses according to the below algorithm – with dose increase based on the mean of the three pre-breakfast SMPGs measured, and dose decrease based on at least one of the three pre-breakfast plasma glucose values equal to or below 3.9 mmol/L (70 mg/dL).

Subject using once daily basal insulin will measure SMPG before breakfast and adjust their dose based on the 3 SMPGs measured on three consecutive days prior to dose adjustment. It is recommended to adjust the basal insulin dose once weekly at the investigator’s discretion.

Subject using twice daily basal insulin will measure pre-breakfast and pre-dinner SMPG and adjust their evening dose based on the three pre-breakfast SMPGs, and their morning dose based on the three pre-dinner SMPGs measured on three consecutive days prior to dose adjustment.

Table 5–2 Increase of basal insulin dose

Mean of three pre-breakfast or pre-dinner SMPG		Increase of basal insulin dose
mmol/L	mg/dL	U
4.0 – 5.0	71 – 90	No adjustment
5.1 – 7.0	91 – 126	+ 2
7.1 – 8.0	127 – 144	+ 4
8.1 – 9.0	145 – 162	+ 6
> 9.0	> 162	+ 8

Table 5–3 Decrease of basal insulin dose

Lowest of three pre-breakfast or pre-dinner SMPG		Reduction of basal insulin dose
mmol/L	mg/dL	U
< 3.1	< 56	- 4 (or 10 % if the dose > 45 U)
3.1 – 3.9	56 – 70	- 2 (or 5 % if the dose >45 U)

Intensification with bolus insulin

Initiation of bolus insulin can be considered after the 5-week escalation period, and only after optimisation of basal insulin dose. These are the steps to take in situations where maximum fasting glycaemic control has been achieved and overall glycaemic control is still sub-optimal, and the investigator judges that bolus insulin is a necessary safety precaution.

Once bolus insulin is initiated, subjects will start measuring 4 SMPGs – pre-breakfast, pre-lunch, pre-dinner and at bedtime, on three consecutive days a week, prior to dose adjustment. It is recommended to adjust the bolus insulin dose once weekly at the investigator's discretion. Bolus dose adjustments may be performed according to the below algorithm ([Table 5-4](#)), using the frequency of pre-prandial and bedtime plasma glucose values as follows:

- Pre-breakfast bolus insulin should be adjusted according to the 3 consecutive pre-lunch SMPGs in the preceding 3 days
- Pre-lunch bolus insulin should be adjusted according to the 3 consecutive pre-dinner SMPGs in the preceding 3 days
- Pre-dinner bolus insulin should be adjusted according to the 3 consecutive bedtime SMPGs in the preceding 3 days

Table 5-4 Bolus insulin adjustment

SMPG values		Adjustment	Frequency rule
mmol/L	mg/dL	U	
≤ 3.9	≤ 70	- 1	≥1 SMPG below target
4.0-6.0	71-108	0	0-1 SMPGs above target No SMPG below target
> 6.0	> 108	+ 1	≥2 SMPGs above target No SMPG below target

Additional face-to-face visits may be scheduled if deemed necessary by site staff to achieve or maintain acceptable glycaemic control.

5.3.3 Counselling (intensive behaviour therapy)

The intensive behaviour therapy (IBT) will consist of counselling on diet, physical activity and other lifestyle modifications. The content of the IBT is based on an abbreviated version of the Diabetes Prevention Program (DPP)^{18, 19} employing the 5A counselling framework (Ask, Assess, Advise, Agree, Assist)^{20, 21}. IBT will be delivered by a registered dietician or similarly qualified healthcare professional according to local standard. The individual performing the IBT is called interventionist in this protocol. Interventionists will be trained in obesity and its behavioural management, prior to beginning the trial and will be provided on-going assistance and share better practice in how to perform IBT during the trial.

Subjects will attend a total of 23 counselling sessions during the 56 weeks period. The structure and content of each IBT session is specified in an IBT guide, consisting of an interventionist part and a subject hand out. Generally each IBT session will begin with the subject being weighed and informed of the weight change. Then the subject and interventionist will review the subject's completion of food and physical activity records (see Section 8.6.2) and the interventionist will assist with solving individual problems.

In addition to the above, each IBT session will cover a specific topic, for example, advice on diet or physical activity as well as lifestyle modification (e.g., challenging negative thoughts, obtaining social support). Most of the topics will be accompanied by a homework assignment from the IBT guide to be completed before the next session with the interventionist.

IBT sessions that cannot be completed on-site (because of illness, travel, etc.), may be completed by phone. However, this will be allowed only in exceptional cases.

Calorie targets

Caloric deficit and diet composition are aligned with clinical evidence-based guidelines for management of overweight and obesity in adults¹⁶.

Daily caloric target throughout the trial for subjects should be based on body weight at randomisation:

- Subjects weighing less than 200 lb (~90 kg) will be prescribed a diet of 1200 kcal/day
- Subjects weighing between 200 lb and 300 lb (~135 kg) will be prescribed a diet calculated as:
*Daily caloric target (kcal) = body weight (lb) * 6 (kcal/lb) or*
*Daily caloric target (kcal) = body weight (kg) * 13.23 (kcal/kg)*
- Subjects weighing more than 300 lb will be prescribed 1800 kcal/day

The initial caloric target will be kept throughout the trial. If a subject achieves a body mass index (BMI) ≤ 22 kg/m², the recommended energy intake will be re-calculated with no caloric deficit for the remainder of the trial.

The diet will consist of conventional foods with approximately 15-20% kcal from protein, 20-35% from fat, and the remainder from carbohydrate. Carbohydrate intake should be monitored by the interventionist. Carbohydrate intake from vegetables, fruits, whole grains, legumes and dairy products should be advised²².

Subjects will be instructed to record their food and calorie intake daily (see Section [8.6.2](#)).

Physical activity targets

All subjects will initially be prescribed 100 minutes physical activity per week (e.g., walking or similar aerobic activity). Subjects should be physically active in bouts of >10 minutes in duration with moderate intensity (such as brisk walking), and the physical activity should be spread equally across 4-5 days each week. Physical activity should progress gradually by 25 minutes every 4 weeks until 250 minutes/week, consistent with targets required for maintenance of lost weight²².

Subjects will be instructed to record their physical activity daily, see Section [8.6.1](#).^{18.20}

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, the subject may be switched to a suitable marketed product at the discretion of the investigator.

After premature discontinuation of trial product (temporary/permanent), the subject should still remain in the trial and follow the IBT sessions and site visits if possible, see Section [8.1](#). In this case, the investigator must note down the current treatment in the medical record and eCRF. If the subject has re-started the trial product, the investigator must note down details in the medical record and eCRF, see Section [5.3.1](#).

5.5 Rationale for treatment

Subjects are treated for a period of 56 weeks in order to be able to evaluate the full effect of treatment with liraglutide 3.0 mg on the primary and secondary endpoints.

The comparator in the trial is placebo in order to evaluate the absolute safety and efficacy of liraglutide 3.0 mg.

Combining frequent behavioural counselling, highly structured hypo-caloric diets and increased physical activity is an effective tool for achieving and maintaining weight loss. It has been shown to be more effective than less intensive lifestyle modification programs for inducing weight loss²³, and

Protocol
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

~~CONFIDENTIAL~~

Date: 14 September 2016
Version: 4.0
Status: Final
Page: 33 of 123

Novo Nordisk

combining IBT and pharmacologic treatment leads to more weight loss than pharmacologic treatment alone²⁴.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised: 400

For Mexico: The estimated number of subjects to be randomised in Mexico is 30.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Diagnosed with type 2 diabetes mellitus
3. Treatment with up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor or sulphonylurea)
4. Stable treatment, at the discretion of the investigator, with any basal insulin according to its label (no requirement of minimum or maximum dose) for at least 90 days prior to screening
5. HbA_{1c} 6.0-10.0% (both inclusive)
6. BMI ≥ 27 kg/m²
7. Age ≥ 18 years at the time of signing informed consent
8. Maximum 5 kg self-reported weight loss within the past 90 days since screening
9. Increased physical activity is considered to be safe as judged by the investigator

6.3 Exclusion criteria

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

1. Diagnosis of type 1 diabetes mellitus
2. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke’s questionnaire question 8
3. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator
4. Unable or unwilling to perform self-monitoring of plasma glucose according to the protocol and to keep a diabetes diary
5. Treatment with any hypoglycaemic medications other than OADs and basal insulin within the past 90 days prior to screening
6. Treatment with a DPP-IV inhibitor within the past 90 days prior to screening
7. Recent history of cardiovascular disease (myocardial infarction or stroke within the past 6 months), severe congestive heart failure (NYHA class III, IV), or second degree or greater heart block
8. Hypersensitivity to liraglutide or any product components

9. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation
10. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 60 ml/min/1.73 m² as defined by KDIGO 2012 classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening
11. Personal or family history of Medullary Thyroid Carcinoma (MTC) or Multiple Endocrine Neoplasia type 2 (MEN2)
12. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice)
For Germany: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner
13. Uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) > 6 mIU/L or < 0.4 mIU/L (at screening visit)
14. Use in past 90 days since screening of medications known to induce significant weight loss (e.g., prescription weight loss medications) or weight gain (e.g., chronic use of oral steroids, second generation antipsychotics)
15. History of (or plans for) weight loss surgery (e.g. bariatric, intra-gastric balloons, maestro system) or implant of weight loss device (e.g., Reshape, vBloc). However, liposuction and/or abdominoplasty performed > 1 year before screening is allowed
16. History of pancreatitis (acute or chronic)
17. History of major depressive disorder within the past 2 years since screening
18. Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
19. A Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15 at screening or randomisation
20. Any lifetime history of a suicide attempt
21. Any suicidal behaviour within the past 30 days since screening
22. Any suicidal ideation of type 4 or 5 on the Columbia-suicide severity rating scale (C-SSRS) within the past 30 days at screening or randomisation
23. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg)
24. History of malignancy (except for non-melanoma skin cancer) within the past 5 years
25. Any disorder, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise subject's safety or compliance with the protocol
26. Known or suspected abuse of alcohol or narcotics
27. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures, including dietary changes and physical activity
28. Subjects from the same household participating in the trial

29. Participation in any clinical trial with or without an investigational medicinal product within the past 90 days before screening
30. Previous participation in this trial. Participation is defined as signed informed consent

6.4 Randomisation criterion

1. Have kept a food diary for at least 5 days (minimum one entry per day) in the period between screening and randomisation

To be randomised, the above randomisation criterion must be answered “yes”.

6.5 Criteria for premature discontinuation of trial product

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial regardless of adherence to randomised treatment, adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial or withdraw consent are considered as withdrawn from the trial (see Section [6.6](#)).

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

The subject must be prematurely discontinued from trial product if the following applies:

1. Included in the trial in violation of any of the inclusion and/or exclusion criteria and/or randomisation criterion
2. Safety concern (not covered by any of below criteria) or unacceptable intolerability to trial product, as judged by the investigator
3. Hypersensitivity to trial product(s). If a hypersensitivity reaction occurs, discontinue trial product and other suspect medications
4. More than one episode of severe hypoglycaemia, or repeated episodes of documented symptomatic hypoglycaemia (ADA classification), despite lowering of insulin dose (as judged by investigator)
5. Pregnancy
6. Intention of becoming pregnant
7. Suspicion of pancreatitis (see Section [8.4.3.2](#) and [8.8.1](#))
8. Suspicion of acute gallstone disease (see Section [8.4.3.2](#) and [8.8.2](#))
9. Suspicion of drug-induced liver injury (DILI) (see Section [8.4.3.2](#) and [8.8.4](#))
10. Calcitonin ≥ 100 ng/L
11. Psychiatric disorder(s) that cannot be adequately treated with psycho- and/or pharmacotherapy (see Section [8.4.3.2](#), [8.6.5](#) and [8.8.5](#))
12. Initiation of anti-obesity medication and/or (plans for) weight loss surgery
13. Initiation of treatment with GLP-1 receptor agonist or DPP-IV inhibitors

14. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product

See Section [8.1](#) for procedures to be performed for subjects discontinuing trial product prematurely.

It is allowed for subjects meeting the premature discontinuation criteria or who have wished to discontinue prematurely to be restarted on the trial product should the suspicion not be confirmed or if the condition has been resolved at the investigator's discretion. Trial product may be restarted for subjects meeting discontinuation criteria 8 should the gallbladder be removed.

6.6 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. See Section [8.1](#) for procedures to be performed for subjects withdrawing consent. The trial drug cannot be re-initiated if the consent has been withdrawn.

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

6.7 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

6.8 Rationale for trial population

Subjects with overweight or obesity and T2DM treated with any basal insulin (with or without up to 2 OADs) were selected for this trial, in alignment with the trial objective. While previously shown to be efficacious and generally well-tolerated in subjects with overweight or obesity and T2DM treated with 0-3 OADs, as an adjunct to a reduced-calorie diet and increased physical activity, liraglutide 3.0 mg has not previously been studied in subjects with overweight or obesity with T2DM treated with basal insulin.

Due to insulin resistance, these patients are often difficult to treat and require high insulin doses to maintain glycaemic control. Escalating insulin dose results in weight gain and reduced patient satisfaction and treatment adherence⁴. By contrast, weight loss improves insulin sensitivity and reduces the use of concomitant diabetes medication (including insulin) and related cost²⁵, but may be difficult to achieve by lifestyle intervention alone²⁶.

To reflect clinical practice, all types of basal insulin products are allowed, at any dose and dosing regimen. Likewise, OAD commonly used by subjects treated with basal insulin will be allowed as

per the inclusion criteria. Subjects are included after treatment with basal insulin for at least 90 days in order to reach effective dose. Subjects treated with DPP-IV inhibitors are excluded from participating in the trial since DPP-IV inhibitors and GLP-1 receptor agonists should not be combined.

Improvement in glycaemic control is not the main focus of this trial (design aimed at achieving similar glycaemic control in both treatment arms), but in recognition of the anticipated glucose-lowering associated with treatment, approximately 1.3% from baseline in the SCALE diabetes trial¹³, a minimum entry HbA_{1c} of 6% is required.

Likewise, a maximum entry HbA_{1c} will allow for inclusion of patients at high unmet need for weight loss, improvement in glycaemic control and insulin dose reduction. The anticipated lower insulin dose requirement with liraglutide 3.0 mg vs. placebo is expected to further amplify weight loss whilst also reducing frequency of hypoglycaemia, both of which reduce exercise-related hypoglycaemia^{27,28}. These are normally considered barriers to effective and sustainable weight management in patients with insulin-treated T2DM.

7 Milestones

Planned duration of recruitment period 16 weeks.

End of trial is defined as last subject last visit (LSLV).

Recruitment

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart, see Section [2](#).

Trial registration

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure²⁹, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)³⁰, the Food and Drug Administration Amendment Act³¹, European Commission Requirements^{32,33} and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart, see Section [2](#).

Informed consent must be obtained before any trial-related activity; see Section [18.2](#).

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

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

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

Fasting requirements

The subjects should be fasting when attending some visits, please see flow chart (Section [2](#)). Fasting is defined as at least 8 hours without food and drink intake, except water and other prescribed medication. Trial product and other glucose lowering agents should be withheld on the day of the visit until blood sampling have been performed. If the subject attends a fasting visit in a non-fasting state the blood sampling should be re-scheduled within the visit window.

Screening failures

For screening failures, the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section [12](#). A screening failure session must be made in the IWRS. The case book must be signed.

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

Premature discontinuation of trial product

The subject may discontinue trial product for several different reasons and after different treatment durations.

If a subject meets a discontinuation criterion, the trial product must be immediately discontinued and the date should be noted in the medical records and eCRF. Discontinuation can be either temporary or permanent. The last paragraph of Section [6.5](#) outlines which discontinuation can be considered temporary. The investigator must also note down the date in the medical record and eCRF once there is resolution and the subject has re-started the trial product.

The subject may also wish to discontinue trial product temporarily or permanently, irrespective meeting any criteria. Discontinuation of treatment with trial product, whether temporary or permanent, must not prompt the investigator to withdraw the subject from the trial. Instead, the subject should maintain adherence to trial visits and procedures to the extent possible.

In cases where the subject is not willing to attend all scheduled visits after discontinuation of trial product, efforts must be made to collect as much of the scheduled data as possible. Especially important is collection of the data points (primarily) at visit 24 (week 56). Statistical considerations emphasizing the importance can be found in Section [17](#).

Premature trial product discontinuation should be registered in the eCRF and in IWRS. The trial product can be interrupted by performing a 'treatment status' session in IWRS, to indicate subject should no longer receive trial product. The primary reason for discontinuation of trial product must be specified when recording the treatment discontinuation in the eCRF. If the discontinuation of trial product is judged permanent or of a longer period, drug accountability until discontinuation must be performed in IWRS.

If the subject has previously discontinued trial product, it is possible, at the discretion of the investigator and at the wish of the subject, to re-initiate treatment with trial product. This will only apply if it can be confirmed that the subject has not withdrawn consent, does not fulfil any of the criteria, leading to permanent discontinuation or if a criterion leading to temporary discontinuation has been resolved. A 'treatment status' session is performed in the IWRS, to indicate that the subject should again receive trial product. See Section [10](#) for registration in IWRS. This should be further noted in the medical records and eCRF.

Withdrawal from trial

A subject who wishes to withdraw their consent must be withdrawn from the trial. If a subject wants to withdraw consent, the investigator must aim to undertake procedures similar to those for end-of-treatment visit, as soon as possible. If the subject agrees, the follow-up visit must be performed at least 30 days after discontinuation of trial product.

The end-of-trial form in the eCRF must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. The investigator must perform a 'treatment status' session in IWRS and discontinue trial product for this subject. The case book must be signed.

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

Lost to follow-up

If a subject loses contact with the study staff or does not come for visit 24 or visit 25, attempts must be made to locate the subject and obtain relevant safety information. A subject cannot be deemed lost to follow-up until at least substantial contacts with family/relatives/family physician have been attempted. Subject information maybe retrieved from other health care professionals, medical records or publicly available records. A subject will only be considered lost to follow-up in case vital status cannot be determined at the time of visit 25 for that subject.

8.2 Subject-related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

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

8.2.2 Diabetes history and diabetes complications

Diabetes history and diabetes complications will be recorded at screening and consists of:

- Date of diagnosis of T2DM
- Information regarding diabetes complications including date of onset in case of:
 - Diabetic retinopathy
 - Diabetic neuropathy
 - Diabetic nephropathy
 - Macroangiopathy (including peripheral vascular disease)

Diabetes history and diabetes complications, must be recorded on the designated form.

8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness must be recorded at screening according to Clarke's questionnaire, question 8³⁴. The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always. Subjects answering 'never, rarely or sometimes' are considered as having reduced awareness of hypoglycaemia.

8.2.4 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the screening visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product. The disease under investigation (T2DM) should not be entered as it is captured under diabetes history and diabetes complications.

Medical history is a medical event that the subject has experienced in the past. Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history described below should only be entered on the specific forms.

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

Any change to a concomitant illness should be recorded during the trial. This also includes changes to diabetes history and diabetes complications. Any clinically significant worsening of a concomitant illness must be reported as an AE.

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

The specific medical history described below should be entered on the specific forms in the eCRF:

History of gallstone disease

Information related to gallstone disease (i.e., gallstone disease and cholecystectomy) must be recorded.

History of breast neoplasm

Information related to history of breast neoplasms must be recorded for all female subjects. Information regarding menopausal status, previous mammograms and outcome, first degree relatives with breast cancer and predisposing factors (alcohol intake above recommended local

guidelines, hormone replacement therapy, age of menarche, number of births, maternal age at first birth, and if the subject ever breastfed) should be recorded.

History of colon neoplasm

Information related to history of colon neoplasms, previous endoscopic examination(s) of the colon, history of inflammatory bowel disease, and first degree relatives with colon neoplasms must be recorded.

History of psychiatric disorders

Information related to psychiatric disorders (specifically history of depression, substance and alcohol abuse, suicidal ideation/behaviour, anxiety, mood disorders, insomnia, or sleep disorders) must be recorded.

8.2.5 Concomitant medication

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

Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each visit as they occur. The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

The products described as NIMP (see Section [5.3.2](#)) are also recorded as concomitant medication in the eCRF. However the adjustments of insulin doses performed during the trial will be recorded in the designated form and these must be assessed by the investigator.

If a change in concomitant medication is due to an AE, then this must be reported according to Section [12](#). If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.6 Childbearing potential

It must be recorded in the eCRF whether female subjects are of childbearing potential.

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section [8.5.2](#). Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1 week after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

8.2.7 Tobacco use

Details of tobacco use must be recorded at visit 1. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.2.8 Amount of alcohol consumed

Details of alcohol use must be recorded at visit 1. Alcohol consumption should be collected. Alcohol use is defined as consumption of minimum one unit of alcohol per week on an average.

8.2.9 Weight history, including weight-related comorbidities

Information regarding maximum lifetime weight, progression of weight pattern, family history of weight and previous weight loss attempts (e.g., maximum weight loss) must be recorded for all subjects.

8.2.10 Barriers and motivation interview

The barriers and motivation interview identifies barriers to lifestyle change and compliance with the protocol. The interview guide will ensure that these are addressed during IBT sessions. The interview guide will be available in local language.

8.2.11 7-day food diary in screening period

A food diary will be dispensed to the subjects at the screening visit to ensure that randomised subjects are able to comply with the protocol requirements for daily recording of food intake. The subjects are expected to fill out the food diary for at least 5 days in the period between screening and randomisation.

8.3 Efficacy assessments

All assessments and samples collected at randomisation will be considered as baseline for efficacy, unless otherwise specified.

8.3.1 Body weight

The body weight should be measured at all visits without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale to the nearest 0.1 kg or lbs using the same scale throughout the trial. The scale must be calibrated yearly as a minimum.

Body mass index will be calculated by the eCRF from visit 1 data and must be in accordance with inclusion criterion #6. BMI will be calculated as follows:

$BMI = \text{weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}$ or

$BMI = (\text{weight (lb)} / \text{height}^2 \text{ (inch}^2\text{)}) * 703$

8.3.2 Height

Height is measured at screening without shoes to the nearest cm or inch with one decimal.

8.3.3 Waist circumference

The waist circumference will be measured at the specified visits (see Section [2](#)) and is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest.

Waist circumference is measured in the horizontal plane and rounded to the nearest cm or inch using a non-stretchable measuring tape. The same measuring tape should be used throughout the trial.

The subject should be measured in a standing position and wearing light clothing. The subject should be standing, feet together with arms at the side and waist accessible. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally.

8.3.4 HbA_{1c}

Blood samples will be drawn at the specified visits (see Section [2](#)) for measurement of HbA_{1c}.

8.3.5 Fasting plasma glucose

FPG is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, see Section [8.1](#).

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

8.3.6 Vital signs (blood pressure)

For blood pressure, measurement with a precision of minimum 2 mmHg must be performed. The value must be used to evaluate eligibility of the subject in relation to exclusion criterion.

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

Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure. Blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported. The subject should be sitting for five minutes before the measurement is taken. The same arm and an appropriate cuff size should be used for blood pressure measurements at all visits.

8.3.7 Self-measured plasma glucose

At visit 1, subjects will be provided with a blood glucose (BG) meter including auxiliaries as well as instructions for use. Only the BG meter provided by Novo Nordisk should be used for the measurements required in the protocol. The subjects will be instructed in how to use the device and the instruction should be repeated at regular intervals as needed.

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.

Subjects should be instructed in how to record the results of the SMPG values in the diabetes diaries. The record of each SMPG value should include date, time and value. This data should not be entered into the eCRF.

The SMPGs should be measured to ensure data for insulin adjustment (see Section [5.3.2.2](#)) and to record 7-point SMPG profile (see Section [8.3.8](#)). In addition, SMPG values are also measured for collecting and reporting hypoglycaemic episodes (see Section [8.4.4](#)). The subject may measure additional values at the discretion of the investigator.

8.3.8 7-point SMPG profile

Subjects will be instructed to perform a 7-point SMPG profile prior to randomisation and at selected visits as specified in the flow chart (see Section [2](#)).

The 7-point profile should be recorded the day before the site visit. The SMPGs should be measured and recorded in the diary at the time points listed in [Table 8-1](#). The record of each SMPG must include date, actual time point and the plasma glucose value. Data must be transcribed into the eCRF during or following the site visit. If a discrepancy is later detected, the values in the eCRF must be corrected.

Table 8–1 Time points for 7-point SMPG profile

Time point	SMPG measurement
Before breakfast	√
90 min after start of breakfast	√
Before lunch	√
90 minutes after start of lunch	√
Before dinner	√
90 min after start of dinner	√
At bedtime	√

8.3.9 Insulin dose

Subjects will be instructed in how to record the insulin use in the provided diabetes diary. The investigator should review the subject's insulin dose as specified in Section [8.1](#). Results of the subject's SMPG measurements should be noted in the diabetes diary and total daily injected dose of basal/bolus insulin prior to each contact will be transcribed into the eCRF and based on these, dose adjustment guidance will be provided. All adjustments of insulin dose level will be captured in the eCRF. From visit 2 and until follow-up, the investigator should record the subject's total daily injected dose of insulin (basal/bolus) prior to each visit in the eCRF.

8.3.10 Clinical outcome assessments

Clinical outcome assessments (COA) are used to collect clinical data for all subjects enrolled in the trial at the visits specified in Section [2](#). The questionnaires are linguistically validated to the fluent language of all subjects participating.

The questionnaires must be completed by the subject and should preferably be completed after conclusion of all fasting-related activities, but before any other visit-related activities. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. Each of the questionnaires takes approximately 10 minutes to complete.

The five questionnaires for efficacy are:

Impact of Weight on Quality of Life-Lite for Clinical Trials Version

The Impact of Weight on Quality of Life Lite for Clinical Trials Version (IWQoL-Lite for CT) questionnaire is a 22-item modified version of an instrument designed to assess weight-related quality of life³⁵.

Alongside this trial in another project, Novo Nordisk is adapting the IWQoL-Lite for CT by conducting additional concept elicitation with patients, cognitive interviewing, consultation with expert clinicians, translatability assessment, and psychometric validation. Development and validation process is aligned with the FDA PRO guidance (2009)³⁶.

Short Form 36 v2.0 acute

Short Form 36 v2.0 acute (SF-36) is a 36-item, patient-reported survey of patient health. SF-36 measures the subject's overall Health Related Quality of Life on 8 domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health³⁷.

In addition, SF-36 is included to validate the outcome of IWQoL-Lite for CT and WRSS questionnaires.

Patients' global impression of change

The patients' global impression of change (PGI-C) assesses subjects' impressions of change during the clinical trial. It is used to establish the Minimal Clinically Important Difference (MCID) as part of the psychometric properties of the WRSS questionnaire.

Patients' global impression of status

The patients' global impression of status (PGI-S) assesses subjects' impressions of status at the time in the clinical trial. It is used to establish the MCID as part of the psychometric properties of the WRSS questionnaire.

Weight related sign and symptom measure

The WRSS measures the presence and bothersome associated with weight related signs and symptoms. It is a tool to assess the multifaceted aspects of obesity on symptom experience in subjects with obesity.

In this trial, Novo Nordisk is validating the WRSS. Development and validation process is aligned with the FDA PRO guidance (2009)³⁶.

8.4 Safety assessments

All assessments and samples collected at randomisation will be considered as baseline for safety, unless otherwise specified.

8.4.1 Physical examination

Physical examination will be performed at the specified visits (Section [2](#)) according to local procedure. Physical examination should include general appearance, thyroid gland, respiratory system, cardiovascular system, abdomen, gastrointestinal system including mouth, musculoskeletal system, central and peripheral nervous system, skin, lymphoid node palpation, and head, ears, eyes, nose, throat and neck, and must be recorded in the subject's medical record and eCRF. Any abnormal, clinically significant findings at screening (visit 1) must be recorded as a concomitant illness (see Section [8.2.4](#)).

Physical examination performed at screening will be considered as baseline.

8.4.2 Eye examination

Dilated funduscopy/fundus photography will be performed at the visit specified in the flow chart (see Section [2](#)) by the investigator or a local ophthalmologist according to local practice. Result of the funduscopy/fundus photography will be interpreted by the investigator.

If a funduscopy/fundus photography has been performed within 90 days prior to randomisation, the procedure does not need to be repeated, unless signs of worsening of visual function have been seen since the last examination.

If the funduscopy/fundus photography is performed before the subject has signed the informed consent form, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

It is allowed to perform the visit 1 funduscopy/fundus photography between visit 1 and visit 2. The results must be available prior to randomisation.

Any clinically significant abnormalities found at visit 1 or as part of the screening procedures, should be recorded as a concomitant illness.

8.4.3 Adverse events

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

8.4.3.1 Medication error

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

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episode(s) or adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section [12.1.4](#).

8.4.3.2 Adverse events requiring additional data collection

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

- Acute gallstone disease
- Neoplasm
- Pancreatitis
- Depression, suicidal ideation/behaviour
- Hepatic event (Suspicion of drug-induced liver injury)

In case any of these events fulfil the criteria for a SAE, please report accordingly (see Section [12](#)).

Acute gallstone disease

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

- Signs and symptoms of acute gallstone disease
- Specific laboratory test supporting a diagnosis of gallstone disease (see Section [8.8.2](#))
- Imaging performed and consistency with gallstone disease
- Treatment given for the event
- Relevant risk factors associated with the event

Neoplasm

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

- Type of neoplasm
- Signs and symptoms leading to identification of event (see Section [8.8.3](#))
- Diagnostic imaging
- Pathological examination results

- Treatment given for the event
- Participation in screening programs
- Relevant risk factors associated with the event

Pancreatitis

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

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis (see Section [8.8.1](#))
- Imaging performed and consistency with pancreatic disease
- Treatment given for the event
- Relevant risk factors associated with the event

Depression, suicidal ideation/behaviour

If an event of depression, suicidal ideation or behaviour or clinical suspicion of this is observed during the trial the following additional information should be reported if available on the psychiatric disorder form:

- Signs and symptoms of depression, suicidal ideation or behaviour
- Treatment given for the event
- Relevant risk factors associated with the event

Hepatic event (suspicion of drug-induced liver injury)

In case of suspicion of drug-induced liver injury (DILI), following additional information should be reported if available on the drug induced liver injury form:

- Signs and symptoms of drug induced liver injury
- Specific laboratory test supporting a diagnosis of drug induced liver injury (see Section [8.8.4](#))
- Treatment given for the event
- Relevant risk factors associated with the event

Prompt testing (at central laboratory) including alanine aminotransaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), international normalised ratio (INR) and total bilirubin (TBL) should be done and trial product should be discontinued until the abnormalities return to normal or baseline state.

Additional clinical information such as related symptoms, risk factors and contributing conditions (e.g., viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatobiliary or pancreatic disorders) should be gathered to seek a possible cause of the observed laboratory test abnormalities.

8.4.4 Hypoglycaemic episodes

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

All plasma glucose values:

- ≤ 3.9 mmol/L (70 mg/dL) or,
- > 3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms

should be reported in the diary according to the instructions below throughout the trial from visit 1 to visit 25.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines³⁴.

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

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

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- The plasma glucose level before treating the episode (if available) and any follow up measurements.
- The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No)
- A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat him/herself

- If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia.
- Date, time and dose of last trial product, insulin and OAD administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Change in any concomitant illness
- Any sign of fever and/or other acute disease
- Whether the subject was asleep when the episode occurred
 - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration³⁴.

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e., medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e., oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e., physical activity, missed meal, diet change, medication error (i.e., overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms³⁸ (layman term used in the diary is specified in brackets if different from the protocol term)?
- Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
- Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
- General malaise: headache or malaise (feeling discomfort/unease)

- Other symptoms

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

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data^{36,39}.

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

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

8.4.5 Vital signs (pulse)

Pulse (beats/minutes) will be recorded in a sitting position after resting for five minutes at the specified visits (see Section [2](#)).

8.4.6 Electrocardiogram

An electrocardiogram (ECG) will be performed at the visits specified in the flow chart (see Section [2](#)). The investigator or delegate must sign, date and interpret the ECG by using the following categories:

- Normal
- Abnormal: Was the result clinically significant? (Yes/No)

Clinically significant is an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.

If the result is clinically significant, the investigator must report such an abnormal finding as an AE or SAE (see Section [12.2](#)).

ECG performed at screening will be considered as baseline.

8.4.7 Patient health questionnaire-9

The patient health questionnaire-9 (PHQ-9)⁴⁰ is a 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders. The questionnaires will be available in a linguistically validated version in subject's fluent language. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The questionnaire takes approximately 10 minutes to complete. A PHQ-9 score ≥ 15 at screening and randomisation excludes the subject from participation in the trial.

8.4.8 Columbia suicidal severity rating scale

The Columbia suicidal severity rating scale (C-SSRS)⁴¹ is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the investigator or a qualified delegate. The questionnaire will be available in a linguistically validated version in the subject's fluent language.

Prior to administering the C-SSRS questionnaire, the investigator or qualified delegate must complete sufficient training. Any suicidal ideation of type 4 or 5 within the past 30 days at screening or randomisation excludes the subject from participation in the trial.

8.4.9 Breast and colon neoplasm follow up

These forms must be completed at the end-of-treatment and follow-up visit, even if a subject prematurely discontinues treatment with trial product.

If a subject withdraws consent, the subject must be encouraged to provide this information.

8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory. The central laboratory may utilise subcontractors.

Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see [Attachment 1](#)).

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section [8.2.4](#) and Section [12](#)).

Laboratory samples may be drawn on another day than the day of the actual visit, as long as it is within the visit window outlined in the flow chart (see Section 2). For some of the samples drawn during the trial, it is required that the subject is fasting. If a subject is not fasting at these visits, the fasting blood sampling must, as a minimum, be re-scheduled within the visit window.

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis.

Samples will be destroyed no later than at finalisation of the clinical trial report (CTR).

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

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

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or not. If clinically significant, the investigator must report these as clinical laboratory adverse events (CLAE) according to Section 12.1.1.

All laboratory report printouts must be reviewed, signed and dated by the investigator or delegate. The evaluation of screening results must be dated and signed prior to visit 2 (randomisation), for the subsequent visits preferably on the day of evaluation.

8.5.1 Laboratory assessments for efficacy

Blood samples for biochemistry must be collected at the specified visits (see Section 2).

- HbA_{1c}
- Fasting plasma glucose (FPG)
- Lipids (TC, LDL cholesterol, HDL cholesterol, VLDL cholesterol, TG, FFA)

A FPG result ≤ 3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section 12.1.1).

8.5.2 Laboratory assessments for safety

Pregnancy test

Females of childbearing potential will have a human chorionic gonadotropin (hCG) serum pregnancy test performed at the visits specified in the flow chart (see Section 2).

Urine pregnancy tests will be performed for females of childbearing potential if there is suspicion of pregnancy or if she missed a menstrual period. She should contact the site to come in for a urine pregnancy test. Urine pregnancy kits will be supplied by the central laboratory.

Pregnancy testing will not be required for women not of childbearing potential (see Section [8.2.6](#)).

Biochemistry

Blood samples for biochemistry must be collected at the specified visits (see Section [2](#)).

- Creatinine
- Urea (blood urea nitrogen)
- Uric acid
- Alanine aminotransaminase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase (ALP)
- Albumin
- Amylase
- Lipase
- Sodium
- Potassium
- Calcium, total
- Calcitonin (please refer to [Appendix A](#) for actions to be taken if calcitonin is ≥ 10 ng/L)
- TSH*
- Bilirubin, total (TBL)
- hs-CRP**
- GFR, estimated

*If TSH levels are out of normal range, the investigator must perform additional testing:

- Total and free T3 and T4 and Free Thyroid Index
- Thyroid peroxidase antibodies

**hs-CRP is only measured at Visit 2 and Visit 24.

Haematology

Blood samples for haematology must be collected at the specified visits (see Section [2](#)).

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes

8.6 Other assessments

8.6.1 Trial product usage

Information on premature discontinuation, and permanent discontinuation of trial product will be collected and recorded in the eCRF. If the trial product is re-started, the investigator must note this in the medical record and eCRF.

8.6.2 Food record and tracking of physical activity

The subjects will be requested to fill in a food diary daily, where all meals and their caloric content are recorded. The interventionist can provide a paper food diary or the subject can use another tracker, tool or app to register food intake, as preferred by the subject.

The subject will be requested to record number of steps daily using a pedometer provided by Novo Nordisk. The subject will be asked to record the steps and minutes of physical activity daily in a paper physical activity diary which will be provided at each site visit.

8.6.3 Diabetes diary

Subjects will be provided with a new diabetes diary at each site visit. Investigator should instruct the subject how to fill in the diary. The diary will be collected at the following site visit and retained as at the site as source data.

The diabetes diary must be reviewed by the investigator to ensure that AEs, or any overall change in health, including medical issues and concomitant medication are reported. In addition the investigator must consider whether the reported values from the SMPG measurements should be reported as hypoglycaemic episodes (see section [8.4.4](#)).

The investigator is only allowed to record the following data in the diary:

- Subjects ID number
- Site contact details
- Date and time of the next visit
- Prescribed dose of trial product

- Doses and values from SMPG measurements from previous diary, if required for the insulin adjustment
- Review signature

The investigator or delegated staff should transcribe data from the diary into the eCRF throughout the trial. Safety data from the diary must be handled according to timelines described in [Figure 12–1](#). If discrepancies are found in entries and clarification in the diary is needed, the subject must be questioned and a conclusion made in the subject’s medical record. Care must be taken not to bias the subject.

The review of the diary must be documented either on the document and/or in the subject’s medical record.

The diaries will contain the below information (filled in by the subject):

- Date of first trial product injection
- Date, time and value of SMPG measurements
- Insulin dose
- Hypoglycaemic episodes
- Any medical issues
- Any changes to concomitant medications(s)
- Date, time and value of the 7-point profile SMPG at selected visits

8.6.4 Training in the PDS290 pen-injector

The subjects must be trained in how to handle the PDS290 pen-injector when handed out the first time. Training must be repeated at each visit if needed in order to ensure correct use of the device. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- When using the pen-injector the first time, the pen should be primed to ensure product flow
- The needle should be kept in the skin while counting slowly to 6 (or as described in the direction for use) after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered.

8.6.5 Inquire about mood

The subject should be asked about the mood as per flow chart (see Section [2](#)), for example – ‘How has your mood been since the last contact?’

In case the subject reports any adverse events, these should be collected and reported as an AE. Depression and suicidal ideation/behaviour should be reported as AEs requiring additional data collection (see Section [8.4.3.2](#) and Section [12](#)).

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Compliance with trial product: At each visit the investigator should ask the subject whether the subject has continuously been using the trial product since last visit. If the subject has stopped using trial product, the investigator should fill in the date for the last dose in the eCRF. If the subject has had a pause using trial product longer than one week since last visit, but has started using trial product again, the investigator should fill in the dates corresponding to the last day on trial product and the first day on trial product in the eCRF.

8.8 Additional safety assessments

8.8.1 Suspicion of acute pancreatitis

If pancreatitis is suspected, trial product must promptly be discontinued (no ‘treatment status’ session should be made in IWRS, before diagnosis of acute pancreatitis is confirmed) and appropriate management should be initiated. Appropriate additional examinations must be performed, including local measurement of amylase and lipase.

The event must be reported as an AE requiring additional data collection (see Section [8.4.3.2](#) and Section [12](#)).

The diagnosis of acute pancreatitis requires two of the following three features:

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on imaging (CT/MRI).

Abdominal pain

Most patients with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back. The onset of the pain may be swift reaching maximum intensity within 30 minutes; it is frequently unbearable and characteristically persists for more than 24 hours without relief. The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding.

Lipase and amylase

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The level of the serum amylase and/or lipase does not correlate with the severity of acute pancreatitis. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.

If acute pancreatitis is confirmed, the subject must be permanently discontinued from the trial product. Appropriate treatment and careful monitoring of the subject should be initiated. Furthermore, the subject should be encouraged to remain in the trial (see Section [8.1](#)).

If acute pancreatitis is ruled out, trial product should be re-initiated at the investigator's discretion.

8.8.2 Suspicion of acute gallstone disease

In case of suspicion of acute gallstone disease or cholelithiasis, the trial product must promptly be discontinued (no 'treatment status' session should be made in IWRS before a diagnosis of acute gallstone disease is confirmed). Appropriate treatment and careful monitoring should be initiated. Furthermore, the subject should remain in the trial (see Section [8.1](#))

The event must be reported as an AE requiring additional data collection (see Section [8.4.3.2](#) and Section [12](#)).

If acute gallstone disease is confirmed, the trial product must be permanently discontinued. However, trial product can be restarted at the investigator's discretion if cholelithiasis is ruled out or the gallbladder has been removed. Appropriate treatment and careful monitoring of the subject should be initiated. Furthermore, the subject should be encouraged to remain in the trial (see Section [8.1](#)).

8.8.3 Neoplasm

In case of neoplasm, please consider if the trial drug should be discontinued (no 'treatment status' session should be made in IWRS before a diagnosis is confirmed). The event must be reported as an AE requiring additional data collection (see Section [8.4.3.2](#) and Section [12](#)). Appropriate treatment and careful monitoring of the subject should be initiated. Furthermore, the subject should be encouraged to remain in the trial (see Section [8.1](#)).

Trial product can be re-initiated at the investigator's discretion if diagnosis is not supported.

8.8.4 Hepatic event (suspicion of drug-induced liver injury)

Please consider discontinuing trial product if :

- 1) ALT or AST >5xUNL, or

2) ALT or AST > 3x UNL and (total bilirubin >2xUNL or INR >1.5), or

3) ALT or AST >3xUNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

For the above events, prompt repeat testing at central laboratory, of ALT, AST, ALP, INR and total bilirubin should be done. Thereafter, repeat testing (at central laboratory) of ALT, AST, ALP, INR and total bilirubin should be done regularly until the abnormalities return to normal or baseline state. Additional clinical information such as related symptoms, risk factors and contributing conditions (e.g. viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatobiliary or pancreatic disorders) should be gathered to seek a possible cause of the observed laboratory test abnormalities. Although the trial product is discontinued, no 'treatment status' session should be made in IWRS and the subject should remain in the trial.

In case of suspicion of DILI, the trial product must promptly be discontinued (no 'treatment status' session should be made in IWRS before a diagnosis is confirmed).

The event must be reported as an AE requiring additional data collection (see Section [8.4.3.2](#) and Section [12](#)).

If DILI is confirmed, the subject should permanently discontinue the trial product. Appropriate treatment and careful monitoring of the subject should be initiated. Furthermore, the subject should be encouraged to remain in the trial (see Section [8.1](#)).

Trial product can be re-initiated at the investigator's discretion if diagnosis of DILI is not supported.

8.8.5 Depression, suicidal ideation/behaviour

In case of depression or suicidal ideation/behaviour, please consider if the trial drug should be discontinued (no 'treatment status' session should be made in IWRS before a diagnosis is confirmed). The event must be reported as an AE requiring additional data collection (see Section [8.4.3.2](#) and Section [12](#)).

Appropriate treatment and careful monitoring of the subject should be initiated as per local clinical practice. A subject should be referred to a MHP if he/she has:

1. symptoms of moderate or more severe depression,
2. or any suicidal behaviour,
3. or any suicidal thoughts with some intent to act, irrespective of whether accompanied by a specific plan.

Protocol
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

~~CONFIDENTIAL~~

Date:	14 September 2016	Novo Nordisk
Version:	4.0	
Status:	Final	
Page:	64 of 123	

In case the subject refuses to consult the MHP, the investigator must state in the medical records whether it is considered safe for the subject to stay in the trial. Trial product can be re-initiated at the investigator's discretion, if a diagnosis is not supported.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the trial materials manual (TMM).

Trial products must not be dispensed to any person not included in the trial.

Trial product comprises investigational medicinal products (IMP); both active and placebo.

Trial product must not be used, if it does not appear clear and colourless or almost colourless.

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Liraglutide 6 mg/mL (IMP)	6 mg/mL	Solution for injection	Subcutaneous injection (s.c.)	3 mL PDS290 pen-injector
Placebo (IMP)	NA			

Basal and bolus insulin and OADs are considered non-investigational medicinal products (NIMPs), hence will not be provided by Novo Nordisk. However, insulins and OADs will be reimbursed if required by the country's regulatory authority or IRB/IEC.

Liraglutide and placebo are visually identical, to ensure double-blinding in the trial.

9.2 Labelling and directions for use

The trial products will be labelled in accordance with Annex 13⁴², local regulations and trial requirements.

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

The investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit (visit 2). At the following visits, the investigator will confirm with the

subject that the direction for use is still available and that the subject is using the trial product correctly.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time ^a
Liraglutide 6 mg/mL		Store below 30°C Do not freeze Protect from light	
Placebo	Store in a refrigerator (2°C-8°C/ 36°F-46°F) Do not freeze Protect from light	US: Store at room temperature (59°F-86°F) or in refrigerator (36°F-46°F) Canada: 30 days at room temperature (not above 30°) or in a refrigerator (2°C-8°C)	Use within 1 month US: Use within 30 days

^a In-use time starts when the product is taken out of the subject's refrigerator

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

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

9.4 Drug accountability and destruction

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

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at randomisation and each dispensing visit. The correct dispensing unit number(s) (DUN[s]) must be dispensed to the subject.

The investigator or delegated person is responsible for ensuring that:

- Drug accountability is performed using the IWRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at end-of-treatment visit

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

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

Dispensed trial product must be accounted for at pen level; either recorded as used/partly used, unused or lost. Distributed and returned pens are subject to be sent for destruction, thus may not be re-allocated to new subjects.

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

9.5 Auxiliary supplies

Auxiliary supplies comprise supplies other than trial products. The following auxiliary supplies will be provided by Novo Nordisk in accordance with the TMM:

- Needles for pre-filled pen (maximum length to be used is 8 mm)
- Directions for use for pre-filled pen
- Blood glucose (BG) meter
- BG auxiliaries including test strips, lancets, instructions and control solution.

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

10 Interactive web response system

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

IWRS is used for:

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

IWRS user manuals will be provided to each trial site.

Premature treatment discontinuation and re-initiation

If the investigator or the subject has decided to discontinue treatment, but the subject has not withdrawn consent, it is possible to re-initiate treatment, if no discontinuation criteria are met (see Section [8.1](#)). The subject will remain in the same treatment arm, and a new dose escalation period will be started, if the subject resumes treatment. The investigator must make a note and record dates of any discontinuation and re-initiation dates in the medical records and eCRF.

To register discontinuation of trial product (temporary or permanent), a 'treatment status' session is performed in the IWRS, to indicate subject should no longer receive trial product. Similarly, if the treatment should later be re-initiated, a 'treatment status' session is performed in the IWRS, to indicate subject should again receive trial product.

Withdrawal

In the case subject has withdrawn consent, a 'treatment status' session must be performed in IWRS, to indicate that subject should no longer receive trial product. If possible after confirmation by the monitor, the subject will be registered as 'withdrawal', to ensure that subject is not allowed to re-initiate trial product.

If the subject is temporarily lost to follow up during the trial, the IWRS session should not be completed until the scheduled Visit 24 at week 56 to confirm the final status.

11 Randomisation procedure and breaking of blinded codes

A randomisation session will be carried out for eligible subjects using the IWRS. The eligible subjects will be randomised centrally 1:1 to either liraglutide 3.0 mg or placebo. In addition, the subjects will be stratified between the two arms.

11.1 Breaking of blinded codes

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

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

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

If the code has been broken, the subject must discontinue treatment with trial product and a treatment session must be completed in IWRS.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

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

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of an AE form [8.4.4](#)

The following three definitions are used when assessing an AE:

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

Relationship between an AE and the relevant trial product(s):

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

- **Final outcome**

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

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening^a experience.
- In-patient hospitalisation^b or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity^c.
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening^a or require hospitalisation^b may be considered a SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE^d.

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

^b. The term “hospitalisation” is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial-related and social purposes

do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

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

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

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

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug or use of wrong device. Note: Use of wrong DUN is not considered a medication error
- Wrong route of administration, such as intramuscular instead of s.c.
- Administration of an overdose with the intention to cause harm, misuse or abuse of trial product
- Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 0.6, 1.2, 1.8, 2.4 and 3.0 mg respectively (within 24 hours). However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur

If the subject discontinues trial product prematurely, this should not be reported as a medication error.

Medication errors must be reported on an AE form and a specific event form for medication error (see Section [8.4.3.1](#)).

12.1.5 Adverse events requiring additional data collection

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

The below lists AEs that require completion of specific event forms in the eCRFs (see Section [8.4.3.2](#)):

- Acute gallstone disease
- Neoplasm
- Pancreatitis
- Hepatic event (suspicion of DILI)
- Depression, suicidal ideation/behaviour

For details of these events, see Section [8.8](#).

12.1.6 Technical complaints

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (30 days). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below in [Figure 12-1](#).

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

In addition, the subject should be asked about the mood for example – ‘How has your mood been since the last contact?’

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

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

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

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

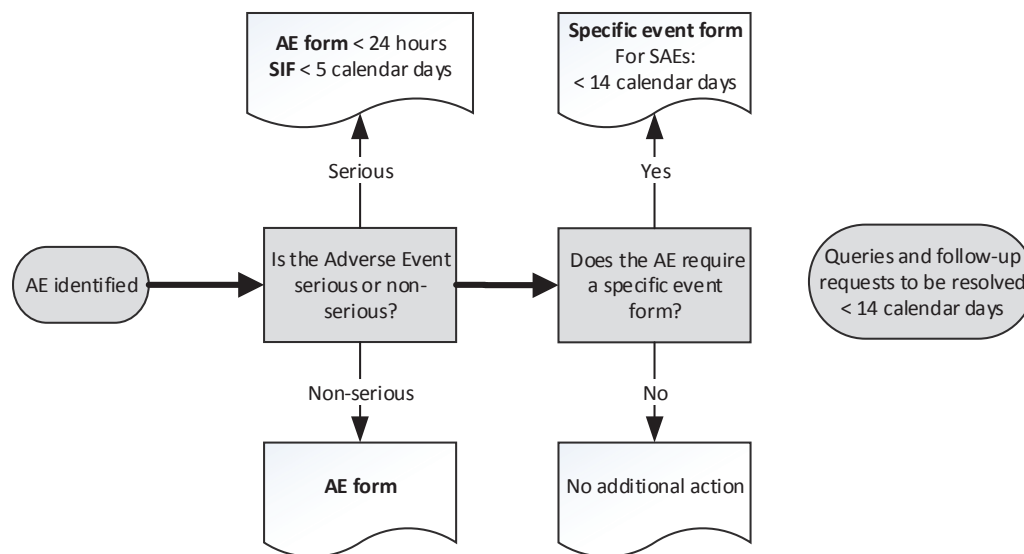
Timelines for initial reporting of AEs

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

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed **within 7 calendar days** from the date the information was entered in the eCRF.
- **For SAEs requiring reporting on a specific event form:** In addition to the above, the specific event form must be completed and signed within **14 calendar days** from the investigator's first knowledge of the AE.

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

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



Timelines are for the completion of forms from the time of investigator's awareness.
AEs requiring specific event forms are described in Section 12.1.4 and 12.1.5.

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness

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

Reporting of trial product-related SUSARs by Novo Nordisk

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

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

Novo Nordisk products used as concomitant medication

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.

12.3 Follow-up of adverse events

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

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

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

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

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

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Liraglutide 6 mg/ml, 3 ml PDS290 pen-injector
- Placebo PDS290 pen-injector
- Novo Nordisk needles for pen-injector

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

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

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

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

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

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

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

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

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

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

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

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

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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

1. Reporting of pregnancy information

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

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

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

2. Reporting of AE information

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

Forms and timelines for reporting AEs:

Non-serious AEs:

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

Serious AEs:

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

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

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

12.6 Precautions and/or overdose

From clinical trials and marketed use of liraglutide overdoses have been reported up to 24 times the recommended dose (72 mg). One case of a \times -fold overdose (\times mg daily) given for \times months has been reported. Generally, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. None of the reports included severe hypoglycaemia.

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

For the US, please refer to the current approved US Saxenda[®] prescribing information, for details concerning overdose.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

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

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

13.1 Corrections to case report forms

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

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

Protocol
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

~~CONFIDENTIAL~~

Date:	14 September 2016	Novo Nordisk
Version:	4.0	
Status:	Final	
Page:	82 of 123	

13.2 Case report form flow

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

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

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LSLV at the trial site.

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

All data must be verifiable in source documentation other than the eCRF. For all data recorded, the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

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

- date for obtaining informed consent
- reason for screening failure
- SAEs (if any)

Source data generated by the trial site can be corrected by a person other than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction. The original of the completed diaries or assessment tools must not be removed from the trial site. The COAs are completed electronically, thus entries at the site-pads are source data and a copy of the entries should be provided to site. The monitor will ensure that the eCRFs are completed and that paper CRFs are collected. Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

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

15 Data management

Data management is the responsibility of Novo Nordisk.

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

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

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

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

Results from the statistical analysis will generally be accompanied by two-sided 95% confidence intervals and two-sided p-values.

Superiority will be claimed if the two-sided p-value is less than 5% and the estimated treatment difference/ratio favours liraglutide 3.0 mg.

Primary endpoints

The two primary endpoints (see Section [4.2.1](#)) are defined as:

- Change in body weight (%) from baseline to week 56
- Proportion of subjects losing at least 5% of baseline body weight at week 56

The primary objective is met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints.

Definition of primary endpoint: % weight change

Change in body weight (%) from baseline to week 56, denoted % weight change, is calculated as body weight at week 56 minus body weight at baseline divided by body weight at baseline and multiplied by 100; therefore

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

A negative value of % weight change indicates a body weight loss from baseline to week 56.

Definition of primary endpoint: 5% responders

The proportion of subjects having lost at least 5% of baseline body weight at week 56, denoted 5% responders, is defined as the proportion having

$$\% \text{ weight change} \leq -5\%.$$

A 5% responder is defined as a subject fulfilling this, therefore

$$5\% \text{ responder} = \begin{cases} 1 & \text{if } \% \text{ weight change} \leq -5\% \\ 0 & \text{if } \% \text{ weight change} > -5\% \end{cases}$$

Definition of Estimands

Effectiveness estimand

The primary estimand is an effectiveness estimand (*de facto*) quantifying the average effect of liraglutide 3.0 mg relative to placebo 56 weeks after randomisation, as adjunct to reduced caloric diet and increased physical activity, in all randomised subjects regardless of adherence to randomised treatment.

Efficacy estimand

In addition, an efficacy estimand (*de jure*) is quantifying the average effect of liraglutide 3.0 mg relative to placebo 56 weeks after randomisation, as adjunct to reduced caloric diet and increased physical activity, if all randomised subjects had adhered to the assigned treatment regimen for the entire planned duration of the trial.

Taxonomy of week 56 assessments being available or missing

A given assessment at week 56 may be available or missing. [Table 17–1](#) describes the taxonomy for this. Note that this is done per assessment not per subject, as subjects may belong to different types for different assessments (a subject may have “available on treatment (AT)” for weight but “missing on treatment (MT)” for waist circumference).

Table 17–1 Taxonomy of week 56 assessments being available or missing

Assessment at week 56	On randomised treatment at week 56	Type description	Type Abbreviation
Available	Yes	Available on randomised treatment: Subjects who did not discontinue randomised treatment prematurely. Include those that stop and restart trial product.	AT
	No	Available drop-outs: Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 56; so-called retrieved drop-outs.	AD
Missing	Yes	Missing on randomised treatment: Subjects who did not discontinue randomised treatment prematurely. Include those that stop and restart trial product.	MT
	No	Missing drop-outs: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 56; so-called non-retrieved drop-outs.	MD

17.1 Sample size calculation

The sample size calculation is based on the analysis approach addressing the primary estimand for the primary endpoints change in body weight (%) from baseline to week 56 (% weight change) and proportion of subjects losing $\geq 5\%$ of baseline body weight at week 56 (5% responders).

The two primary endpoints and all confirmatory secondary endpoints will be tested in a hierarchical order.

The study design is a 1:1 randomisation, stratified by sulphonylurea (yes/no) with 400 subjects in total (200 subjects in each arm). The sample size calculation does not take stratification into account. Please see [Table 17-2](#) for general specifications on sample size and power calculation.

Table 17-2 General specifications for sample size and power calculation

Endpoint	Statistical test	Minimum required power (%)
% weight change	Two-group Satterthwaite unpooled <i>t</i> test on the mean difference with $\alpha=0.05$ assuming unequal variances	90.0 (marginal)
5% responders	Pearson chi-square test for two independent proportions with $\alpha=0.05$	90.0 (marginal)

α : two-sided significance level

In the following paragraphs treatment differences and standard deviations (SD) are given without units.

Body weight measurements from returning discontinuing subjects will be used in the primary analysis. But for the sample size calculations, it is assumed that all subjects who discontinue will not return at week 56 and assume that they have a % weight change like placebo subjects who completed the trial. It is expected that % weight change for liraglutide 3.0 mg subjects who discontinue might be somewhere in between completing placebo subjects and completing liraglutide 3.0 mg subjects. The assumption is thus expected to lead to a conservative effect estimate. A 30% discontinuation is assumed based on findings in trial NN8022-1922.

Based on findings from NN8022-1922, a difference in % weight change between liraglutide 3.0 mg and placebo of -4 (-6% vs. -2% , $SD=6$) is assumed among completing subjects. Adjusting for 30% discontinuation and using a mixture distribution, a difference of -2.8 is expected in the primary analysis. A sample size of 400 subjects (200 in each arm), gives a marginal power of 99.5%.

For the primary endpoint 5% responders, the expected proportions were calculated based on the same assumptions as above. Adjusting for 30% discontinuation gives an expected 5% responders proportion of 49% in the liraglutide 3.0 mg arm and 31% in the placebo arm. With 400 subjects, this results in a marginal power of 95.7%.

Given these assumptions, the sample size of 400 subjects (200 in each arm), results in a combined power (marginal powers multiplied) of 95.2%.

The tests of superiority of liraglutide 3.0 mg to placebo for each of the confirmatory endpoints are performed hierarchically in the order in which the endpoints are presented (see Sections 4.2.1 and 4.2.2.1). The two primary endpoints are included in the statistical testing hierarchy, and the primary objective will be met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints. The test hierarchy is given in Table 17-3 with underlying assumptions, marginal power and effective power. The effective power is calculated using a naïve and conservative approach, which assumes no correlation of endpoints by multiplying the respective marginal powers. Assumptions made to calculate the power for the two primary endpoints and all confirmatory secondary endpoints are also presented in Table 17-3.

Table 17-3 Assumptions, marginal power and effective power for each confirmatory endpoint in the hierarchical testing procedure given an anticipated number of 400 randomised subjects

	Assumed mean (\pm SD) / proportion for completers		Expected mean (\pm SD) / proportion	Expected difference #	Marginal power (%)	Effective power (%)
	liraglutide 3.0 mg	placebo	liraglutide 3.0 mg #			
% weight change	-6.0 (\pm 6.0)	-2.0 (\pm 6.0)	-4.8 (\pm 6.3)	-2.8	99.5	99.5
5% responders	57%	31%	49%	18	95.7	95.2
10% responders	25%	9%	20%	11	89.0	84.7
WC	-6.0 (\pm 5.9)	-3.1 (\pm 5.9)	-5.1 (\pm 6.0)	-2.0	92.4	78.3
HbA1c	-1.4 (\pm 1.0)	-0.5 (\pm 1.0)	-1.1 (\pm 1.1)	0.6	99.9	78.2
Fasting glucose	-2.2 (\pm 2.0)	-0.4 (\pm 2.0)	-1.7 (\pm 2.2)	1.3	99.9	78.1
sBP	-2.6 (\pm 11.7)	-0.3 (\pm 11.7)	-1.9 (\pm 11.7)	-1.6	27.8	21.7
Physical score *	15.0 (\pm 14.5)	10.6 (\pm 14.5)	13.7 (\pm 14.6)	3.1	55.9	12.1
Mental score *	12.0 (\pm 18.0)	9.6 (\pm 18.0)	11.3 (\pm 18.0)	1.7	15.3	1.9

SD standard deviation, WC waist circumference, sBP systolic blood pressure;
 # Adjusted for 30% discontinuation; * IWQoL-Lite Clinical Trial Version;
 Assumptions are based on findings from NN9068-3951.

17.2 Definition of analysis sets

Two analysis sets are defined:

- The *full analysis set* (FAS) includes all randomised subjects according to the intention-to-treat principle.
- The *safety analysis set* includes all randomised subjects exposed to at least one dose of randomised treatment.

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

17.3 Primary endpoints

The two primary endpoints are as mentioned previously (see start of Section [17](#)):

- % weight change
- 5% responders

17.3.1 Analytical methods addressing the effectiveness estimand for the primary endpoints

These analyses will use the FAS. The analyses of the primary endpoints use baseline body weight and body weight at week 56, and assessments at week 56 may be missing (“missing on treatment [MT]” and “missing drop-outs [MD]”). First, a description of the statistical models for the primary endpoints is given under the assumption of no missing values (i.e. all subjects have body weight measurements at baseline and week 56). Subsequently, handling of missing data is described.

17.3.1.1 Statistical model for the primary endpoint % weight change

The primary endpoint % weight change will be analysed using analysis of covariance (ANCOVA) including the factors and covariates listed in [Table 17–4](#).

Table 17–4 Factors and covariates for the analysis of the primary endpoints

Factors and covariates at baseline	Type	Categories
Randomised treatment	Factor	Liraglutide 3.0 mg, placebo
Sulphonylurea	Factor	Yes, no
Body weight (kg)	Covariate	<i>Not applicable</i>
BMI (kg/m ²)	Factor	[27,30[, [30,35[, [35,40[, ≥40
Gender	Factor	Male, female
Insulin type	Factor	Insulin detemir, other basal insulin
Insulin dose	Covariate	<i>Not applicable</i>
HbA1c	Factor	≤ 8.0%, > 8.0%

The factors and covariates will be included in the model as main effects in an additive structure. The estimated treatment difference between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

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

Let $\mu_{\text{liraglutide}}$ and μ_{placebo} denote the true mean of % weight change for liraglutide 3.0 mg and placebo group, respectively. The hypothesis and the alternative are

H: $\mu_{\text{liraglutide}} \geq \mu_{\text{placebo}}$ against the alternative $H_A: \mu_{\text{liraglutide}} < \mu_{\text{placebo}}$.

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

17.3.1.2 Statistical model for the primary endpoint 5% responders

This binary endpoint will be analysed using a logistic regression model. Factors and covariates will be those listed in [Table 17-4](#). The estimated odds ratio (OR) between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

Let $OR_{\text{liraglutide/placebo}}$ denote the true odds ratio between liraglutide 3.0 mg and placebo. The hypothesis and the alternative are:

H: $OR_{\text{liraglutide/placebo}} \leq 1$ against the alternative $H_A: OR_{\text{liraglutide/placebo}} > 1$

The hypothesis will be rejected and superiority claimed, if the lower limit of the estimated two-sided 95% CI is above 1.

17.3.2 Handling of missing values for the effectiveness estimand

17.3.2.1 Handling of missing values at baseline

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.

17.3.2.2 Handling of missing values at week 56

Missing values at week 56 will be imputed and the relevant endpoints will be derived from the imputed values. Several approaches for imputation of missing values at week 56 will be applied. First, a description of the primary imputation approach used to address the effectiveness estimand for the primary endpoints is given. This is followed by a description of a number of sensitivity analyses.

Primary approach for handling of missing values

The primary approach for multiple imputations of missing values of body weight at week 56 (type MT+MD) for both the liraglutide 3.0 mg and placebo group is by sampling among all available assessments at week 56 in the placebo group (type AT+AD). This approach is also known as jump to reference and makes the assumption that subjects instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to diet and exercise⁴³. Body weight measurements at visits between baseline and week 56 are not used for this imputation approach. The multiple imputation approach is done in three steps.

- **Imputation:** Step 1 defines an imputation model based on placebo subjects, which is used to impute missing body weight values at week 56 in both arms. This will be done 100 times and results in 100 complete data sets. A more detailed explanation of this step is given below.
- **Analysis:** Step 2 analyses each of the 100 complete data sets, using the statistical model defined in Sections [17.3.1.1](#) and [17.3.1.2](#), and saves the 100 estimation results.
- **Pooling:** Step 3 integrates the 100 estimation results into a final result using Rubin's formula.

The imputation model in step 1, uses placebo subjects from FAS with non-missing body weight measurements at baseline and week 56. The imputation model is a linear regression of body weight (kg) at week 56 on the factors and covariates listed in [Table 17-4](#) (except randomised treatment arm) with no interactions. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model is then used to impute missing week 56 body weight values for both randomised treatment arms.

If 100 copies are not sufficient to establish stable results, a higher number will be used. The multiple imputations will be generated using Novo Nordisk trial number 80224272 as seed number.

Sensitivity analyses for the analysis of the primary endpoints for the effectiveness estimand

The sensitivity analyses will address the robustness of the primary approach for handling of missing values. In particular the sensitivity analyses address how assumptions on how body weight progresses after discontinuation of randomised treatment impact the estimated treatment difference between liraglutide 3.0 mg and placebo. The sensitivity analyses include the following.

- A multiple imputation approach as described by McEvoy⁴⁴ where missing body weight measurement at week 56 for non-retrieved drop-outs (type MD) are imputed by sampling from values obtained from retrieved drop-outs (type AD) in each randomised treatment arm and according to the timing (monthly) of last available observation (of body weight) on randomised treatment (LAO-OT). Missing body weight measurements at week 56 for subjects on drug treatment (type MT) are imputed by sampling from type AT in the relevant randomised treatment arm. Thus, the imputation model for each randomised treatment arm and timing of LAO-OT is a linear regression of body weight (kg) at week 56 on the factors and covariates listed in [Table 17-4](#) (except randomised treatment arm) with no interactions and including LAO-OT of body weight as covariate. If timing by month is too restrictive, quarters, half-years, or excluding timing will be used.
- A weighted ANCOVA (wANCOVA) where returning drug discontinuing subjects (AD) are up-weighted relative to their proportion of all drug discontinuing subjects (AD+MD) to account for the subjects not returning for assessments at week 56⁴⁴. Similarly, AT subjects

are up-weighted relative to their proportion of all drug continuing subjects (AT+MT). The up-weighting is done by randomised treatment arm and the timing of LAO-OT. Subjects who are missing the weight measurement at week 56 (MD+MT) are assigned a weight of 0 (zero).

- A single imputation approach as done by Sacks⁴⁵. Missing weight measurement at week 56 for subjects who drop-out (type MD) are imputed using a weight regain rate of 0.3 kg/month after last available observation (LAO) of body weight. Change from baseline is truncated whenever the extrapolation would lead to a positive weight gain relative to baseline. LAO does not need to be the same as LAO-OT as subjects are allowed to come to scheduled visits after discontinuing randomised treatment. When a subject's LAO represents a gain in weight relative to baseline, no additional gain will be imputed, and the unfavourable gain is carried forward to week 56. Missing weight measurement at week 56 for subjects on treatment (type MT) will be imputed using the LAO. The weight regain imputation will be done for both randomised treatment arms. Additionally, a version where only the liraglutide 3.0 mg arm uses the regain rate while the placebo arm uses LAO (corresponding to a weight regain rate of 0 kg/month) will be performed.
- Tipping point analysis. In a similar manner as above for a range of weight regain rates (starting from 0.1 kg/month and in intervals of 0.1 kg/month) for MD in liraglutide 3.0 mg arm will be used to define a tipping point in which superiority of liraglutide 3.0 mg disappears. In this analysis, the placebo arm will be imputed by LAO.

[Figure 17-1](#) and [Table 17-5](#) give an overview of the handling of missing values at week 56 assessments.

Additional sensitivity analyses

Additional analyses will investigate how sensitive the primary statistical models (for primary endpoints) are to the choice of factors and covariates in the model as follows. A model resembling the primary analysis models using the same imputation method (jump to reference) adjusting only for baseline body weight and randomised treatment arm. The imputation model (step 1) will be same as for the primary approach.

For the binary primary endpoint, the risk difference (unadjusted for any factors and covariates) and corresponding 95% CI will also be calculated.

17.3.3 Analysis method addressing the efficacy estimand for the primary endpoints

The efficacy estimand for % weight change will be assessed using a mixed model for repeated measurements (MMRM). The MMRM will use assessments only from subjects who are taking the randomised treatment until end of trial or at first discontinuing of trial drug (either temporarily or

permanently). A pause of less than three consecutive days is not regarded as discontinuation for this analysis. This means that assessments at week 56 for retrieved drop-outs (type AD) will be discarded. The MMRM will be fitted using % weight change and the same factors and covariates (see [Table 17-4](#)) 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.

The efficacy estimand for 5% responders will be assessed using the same MMRM. From the MMRM individually predicted values for % weight change at week 56 will be used to classify each subject as 5% responder or not. This classification will then be analysed using a logistic regression model with treatment and sulphonylurea (yes/no) as the only factors.

17.3.4 Subgroup analyses for primary endpoints

For the effectiveness estimand, subgroup analyses will be done for the factors listed and categorised as in [Table 17-4](#). For baseline weight and insulin dose, categories based on quartiles will be used. The subgroup analyses will be done separately for each of these by including interaction term(s) with randomised treatment arm in the respective models (ANCOVA or logistic regression).

Figure 17–1 Illustration of imputation approaches

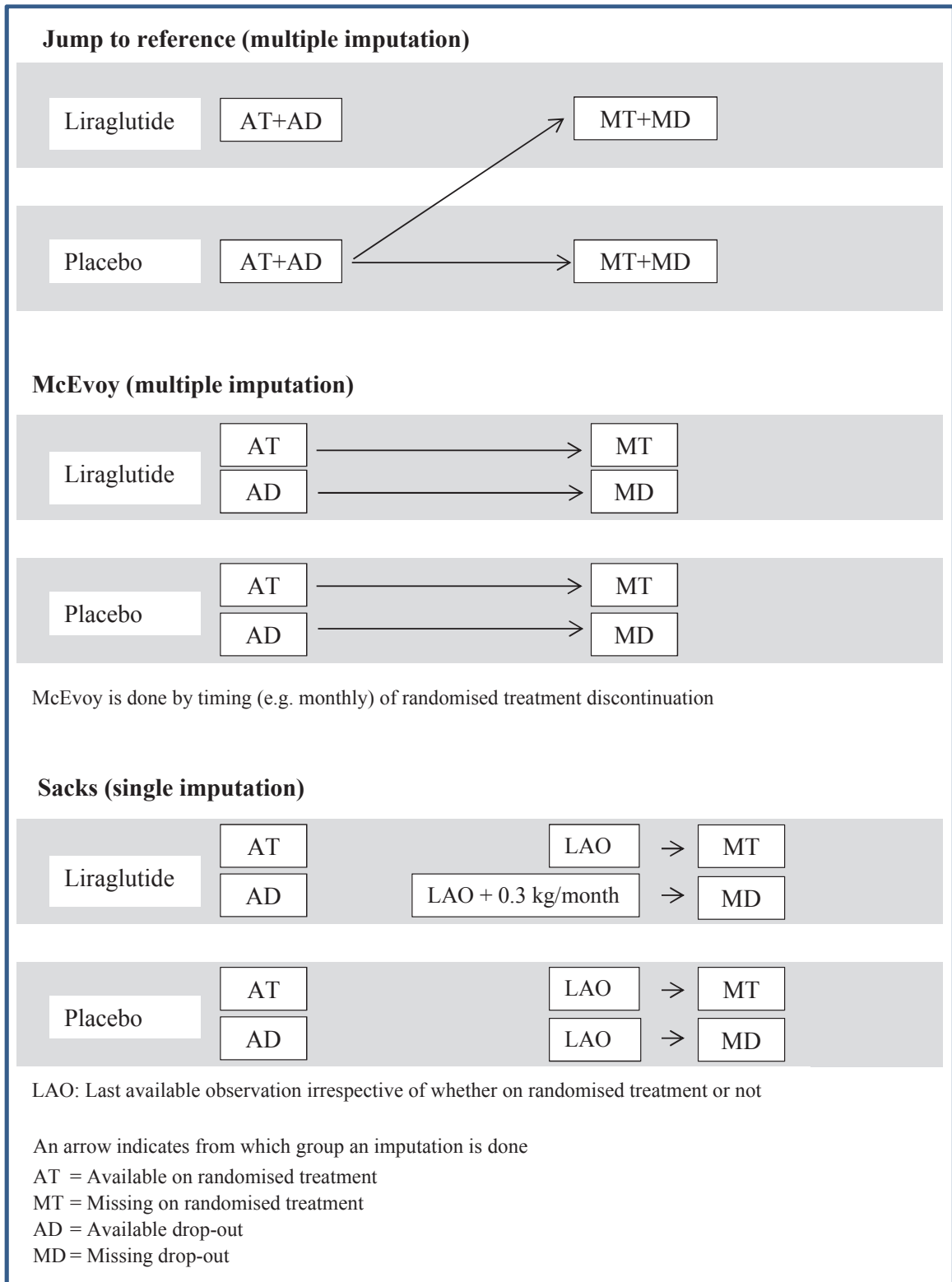


Table 17–5 Overview of handling of missing values

Approach	Description	Assumptions
Jump to reference (multiple imputation)	Liraglutide and placebo MT+MD imputed from placebo AT+AD (i.e., all available placebo assessments at week 56)	- Liraglutide MD lose any treatment effect instantly after drop-out - Placebo AT and placebo AD are assumed to have same weight loss
McEvoy (multiple imputation)	Separately for the two randomised treatment arms: MD imputed from AD by matching on time (month) of drop-out MT imputed from AT	- AD is representative of the MD for each randomised treatment arm - AT is representative of the MT for each randomised treatment arm
Weighted ANCOVA (wANCOVA)	No imputation. Separately for the two randomised treatment arms: AD subjects are up-weighted relative to their proportion of AD+MD and timing of drop-out AT subjects are up-weighted relative to their proportion of AT+MT	- AD is representative of the MD for each randomised treatment arm - AT is representative of the MT for each randomised treatment arm
Sacks (single imputation)	Liraglutide MD imputed by minimum of LAO+0.3 kg and baseline value for each month from drop-out to week 56 and either a) Placebo MD imputed by minimum of LAO+0.3 kg and baseline value for each month from drop-out to week 56 or b) MT (both randomised treatment arms) and placebo MD are imputed by LAO	a) Liraglutide and placebo MD lose any treatment effect linearly after drop-out. b) Only liraglutide MD lose any treatment effect linearly after drop-out. No change in treatment effect since LAO for others.
Tipping point (single imputation)	Liraglutide MD imputed by minimum of LAO+X kg (X in steps of 0.1) and baseline value for each month from drop-out to week 56. MT (both randomised treatment arms) and placebo MD are imputed by LAO	Only liraglutide MD lose any treatment effect linearly after drop-out. No change in treatment effect since LAO for others

AT available on randomised treatment, MT missing on randomised treatment, AD available drop-out, MD missing drop-out, LAO last available observation, LAO-OT last available observation on randomised treatment.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints are listed in Section [4.2.2.1](#).

All confirmatory secondary endpoints are planned to be assessed at week 56 and will be analysed using the same MI approach as used for the primary endpoints and to address the effectiveness estimand. The statistical models for continuous endpoints will be ANCOVA with factors and covariates listed in [Table 17-4](#) with baseline body weight replaced by baseline measurement of endpoint to be analysed. The statistical model for 10% responders will be analysed using logistic regression in the same way as for 5% responders.

Sensitivity analyses will be carried out for all confirmatory secondary endpoints. See [Table 17-6](#) for details on planned analysis methods, multiple imputation approach and sensitivity analyses.

The efficacy estimand will also be assessed for confirmatory secondary endpoints using MMRM as described for the primary endpoints.

17.4.1.1 Description of the testing procedure to address the effectiveness estimand for primary and confirmatory secondary endpoints

The tests of superiority of liraglutide 3.0 mg to placebo for each of the endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. The two primary endpoints are included in the statistical testing hierarchy below, even though the primary objective will only be met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints. The test hierarchy is given in [Table 17-6](#). The first endpoints to be tested are all assessing aspects of weight loss (e.g., relative change in body weight, achieving a certain magnitude of weight loss, and change in waist circumference); these endpoints are followed by endpoints assessing change in weight-related comorbidities and/or consequences of excess body weight and ‘feeling and function’ indicators.

Table 17–6 Hierarchical order and type of statistical model to address the effectiveness estimand for primary and confirmatory secondary endpoints

Test order	Endpoint	Endpoint type	Statistical model	MI approach	Sensitivity analyses #
Primary endpoint					
1	Change in body weight (%) from baseline to week 56	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Sacks Tipping point Unadjusted ANCOVA
2	Proportion of subjects losing at least 5% of baseline body weight at week 56	Binary	Logistic Regression	Jump to reference	McEvoy Sacks Tipping point Risk difference
Confirmatory secondary endpoints					
3	Proportion of subjects losing more than 10% of baseline body weight at week 56	Binary	Logistic Regression	Jump to reference	McEvoy Tipping point
4	Change from baseline to week 56 in waist circumference (cm)	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
5	Change from baseline to week 56 in HbA1c (%)	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
6	Change from baseline to week 56 in fasting glucose (%)	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
7	Change from baseline to week 56 in systolic blood pressure (sBP) (mmHg)	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
8	Change from baseline to week 56 in impact of Weight on Quality of Life-Lite (IWQoL-Lite for CT), physical functioning score	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
9	Change from baseline to week 56 in impact of Weight on Quality of Life-Lite (IWQoL-Lite for CT), mental/emotional function score	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point

MI Multiple Imputation;

See [Table 17–5](#)

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

Supportive secondary endpoints are listed in Section [4.2.2.2](#).

Supportive secondary endpoints will be evaluated to address the effectiveness estimand. These endpoints will be analysed using the same MI approach as used for the primary and confirmatory secondary endpoints.

The endpoint mean daytime glucose value will be calculated from the 7-point SMPG profile as area under the curve (AUC) divided by length of time-interval. AUC will be calculated using the linear trapezoidal method. Missing points in the 7-point SMPG profile are ignored for the calculation.

The statistical model for continuous endpoints will be ANCOVA with factors and covariates listed in [Table 17-4](#) with baseline body weight replaced by baseline measurement of endpoint to be analysed. The statistical model for proportions will be analysed using logistic regression.

17.4.2.2 Safety endpoints

Descriptive statistics for all safety endpoints will be provided with the aim to compare liraglutide 3.0 mg and placebo. All analyses and tabulations will be done using the safety analysis set. Unless otherwise stated, no formal statistical analyses are planned for the safety endpoints.

Adverse events and hypoglycaemic episodes will be classified and analysed as ‘in trial’ and ‘on drug’ defined in terms of patient years of observation (PYO) and patient years of exposure (PYE), respectively. For each subject PYO is defined as number of days from date of randomisation until and including date of follow-up visit or date of last contact. For each subject PYE is defined as time intervals of exposure to trial drug including an ascertainment window of 14 days for each exposure interval.

Adverse events

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be presented based on system organ class, high level group term and preferred terms.

AEs, which occurred while the subject was in trial or on drug will be summarised descriptively, whereas AEs, which occurred before first exposure to trial drug or after the follow-up visit will only be presented in listings. AEs will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Furthermore, AEs will be summarised by seriousness, severity, relation to trial drug, premature treatment discontinuation due to AE and outcome.

Summary tables by system organ class, high level group term and preferred term will be made for all AEs, SAEs, AEs possibly or probably related to trial drug, severe AEs, AEs occurring in at least 5% of the subjects in any arm, and AEs occurring in at least 1% of the subjects in any treatment arm.

AEs requiring completion of specific event forms will be presented in tables and listings. In addition, time to occurrence of these AEs will be presented in cumulative incidence plots.

Hypoglycaemic episodes

All hypoglycaemic episodes will be summarised in terms of N, %, E, rate as on drug (PYE) and in trial (PYO) and using same ascertainment window of 14 days as for AEs.

Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs during on drug time intervals.

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

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 17-2](#)) and the ADA classification of hypoglycaemia (see [Figure 17-3](#)).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)²⁰ Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see [Figure 17-2](#)) in addition to the ADA classification:

Severe hypoglycaemia according to the ADA classification¹¹.

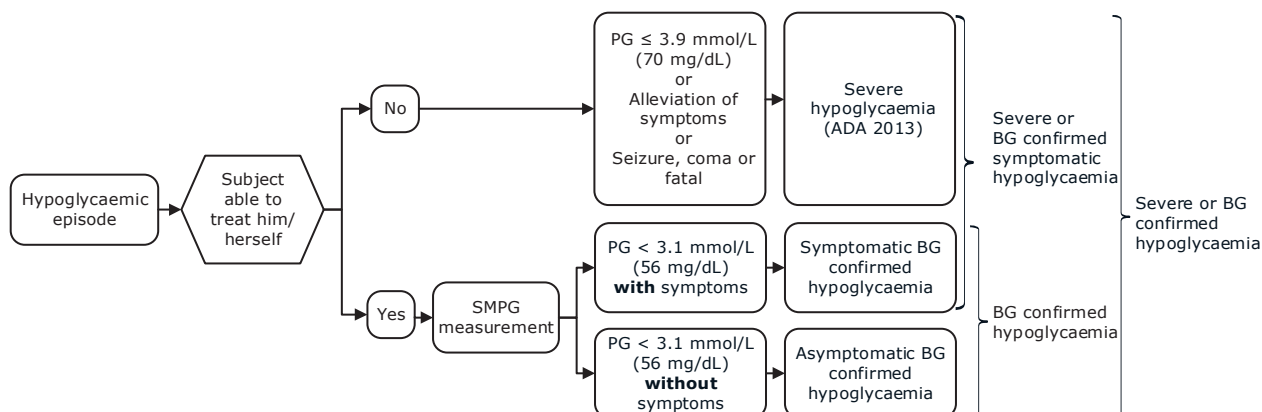
Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.

Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification¹¹ or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.

Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification¹¹ or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



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

Figure 17–2 Novo Nordisk classification of hypoglycaemia

ADA classification¹¹ of hypoglycaemia

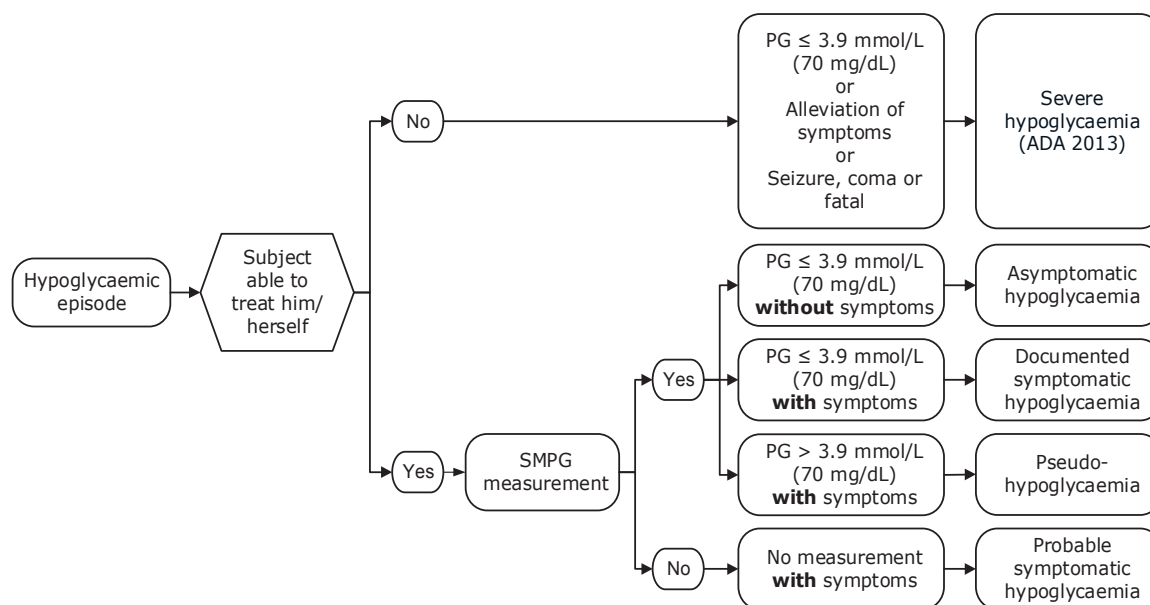
Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.

Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

Figure 17–3 ADA classification of hypoglycaemia

Physical examination

Outcome of the physical examination at screening and change in the physical examination category at week 56 will be summarised in tables.

Pulse

Pulse (beats/min) at baseline and change of pulse at week 56 will be summarised in tables by week and treatment. Categories based on the maximum change from baseline until week 56 (>0, >5, >10, >20 beats/min) and categories based on the maximum value until week 56 (>80, >90, >100 beats/min) will be included in summary tables. Additionally, change in pulse from baseline to week 56 will be evaluated in the in trial observation period similar as in the primary analysis for the primary estimand but using the safety analysis.

ECG

Shifts in the ECG category from screening to week 56 will be summarised in tables.

Laboratory measurements

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

Laboratory safety parameters are measured throughout the trial and comprise haematology and biochemistry as defined in the flow chart.

The distribution of each continuous laboratory parameter will be presented using box plots by treatment and week. Continuous laboratory parameters will be compared to the relevant reference ranges and results will be presented.

Amylase and lipase

Shifts from baseline to highest value in trial period to UNL, 2xUNL and 3xUNL will be summarised in tables.

Mean plots, geometric mean plots and box plots by gender, visit and treatment will be prepared. Change from week 0 to week 56 will also be presented by empirical distribution plots.

Number and percentage of subjects with amylase and lipase levels \geq UNL, \geq 2xUNL or \geq 3xUNL will be tabulated by week and treatment. Subjects with values \geq 2xUNL will additionally be presented with spaghetti plots.

Additionally, change in amylase and lipase from baseline to week 56 will be evaluated in the in trial observation period similar to the primary analysis for the primary estimand but using the safety analysis set.

Calcitonin

Number, percentage and incidence of subjects with persistent (all post-baseline measurements) and incidental (at least one post-baseline measurement) increases in calcitonin for the criteria below will be tabulated for all subjects, males and females.

- From baseline $<$ UNL to \geq UNL
- From baseline $<$ UNL to \geq 20 ng/L
- From baseline $<$ UNL to \geq 50 ng/L
- From baseline $<$ 20 ng/L to \geq 20 ng/L
- From baseline $<$ 50 ng/L to \geq 50 ng/L

Number and percentage of subjects with calcitonin levels \geq UNL, \geq 1.5xUNL or \geq 20 ng/L and \geq 50 ng/L will be tabulated by visit and treatment.

A summary table showing number and percentage of observations $<$ and \geq LLOQ, minimum, Q25, median, Q75, maximum and geometric mean will be prepared by gender, visit and treatment.

The distribution of the calcitonin values across treatment group and time will be shown in plots by gender and total actual levels. Geometric means will be plotted by visit and treatment in order to assess the pattern of the longitudinal changes.

In addition, a scatter plot of baseline vs. maximum post-baseline calcitonin value will be prepared.

Longitudinal changes with calcitonin ≥ 20 ng/L will be evaluated with spaghetti plots.

Subjects with at least one post-baseline calcitonin value above 20 ng/L will be listed.

The listings will include treatment, age, gender, smoking habits at baseline, risk factor information (use of relevant concomitant medication at time of assessment [proton pump inhibitors and H2 blockers] and medical history of thyroid disorder) and calcitonin values.

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial will be conducted in compliance with ICH GCP¹, applicable regulatory requirements and in accordance with the Declaration of Helsinki².

Risks and precautions

The sections below describe identified and potential risks associated with liraglutide treatment. The identified/potential risks are based on findings in non-clinical and clinical trials with liraglutide as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

Neoplasms

Subjects with overweight and obesity have an increased risk of certain types of cancer. In the clinical development programme for liraglutide 3.0 mg, the reporting rate of neoplasm events confirmed by external independent event adjudication committee was similar with liraglutide and placebo. Thus, the overall risk of neoplasms and cancer in the weight management trials was low and balanced between treatment groups.

Thyroid C-cell tumours

Liraglutide causes thyroid C-cell tumours (MTC) at clinically relevant exposures in both genders of rats and mice. Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the rearranged during transfection (RET) protooncogene in thyroid C-cells. Human relevance of thyroid C-cell tumours in mice and rats is unknown and has not been determined by clinical or nonclinical studies. Data from the intensive monitoring of calcitonin (a marker for MTC) in plasma in the liraglutide clinical development programme, do not support an effect of liraglutide on calcitonin levels in humans. As a precaution subjects with personal or family history of MTC, or MEN2 will not be enrolled in the trial. Calcitonin will be monitored as per flow chart, see Section 2. Subjects with elevated calcitonin (≥ 100 ng/L) will be discontinued on liraglutide 3.0 mg and appropriate clinical follow-up will be initiated.

Breast and colon tumours

Based on a limited number of reports in the clinical development programme for liraglutide 3.0 mg, a numerical imbalance was observed for events of breast neoplasms in females and colorectal adenomas in males. There were too few cases to determine whether these cases were related to liraglutide. In addition, there are insufficient data to determine whether liraglutide has an effect on pre-existing breast neoplasia. Two positively adjudicated cases of malignant colorectal carcinoma were reported in liraglutide-treated subjects and none in placebo-treated subjects.

Allergic reactions

As in the case with all protein-based pharmaceuticals, treatment with liraglutide may evoke allergic reactions. These may include urticaria, rash, pruritus as well as anaphylactic reactions. As a precaution, subjects with known or suspected hypersensitivity to trial product(s) or related products will not be enrolled in the trial. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction occurs

Pancreatitis

An association between the use of GLP-1RAs and pancreatitis has been suggested based on case reports received in clinical trials and during the post-marketing experience with liraglutide (in T2DM) and other GLP-1RAs. Few events of pancreatitis have been reported in clinical trials with liraglutide in weight management. After initiation of liraglutide 3.0 mg, subjects must be observed carefully for signs and symptoms of pancreatitis (see Section [8.6.5](#)). If pancreatitis is suspected, liraglutide 3.0 mg should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, liraglutide 3.0 mg should not be restarted. Subjects with a history of pancreatitis are excluded from participation in the trial.

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 in the clinical development programme for liraglutide 3.0 mg. From literature, it is well-known that obesity carries an increased risk of cholelithiasis and that an association between rapid and/or marked weight loss and the development of cholelithiasis is present⁴⁶. If cholelithiasis is suspected, treatment should be discontinued and gallbladder examination and appropriate clinical follow-up should be initiated.

Hypoglycaemic episodes

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. Subjects blood glucose parameters will be monitored prior to starting liraglutide 3.0 mg and during treatment. To minimise the risk of hypoglycemia, insulin dose will be reduced by 15-20% for subjects with $HbA_{1c} \leq 8\%$ at randomisation. Adjustment of insulin dose may be initiated one week after randomisation; however, in the first five weeks of the trial, the basal insulin dose should not exceed the pre-trial dose and bolus insulin should not be initiated, unless deemed necessary by investigator to control unacceptable hyperglycaemia. In addition, the dose of sulphonylurea may be reduced by 50% at investigator's discretion in patients using this OAD since hypoglycaemic events are more frequent when combining liraglutide with sulphonylurea than with other OADs.

Heart rate increase

In the clinical development programme, mean increase in resting heart rate (by 2-3 beats per minute) as well as a slight decrease in systolic blood pressure has been observed. The long-term clinical effects of the increase in resting heart rate have not been established. There is no indication that the effect on resting heart rate is dose dependent and the increase in heart rate disappears upon treatment discontinuation. When initiating treatment with liraglutide 3.0 mg, heart rate should be monitored at regular intervals consistent with usual clinical practice.

Gastrointestinal adverse events

The most frequently reported adverse events in subjects treated with liraglutide 3.0 mg were gastrointestinal (nausea and diarrhoea), with onset during the first weeks; these were mostly mild to moderate, and transient. Other gastrointestinal adverse events (GI AEs) included: dyspepsia, vomiting, constipation, and abdominal pain. Clinical trials have indicated that a low starting dose with gradual dose escalation diminishes GI AEs compared with more aggressive dosing regimens. If subjects do not tolerate an increased dose during dose escalation, dose escalation may be delayed for approximately one additional week.

Renal impairment

GLP-1 RAs may cause nausea, vomiting or diarrhoea leading to loss of fluids (dehydration). Dehydration may cause renal impairment and acute renal failure. Subjects treated with liraglutide 3.0 mg should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Benefits

In the present trial, subjects 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. Results from the clinical development programme demonstrated that liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, was effective for weight loss in subjects with overweight or obesity and T2DM treated with 0-3 OADs (metformin, glitazone, sulphonylurea). The anticipated lower insulin requirement in the present trial with liraglutide 3.0 mg vs. placebo is expected to further amplify weight loss. Even a modest weight loss may improve glycaemic control and decreases the risk of hypertension and premature cardiovascular death in patients with obesity⁴⁷⁻⁴⁹. Finally, improvements in patient reported health-related quality of life and physical function have been observed with weight loss. Although subjects will have to spend time on site visits and procedures required by trial participation, it is expected that all subjects (including those subjects randomised to placebo) will benefit from the behavioural counselling and increased physical activity, with close follow-up of their obesity and a careful medical examination. All of which will result in an intensified management of their obesity.

Conclusion

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. It is important to note that the target population for liraglutide 3.0 mg is already at serious risk from obesity and its associated major co-morbidities. The overall efficacy and safety results from the weight management programme, demonstrated that the benefit-risk balance is in favour of liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, within the investigated population of subjects with overweight and obesity.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP¹ and the requirements in the Declaration of Helsinki².

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

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products. A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The investigator must ensure the subject has ample time to come to a decision whether or not to participate in the trial. The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

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

18.3 Data handling

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

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

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

18.4 Information to subjects during trial

During the trial, the subjects may receive information that could include a “welcome to the trial letter”, newsletter(s) and a “thank you for your participation letter” after completion of the trial, if locally acceptable.

Initiatives for subject retention will be instituted for this trial. These may include retention activities, materials and items, if locally acceptable. The retention items will be relevant for the subjects' participation in the trial and/or their obesity and will not exceed local fair market value.

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

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

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

Considerable effort must be made by the investigator to avoid missing data, including minimising the number of subjects withdrawing from the trial.

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites. The subjects will be carefully informed about the trial procedures before signing informed consent, so that they are fully aware of the implications of participating in the trial.

Measures will be implemented during trial conduct to encourage subjects to complete the trials; these will be described in detail in trial specific retention mitigation plans and may include subject newsletters, appreciation items and various local initiatives.

For subjects discontinuing treatment, the investigator should encourage continued attendance for all visits including the IBT visits until the primary outcome measure at 56 weeks. Furthermore, re-initiation of treatment is allowed at the discretion of investigator, as described Section [8.1](#).

Surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to initiate mitigations as needed in collaboration with the trial sites.

19.3 Protocol compliance for Mexico

The trial will be conducted in compliance with this protocol, ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

The above will include the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility: a) Investigation follow-up b) Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of

Protocol
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT no.: 2015-005619-33

~~CONFIDENTIAL~~

Date:	14 September 2016	Novo Nordisk
Version:	4.0	
Status:	Final	
Page:	111 of 123	

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.

20 Audits and inspections

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

21 Critical documents

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

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

For sites outside the US:

All investigators outside of the US will not sign FDA form 1572

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

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP¹, applicable regulatory requirements and the Declaration of Helsinki².

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

22 Responsibilities

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

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

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

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

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications⁵⁰.

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure²⁹.

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

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

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors⁵⁰ (sometimes referred to as the Vancouver Criteria).

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

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

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

23.2 Investigator access to data and review of results

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

24 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g., the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to investigator's brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the CTR synopsis to the IRB/IEC.

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

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

Regulatory Authorities

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

26 Indemnity statement

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

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

For Germany: Novo Nordisk accepts liability in accordance with: German Drug Law dated 24 August 1976 in the version published on 12 Dec 2005 (BGBl. I S. 3394), last amended by Article 3 of the Law of 04 Apr 2016 (BGBl. I S. 569)

For Mexico: Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance. If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the trial medication and/or a trial procedure that otherwise would not have been part of his/her regular care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the trial by his own will or by a decision from the investigator. By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

27 References

1. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1), Step 4. 10 June 1996.
2. 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.
3. Buse J. Combining insulin and oral agents. *Am J Med.* 2000;108 Suppl 6a:23S-32S.
4. Pi-Sunyer FX. The impact of weight gain on motivation, compliance, and metabolic control in patients with type 2 diabetes mellitus. *Postgrad Med.* 2009;121(5):94-107.
5. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. *JAMA.* 2015;314(7):687-99.
6. 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.
7. Novo Nordisk A/S. Saxenda[®] (liraglutide), US Prescribing information (PI) (Revised Nov 2014). Available from:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf.
8. Novo Nordisk A/S. Saxenda[®] (liraglutide), EU Summary of product characteristics (SmPc) (last updated 16 Apr 2015). Available from:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003780/WC500185786.pdf.
9. Novo Nordisk CA. Saxenda[®] (liraglutide), CA Product monograph (approved 06 Oct 2015). Available from: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=92226&lang=eng>.
10. Novo Nordisk A/S. Victoza[®] (liraglutide), EU Summary of product characteristics (SmPc) (last updated 24 Nov 2015). Available from:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf.
11. Novo Nordisk A/S. Victoza[®] (liraglutide), US Prescribing information (PI) (revised Jan 2010). Available from:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf.
12. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2015;100(2):342-62.
13. Davies MJ, Gross JL, Ono Y, Sasaki T, Bantwal G, Gall MA, et al. Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. *Diabetes Obesity & Metabolism.* 2014;16(10):922-30.
14. Department of Health, FDA, CDER. Reviewer Guidance Evaluating the Risks of Drug Exposure in Human Pregnancies. 2005.
15. Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, et al. American Association of Clinical Endocrinologists and American College of Endocrinology

- Position Statement on the 2014 Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease. *Endocrine Practice*. 2014;20(9):977-89.
16. Jensen MD, Ryan DH, Apovian CM, Loria CM, Ard JD, Millen BE, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2013;129(25 Supplement 2):S102-40.
 17. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2016 executive summary. *Endocr Pract*. 2016;22(1):84-113.
 18. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
 19. DPPOS research group. Diabetes prevention program outcomes study. Available from: <https://dppos.bsc.gwu.edu/web/dppos/lifestyle>.
 20. Wadden TA, Volger S, Sarwer DB, Vetter ML, Tsai AG, Berkowitz RI, et al. A two-year randomized trial of obesity treatment in primary care practice. *N Engl J Med*. 2011;365(21):1969-79.
 21. U.S. Preventive Services Task Force. Behavioral counseling interventions: An evidence-based approach. January 2015. Available from: <http://www.uspreventiveservicestaskforce.org/Page/Name/behavioral-counseling-interventions-an-evidence-based-approach>.
 22. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2014;37 Suppl 1:S120-43.
 23. Group LAR, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Archives of Internal Medicine*. 2010;170(17):1566-75.
 24. Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, Steinberg C. Benefits of lifestyle modification in the pharmacologic treatment of obesity: a randomized trial. *Arch Intern Med*. 2001;161(2):218-27.
 25. Redmon JB, Bertoni AG, Connelly S, Feeney PA, Glasser SP, Glick H, et al. Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care*. 2010;33(6):1153-8.
 26. Wadden TA, Neiberg RH, Wing RR, Clark JM, Delahanty LM, Hill JO, et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)*. 2011;19(10):1987-98.
 27. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-53.
 28. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and Type 2 Diabetes The American College of Sports Medicine and the American Diabetes

- Association joint position statement executive summary. *Diabetes Care*. 2010;33(12):2692-6.
29. Novo Nordisk Code of Conduct for Clinical Trial Disclosure. Available from: <http://novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx>. 11 Jan 2015.
30. 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.
31. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007. Available from: <http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm>.
32. 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*. 1 May 2001.
33. 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. *Official Journal of the European Communities*. 2004.
34. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care*. 1995;18(4):517-22.
35. Kolotkin RL, Head S, Hamilton M, Tse CK. Assessing Impact of Weight on Quality of Life. *Obes Res*. 1995;3(1):49-56.
36. 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. December 2009.
37. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-83.
38. 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.
39. Rewers MJ, Pillay K, de Beaufort C, Craig ME, Hanas R, Acerini CL, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15 Suppl 20:102-14.
40. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 - Validity of a brief depression severity measure. *Journal of General Internal Medicine*. 2001;16(9):606-13.
41. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035-43.

42. European Medicines Agency. Ethical considerations for clinical trials on medicinal products with the paediatric population. Recommendations of the Ad hoc 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. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. *J Biopharm Stat.* 2013;23(6):1352-71.
44. McEvoy BW. Missing data in clinical trials for weight management. *J Biopharm Stat.* 2016;26(1):30-6.
45. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med.* 2009;360(9):859-73.
46. Erlinger S. Gallstones in obesity and weight loss. *Eur J Gastroenterol Hepatol.* 2000;12(12):1347-52.
47. Pi-Sunyer FX. Weight loss and mortality in type 2 diabetes. *Diabetes Care.* 2000;23(10):1451-2.
48. Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. *Obes Res.* 2000;8(3):270-8.
49. Kritchevsky SB, Beavers KM, Miller ME, Shea MK, Houston DK, Kitzman DW, et al. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. *PLoS One.* 2015;10(3):e0121993.
50. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest.* 1987;79(3):777-81.

Liraglutide
Trial ID: NN8022-4272
Protocol - Appendix A
EudraCT No.: 2015-005619-33

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

14 September 2016
4.0
Final
1 of 6

Novo Nordisk

Appendix A

NN8022-4272

Monitoring of calcitonin

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.~~

Table of Contents

	Page
Table of Contents	2
1 Background	3
2 Calcitonin monitoring	4
2.1 Calcitonin \geq 100 ng/L	4
2.2 Calcitonin \geq 50 and $<$ 100 ng/L	4
2.3 Calcitonin \geq 10 and $<$ 50 ng/L	5
3 References	6

1 Background

Treatment with GLP-1 receptor agonists has shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. 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) is likely indicative of C-cell neoplasia; the interpretation of values between upper normal range (5.0 and 8.4 ng/L for women and men, respectively) and 100 ng/L is less clear with regards to indication of the neoplasia.

There are several known confounding factors affecting calcitonin levels, e.g.:

- renal dysfunction
- smoking
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H₂-blockers and glucocorticoids)

Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

2 Calcitonin monitoring

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin.

In case a subject has a calcitonin value ≥ 10 ng/L, the algorithm outlined below should be followed. The algorithm applies for all calcitonin values including screening values.

Please report clinically significant abnormal values as an adverse event (see Section 12 in the protocol).

2.1 Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see protocol section 6.5 premature discontinuation of trial product). The subject can remain in the trial; however, all suspected medications 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.¹ All of these patients were diagnosed with MTC resulting in a positive predictive value of 100 %.

Diagnostic evaluation should include:

- thyroid ultrasound
- 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.

2.2 Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) must be referred to a thyroid specialist for further evaluation. The subject can remain in the trial and continue on trial product.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease.¹ 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 there are no contraindication, a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests should be considered to undergo surgery

- if pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information about the need for surgery.

2.3 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 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.¹ 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 10-20 ng/L Costante et al¹ identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of CT > 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^{2,3}

3 References

1. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. *J Clin Endocrinol Metab.* 2007;92(2):450-5.
2. 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.
3. 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.

Liraglutide 3.0 mg
Trial ID: NN8022-4272
Clinical Trial Report
Appendix 16.1.1

~~CONFIDENTIAL~~

Date:
Version:
Status:

19 February 2019 | **Novo Nordisk**
1.0
Final

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT No.: 2015-005619-33

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

14 November 2016
2.0
Final
1 of 4

Novo Nordisk

Protocol Amendment
no 1
to Protocol, final version 4.0
dated 14 September 2016

Trial ID: NN8022-4272

SCALE™ Insulin
Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2
diabetes mellitus treated with basal insulin

Trial phase: 3b

Applicable to all countries

Amendment originator:



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.~~

Table of Contents

	Page
Table of Contents.....	2
1 Introduction including rationale for the protocol amendment.....	3
2 Changes.....	3
2.1 Section 2 Flow chart.....	3
2.2 Section 5.3.2.2 Treatment with insulin throughout the trial.....	3
2.3 Section 8.2.5 Concomitant medication.....	3
2.4 Section 8.3.9 Insulin dose.....	3
2.5 Section 8.5.2 Laboratory assessments for safety.....	4

1 Introduction including rationale for the protocol amendment

Rationale for the changes:

- Addition of bicarbonate as a part of the biochemistry laboratory assessment. The FDA has requested that bicarbonate is added as a routine laboratory test in trials where sodium-glucose cotransporter-2 (SGLT2) inhibitors are used as background medication, because SGLT2-inhibitors have been associated with a risk for metabolic acidosis. Hence, serum bicarbonate assay has been included to collect additional safety information in alignment with other Novo Nordisk trials where trial product is add-on to an SGLT2 inhibitor. There is no safety risk for those subjects who do not have the bicarbonate assay performed during their treatment.
- Inconsistent wording in reporting of insulin dose and transcription of insulin dose to eCRF.
- Discrepancy regarding the time period of an eye examination performed prior to randomisation.

In this protocol amendment:

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

2 Changes

2.1 Section 2 Flow chart

³Only if not available within last 90 days before ~~screening~~ randomisation

2.2 Section 5.3.2.2 Treatment with insulin throughout the trial

~~The insulin dose adjustments recorded in the diabetes diary, must be entered in the electronic case report form (eCRF).~~

2.3 Section 8.2.5 Concomitant medication

The products described as NIMP (see Section 5.3.2) are also recorded as concomitant medication in the eCRF. However the adjustments of insulin doses performed during the trial will be recorded in the designated ~~form~~ *diabetes diary* and these must be assessed by the investigator.

2.4 Section 8.3.9 Insulin dose

Subjects will be instructed in how to record the insulin use in the provided diabetes diary *and* the investigator should review the subject's insulin dose. ~~as specified in Section 8.1.~~ *From visit 2 and until but not including the follow-up visit, the investigator must record the subject's basal and bolus (if applicable) daily injected doses, respectively, prior to each scheduled visit in the eCRF. Results of the subject's SMPG measurements should be noted in the diabetes diary and total daily injected dose of basal/bolus insulin prior to each contact will be transcribed into the eCRF and*

~~based on these, dose adjustment guidance will be provided. All adjustments of insulin dose level will be captured in the eCRF. From visit 2 and until follow up, the investigator should record the subject's total daily injected dose of insulin (basal/bolus) prior to each visit in the eCRF.~~

2.5 Section 8.5.2 Laboratory assessments for safety

Biochemistry

Blood samples for biochemistry must be collected at the specified visits (see Section 2).

- Creatinine
- Urea (blood urea nitrogen)
- Uric acid
- Alanine aminotransaminase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase (ALP)
- Albumin
- Amylase
- *Bicarbonate*
- Lipase
- Sodium
- Potassium
- Calcium, total
- Calcitonin (please refer to Appendix A for actions to be taken if calcitonin is ≥ 10 ng/L)
- TSH*
- Bilirubin, total (TBL)
- hs-CRP**
- GFR, estimated

*If TSH levels are out of normal range, the investigator must perform additional testing:

- Total and free T3 and T4 and Free Thyroid Index
- Thyroid peroxidase antibodies

**hs-CRP is only measured at Visit 2 and Visit 24.

Protocol Amendment no. 2
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT No.: 2015-005619-33

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

15 March 2017 | **Novo Nordisk**
1.0
Final
1 of 5

Protocol Amendment
no 2
to Protocol, final version 6.0
dated 15 November 2016

Trial ID: NN8022-4272

SCALE™ Insulin
Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2
diabetes mellitus treated with basal insulin

Trial phase: 3b

Applicable to all countries

Amendment originator:



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.~~

Table of Contents

	Page
Table of Contents.....	2
1 Introduction including rationale for the protocol amendment.....	3
2 Changes.....	3
2.1 Section 1 Summary.....	3
2.2 Section 4.1 Objectives.....	4
2.3 Section 5.1 Type of trial.....	5
2.4 Section 5.3.2.1 Oral antidiabetic medication.....	5
2.5 Section 5.3.2.2 Treatment with insulin throughout the trial.....	5
2.6 Section 6.2 Inclusion criteria.....	5

1 Introduction including rationale for the protocol amendment

Rationale for the changes:

- Inclusion criterion 3 updated to allow for two additional oral antidiabetic drug (OAD) classes (alpha glucosidase inhibitors and glinides) which are currently not permitted. There are no medical reasons for not including them.
- Inclusion criterion 4 updated to allow subjects to continue on their standard insulin treatment. Currently the inclusion criterion states that subjects should be treated with any basal insulin according to its label. However, some subjects with type 2 diabetes mellitus and obesity are using insulin glargine twice daily (BID), due to the high dose based on the subjects' high body weight.

In this protocol amendment:

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

2 Changes

2.1 Section 1 Summary

Objectives and endpoints

Primary objective

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on weight loss effectiveness in subjects with overweight or obesity and type 2 diabetes mellitus (T2DM) treated with a basal insulin and up to 2 oral antidiabetic (OAD) medications (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea).

Secondary objectives

To establish the effects of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on relevant efficacy endpoints in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea)

To establish the safety and tolerability of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea)

Trial design

This is a 56-week randomised, double-blind, multi-national, multi-centre, placebo-controlled and two-armed trial in subjects with overweight or obesity and T2DM treated with basal insulin and up to two OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea).

Key inclusion criteria

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Diagnosed with type 2 diabetes mellitus
3. Treatment with up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea),
4. Stable treatment with basal insulin ~~according to its label~~ (no requirement of minimum or maximum dose) for at least 90 days prior to screening, as judged by the investigator
5. HbA_{1c} 6.0-10.0% (both inclusive)
6. BMI ≥ 27 kg/m²
7. Age ≥ 18 years at the time of signing informed consent

2.2 Section 4.1 Objectives

Primary objective

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on weight loss effectiveness in subjects with overweight or obesity and type 2 diabetes mellitus (T2DM) treated with a basal insulin and up to 2 oral antidiabetic (OAD) medications (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea).

Secondary objectives

- To establish the effects of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on relevant efficacy endpoints in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea)
- To establish the safety and tolerability of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea)

2.3 Section 5.1 Type of trial

This is a 56-week randomised, double-blind, multi-national, multi-centre, placebo-controlled and two-armed trial in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea).

2.4 Section 5.3.2.1 Oral antidiabetic medication

Any approved and marketed metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea product or combination products are allowed. Subjects treated with dipeptidyl peptidase-IV (DPP-IV) inhibitors are excluded from participating in the trial since DPP-IV inhibitors and GLP-1 receptor agonists should not be combined.

2.5 Section 5.3.2.2 Treatment with insulin throughout the trial

Any approved and marketed basal insulin (NPH insulin or insulin analogue) is allowed, at any dose, ~~if used according to its prescribing information at screening~~. Once-daily or twice-daily dosing is allowed, according to dosing schedule at baseline.

2.6 Section 6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Diagnosed with type 2 diabetes mellitus
3. Treatment with up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, *alpha glucosidase inhibitor*, *glinide* or sulphonylurea)
4. Stable treatment, at the discretion of the investigator, with any basal insulin ~~according to its label~~ (no requirement of minimum or maximum dose) for at least 90 days prior to screening
5. HbA_{1c} 6.0-10.0% (both inclusive)
6. BMI ≥ 27 kg/m²
7. Age ≥ 18 years at the time of signing informed consent
8. Maximum 5 kg self-reported weight loss within the past 90 days since screening
9. Increased physical activity is considered to be safe as judged by the investigator

Protocol Amendment no 3
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT No.: 2015-005619-33

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

19 February 2018
1.0
Final
1 of 8

Novo Nordisk

Protocol Amendment

no 3

**to Protocol, version 4.0
dated 14 September 2016**

Trial ID: NN8022-4272

SCALE™ Insulin

**Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2
diabetes mellitus treated with basal insulin**

Trial phase: 3b

Applicable to all countries

~~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.~~

Table of Contents

1	Introduction including rationale for the protocol amendment.....	3
2	Changes	3
2.1	Section 1 Key secondary endpoints	3
2.2	Section 2 Flow chart.....	4
2.3	Section 4.2.2.1 Confirmatory secondary endpoints	5
2.4	Section 4.2.2.2 Supportive secondary endpoints	5
2.5	Section 8.4.4 Hypoglycaemic episodes	6
2.6	Section 8.5.2 Laboratory assessments for safety	6
2.7	Section 17.1 Sample size calculation	7
2.8	Section 17.4.1.1 Description of the testing procedure to address the effectiveness estimand for primary and confirmatory secondary endpoints	7

1 Introduction including rationale for the protocol amendment

Rationale for the changes:

- To reflect the outcome of the Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQoL-Lite for CT) questionnaire validation and the recommendations from regulatory authorities to include the Short-form 36 (SF-36) questionnaire as a confirmatory secondary endpoint; the endpoint section and statistical hierarchy have been updated.
- Due to the low power to demonstrate a difference between active treatment and placebo, systolic blood pressure has been added as a supportive secondary endpoint and removed as a confirmatory secondary endpoint.
- Minor edits to Flow chart for clarity and accuracy.

In this protocol amendment:

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

2 Changes

2.1 Section 1 Key secondary endpoints

Change from baseline to week 56 in:

- Waist circumference
- ~~Systolic blood pressure~~
- HbA_{1c}
- Fasting plasma glucose
- *Short Form-36 (SF-36) v2.0 acute, physical functioning score*
- Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), ~~physical functioning~~ *physical function domain (5-items) score*
- ~~IWQoL-Lite for CT, mental/emotional functioning score~~

2.3 Section 4.2.2.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints addressing the secondary efficacy objective:

- Proportion of subjects losing more than 10% of baseline body weight at week 56

Change from baseline to week 56 in:

- Waist circumference
- ~~Systolic blood pressure~~
- HbA_{1c}
- Fasting plasma glucose
- *Short Form-36 (SF-36) v2.0 acute, physical functioning score*
- *Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical function domain (5-items) score*
- ~~IWQoL-Lite for CT, physical functioning score~~
- ~~IWQoL-Lite for CT, mental/emotional function score~~

2.4 Section 4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline to week 56 in:

- Total daily basal insulin dose (% of pre-trial dose in U)
- Total daily basal insulin dose (U/kg)
- Total daily insulin dose (U)
- Total daily insulin dose (U/kg)
- 7-point self-measured plasma glucose (SMPG) profile, mean daytime glucose value
- *Systolic blood pressure*
- Diastolic blood pressure
- Lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides [TG], free fatty acids [FFA])
- ~~Short Form-36 v2.0 acute (SF-36) (physical component summary (PCS), mental component summary (MCS) and subdomains)~~
- *SF-36 v.2.0 acute:*
 - *role-physical score*
 - *bodily pain score*
 - *general health score*
 - *vitality score*
 - *social functioning score*
 - *role-emotional score*
 - *mental health score*
 - *physical component summary (PCS)*

- *mental component summary (MCS)*
- *IWQoL-Lite for CT*
 - *pain/discomfort domain score*
 - *psychosocial domain score*
 - *total score*
- Weight related sign and symptom (WRSS) measure, total score

~~Proportion of subjects with the following at week 56:~~

~~Subjects who after 56 weeks achieve (yes/no):~~

- $HbA_{1c} < 7\%$ and weight loss $\geq 5\%$
- $HbA_{1c} < 7\%$, weight loss $\geq 5\%$ and no documented symptomatic hypoglycaemia
- ≥ 4.3 T-score points increase from baseline in SF-36 physical functioning score
- $\geq 2-3.8$ T-score points increase from baseline in SF-36 PCS
- $\geq 3-4.6$ T-score points increase from baseline in SF-36 MCS
- *Responder definition value for IWQoL-Lite for CT physical function domain (5-items) score*

2.5 Section 8.4.4 Hypoglycaemic episodes

All plasma glucose values:

- ≤ 3.9 mmol/L (70 mg/dL) or,
- > 3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms

should be reported in the diary according to the instructions below throughout the trial from visit 1 to visit 25.

2.6 Section 8.5.2 Laboratory assessments for safety

Biochemistry

*If TSH levels are out of normal range, the investigator must perform additional testing:

- Total and free T3 and T4 and Free Thyroid Thyroxine Index
- Thyroid peroxidase antibodies

2.7 Section 17.1 Sample size calculation

Table 17-3 Assumptions, marginal power and effective power for each confirmatory endpoints in the hierarchical testing procedure given an anticipated number of 400 randomised subjects

	Assumed mean (\pm SD) / proportion for completers		Expected mean (\pm SD) / proportion liraglutide 3.0 mg #	Expected difference #	Marginal power (%)	Effective power (%)
	liraglutide 3.0 mg	placebo				
% weight change	-6.0 (\pm 6.0)	-2.0 (\pm 6.0)	-4.8 (\pm 6.3)	-2.8	99.5	99.5
5% responders	57%	31%	49%	18	95.7	95.2
10% responders	25%	9%	20%	11	89.0	84.7
WC	-6.0 (\pm 5.9)	-3.1 (\pm 5.9)	-5.1 (\pm 6.0)	-2.0	92.4	78.3
HbA1c	-1.4 (\pm 1.0)	-0.5 (\pm 1.0)	-1.1 (\pm 1.1)	0.6	99.9	78.2
Fasting glucose	-2.2 (\pm 2.0)	-0.4 (\pm 2.0)	-1.7 (\pm 2.2)	1.3	99.9	78.1
sBP	-2.6 (\pm 11.7)	-0.3 (\pm 11.7)	-1.9 (\pm 11.7)	-1.6	27.8	21.7
SF-36 PF	3.7 (\pm 8.0)	2.4 (\pm 8.0)	3.3 (\pm 8.0)	0.9	20.5	16.0
IWQoL-Lite for CT PF *	15.0 (\pm 14.5)	10.6 (\pm 14.5)	13.7 (\pm 14.6)	3.1	55.9	8.9
Mental score *	12.0 (\pm 18.0)	9.6 (\pm 18.0)	11.3 (\pm 18.0)	1.7	15.3	1.9

SD standard deviation, WC waist circumference, sBP systolic blood pressure; SF-36 PF Short Form-36 v2.0 acute physical functioning score, IWQoL-Lite for CT PF Physical function domain (5 items) score

Adjusted for 30% discontinuation; * IWQoL-Lite Clinical Trial Version;

Assumptions are based on findings from ~~NN0068-3951~~ NN8022-1922

2.8 Section 17.4.1.1 Description of the testing procedure to address the effectiveness estimand for primary and confirmatory secondary endpoints

Table 17-6 Hierarchical order and type of statistical model to address the effectiveness estimand for primary and confirmatory secondary endpoints

Test order	Endpoint	Endpoint type	Statistical model	MI approach	Sensitivity analyses #
Confirmatory secondary endpoints					
7	Change from baseline to week 56 in systolic blood pressure (sBP) (mmHg) Change from baseline to week 56 in Short Form-36 (SF-36) v2.0 acute physical functioning score	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
8	Change from baseline to week 56 in impact of Weight on Quality of Life-Lite (IWQoL-Lite for CT), physical functioning domain (5-items) score	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
9	Change from baseline to week 56 in impact of Weight on Quality of	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA

Protocol Amendment no 3
Trial ID: NN8022-4272
UTN: U1111-1177-4903
EudraCT No.: 2015-005619-33

~~CONFIDENTIAL~~

Date: 19 February 2018
Version: 1.0
Status: Final
Page: 8 of 8

Novo Nordisk

	Life Lite (IWQoL Lite for CT); mental/emotional function score			Tipping point
--	---	--	--	---------------