Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02964247
Sponsor trial ID:	NN2211-4315
Official title of study:	LIRA-ADD2SGLT2i – liraglutide versus placebo as add-on to SGLT2 inhibitors
Document date:	26 September 2018

16.1.1 Protocol and protocol amendments

List of contents

Protocol version 1.0 ..... Link

Protocol amendment 1 global ..... Link

Protocol amendment 2 global ..... Link

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Trial ID: NN2211-4315

LIRA-ADD2SGLT2i – liraglutide versus placebo as add-on to SGLT2 inhibitors

Trial phase: 3b

Protocol originator

[redacted]

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 ~~No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk.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

Table of Figures **6**

Table of Tables **6**

List of abbreviations **7**

1 Summary **10**

2 Flow chart **13**

3 Background information and rationale for the trial **16**
3.1 Type 2 diabetes mellitus 16
3.2 Liraglutide 16
3.3 Rationale for the trial 17

4 Objectives and endpoints **18**
4.1 Objectives 18
4.1.1 Primary objective 18
4.1.2 Secondary objective 18
4.2 Endpoints 18
4.2.1 Primary endpoint 18
4.2.2 Secondary endpoints 18
4.2.2.1 Confirmatory secondary endpoints 18
4.2.2.2 Supportive secondary endpoints 18

5 Trial design **20**
5.1 Type of trial 20
5.2 Rationale for trial design 21
5.3 Treatment of subjects 22
5.3.1 Liraglutide and placebo 22
5.3.2 Background medication 23
5.3.2.1 SGLT2 inhibitors 23
5.3.2.2 Metformin 24
5.3.3 Rescue medication 24
5.4 Treatment after discontinuation of trial product 24
5.5 Rationale for treatment 25

6 Trial population **26**
6.1 Number of subjects 26
6.2 Inclusion criteria 26
6.3 Exclusion criteria 26
6.4 Rescue criteria 28
6.5 Criteria for premature discontinuation of trial product 29
6.6 Withdrawal from trial 29
6.7 Subject replacement 30
6.8 Rationale for trial population 30

7 Milestones **31**

8 Methods and assessments 32
8.1 Visit procedures 32
8.1.1 Informed consent 32
8.1.2 Investigator site logs 32
8.1.3 Screening (visit 1) 32
8.1.4 Re-screening 32
8.1.5 Fasting visits 32
8.1.6 Missed visits 33
8.1.7 Rescue medication visit 33
8.1.8 Premature discontinuation of trial product visit 33
8.1.9 Withdrawal from trial 33
8.2 Assessments 34
8.2.1 Subject related information/assessments 34
8.2.1.1 Demography 34
8.2.1.2 Diabetes history and diabetes complications 34
8.2.1.3 Concomitant illness and medical history 34
8.2.1.4 Concomitant medication 35
8.2.1.5 Childbearing potential 35
8.2.1.6 Tobacco use 36
8.2.2 Efficacy assessments 36
8.2.2.1 Body measurements 36
8.2.2.2 Vital signs 37
8.2.2.3 Self-measured plasma glucose (SMPG) 37
8.2.2.4 7-point self-measured plasma glucose profile 37
8.2.2.5 Glucose metabolism and lipids 38
8.2.3 Safety assessments 39
8.2.3.1 Physical examination 39
8.2.3.2 ECG-12 lead 39
8.2.3.3 NYHA 40
8.2.3.4 Urinalysis 40
8.2.3.5 Biochemistry and Haematology 41
8.2.3.6 Pregnancy test 41
8.2.3.7 Adverse events 42
8.2.3.8 Hypoglycaemic episodes 43
8.2.4 Laboratory assessments 45
8.3 Subject training 46
8.3.1 Diaries 46
8.3.2 Blood glucose meter 46
8.3.3 Training in the prefilled pen-injector 46
8.4 Subject compliance 47

9 Trial supplies 48
9.1 Trial products 48
9.2 Labelling 48
9.3 Storage 49
9.4 Drug accountability and destruction 49
9.5 Auxiliary supplies 50

10 Interactive voice/web response system 50

11 Randomisation procedure and breaking of blinded codes 51
11.1 Breaking of blinded codes 51

12 Adverse events, and technical complaints and pregnancies 52
12.1 Definitions 52
12.1.1 Adverse event 52
12.1.2 Serious adverse event 53
12.1.3 Non-serious adverse event 54
12.1.4 Medication errors 54
12.1.5 Adverse events requiring additional data collection 55
12.1.6 Technical complaints 55
12.2 Reporting of adverse events 55
12.3 Follow-up of adverse events 57
12.4 Technical complaints and technical complaint samples 58
12.4.1 Reporting of technical complaints 58
12.4.2 Collection, storage and shipment of technical complaint samples 59
12.5 Pregnancies 59
12.5.1 Pregnancies in female subjects 59
12.5.2 Pregnancies in female partners of male subjects (*for US only*) 61
12.6 Precautions and/or overdose 61
12.7 Committees related to safety 62

13 Case report forms 62
13.1 Corrections to case report forms 63
13.2 Case report form flow 63

14 Monitoring procedures 63

15 Data management 64

16 Computerised systems 65

17 Statistical considerations 65
17.1 Sample size calculation 67
17.2 Definition of analysis sets 68
17.3 Primary endpoint 71
17.3.1 Primary analysis for the primary estimand 71
17.3.2 Primary analysis for the secondary estimand 72
17.3.3 Sensitivity Analysis 72
17.3.3.1 Pattern mixture models 73
17.3.3.2 Assessment of sensitivity analyses 74
17.4 Secondary endpoints 74
17.4.1 Confirmatory secondary endpoints 74
17.4.2 Supportive secondary endpoints 74
17.4.2.1 Efficacy endpoints 75
17.4.2.2 Safety endpoints 76

18 Ethics 80
18.1 Benefit-risk assessment of the trial 80
18.2 Informed consent 81
18.3 Data handling 82
18.4 Information to subjects during trial 82

18.5 Premature termination of the trial and/or trial site 82

19 Protocol compliance 82
19.1 Protocol deviations 82
19.2 Prevention of missing data 83

20 Audits and inspections 83

21 Critical documents 83

22 Responsibilities 84

23 Reports and publications 85
23.1 Communication of results 86
23.1.1 Authorship 87
23.1.2 Site-specific publication(s) by investigator(s) 87
23.2 Investigator access to data and review of results 87

24 Retention of clinical trial documentation 88
24.1 Retention of clinical trial documentation 88

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities 88

26 Indemnity statement 89

27 References 91

Attachment I – Global list of key staff and relevant departments and suppliers
Attachment II – Country list of key staff and relevant departments

Table of Figures

Page

Figure 5–1 Schematic overview of the trial design....21
Figure 12–1 Reporting of AEs....56
Figure 17–1 ADA classification of hypoglycaemia....79

Table of Tables

Page

Table 8–1 NYHA criteria for functional capacity....40
Table 9–1 Trial products....48
Table 9–2 Storage conditions....49
Table 17–1 Assumptions used in the sample size calculation....68
Table 17–2 Marginal powers for meeting individual hypothesis....68

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
AKD	acute kidney disease
AKI	acute kidney injury
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CCDS	Company Core Data Sheet
CKD	chronic kidney disease
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration formula
CRF	case report form
DPP-4	dipeptidyl peptidase-4
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomular filtration rate
EOT	end of treatment
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin

hCG	human chorionic gonadotrophin
HDL	high-density lipoprotein
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
IRB	institutional review board
IWRS	interactive voice/web response system
KDIGO	Kidney Disease Improving Global Outcomes
LDL	low-density lipoprotein
LSFV	last subject first visit
LSLV	last subject last visit
MAR	missing at random
MedRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OAD	oral antidiabetic drug
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SDV	source data verification
SGLT2	sodium-glucose co-transporter 2
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TE	Treatment effect
TMM	Trial Materials Manual

T2DM	Type 2 Diabetes Mellitus
TZD	thiazolidinedione
UACR	urine albumin creatinine ratio
UTN	universal trial number
VLDL	very low density lipoprotein

1 Summary

Objective(s) and endpoint(s):

Primary objective
To compare the effect of liraglutide 1.8 mg/day versus placebo as add-on to an SGLT2 inhibitor ± metformin on glycaemic control in subjects with type 2 diabetes mellitus.

Secondary objectives
To compare the effect of liraglutide 1.8 mg/day versus placebo as add-on to an SGLT2 inhibitor ± metformin in subjects with type 2 diabetes mellitus with regards to:

- Body weight related parameters
- Selected cardiovascular risk factors
- Safety

To compare the effect of liraglutide 1.8 mg/day versus placebo as add-on to an SGLT2 inhibitor ± metformin weeks in subjects with type 2 diabetes mellitus with regards to:

- selected glucose metabolism parameters

Primary endpoint
Change from baseline to week 26 in HbA_{1c}

Confirmatory secondary endpoint
Change from baseline to week 26 in body weight

Key supportive secondary efficacy endpoints
Change from baseline to week 26 in:

- Fasting plasma glucose
- Systolic and diastolic blood pressure

Subjects who after 26 weeks achieve (yes/no):

- HbA_{1c} <7.0% (53 mmol/mol), American Diabetes Association target
- HbA_{1c} ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists target
- HbA_{1c} <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} reduction ≥1% (11mmol/mol) and weight loss ≥3%

Key supportive secondary safety endpoints

- Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during 26 weeks

Trial design:

This is a 26-week, 2:1 randomised, placebo controlled, double blind, multicentre, multinational, confirmatory, two arm trial investigating the effect and safety of liraglutide versus placebo as add-on to an SGLT2 inhibitor with or without metformin in subjects with type 2 diabetes mellitus who have not achieved adequate glycaemic control despite stable treatment with SGLT2 inhibitor ± metformin.

Eligible subjects will be randomised in a 2:1 manner to receive a once daily dose of either liraglutide (1.8 mg) or placebo added to pre-trial SGLT2 inhibitor ± metformin. Randomisation will be stratified by metformin use at baseline (yes versus no).

The maximum overall duration of the trial participation including screening and follow up will be 29 weeks.

Trial population:

It is planned to randomise 303 subjects (liraglutide N=202; placebo N=101) in this trial.

Key inclusion criteria

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
- Male or female, age ≥ 18 years at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus.
- HbA_{1c} of 7.0-9.5% (53-80 mmol/mol) (both inclusive).
- Stable dose of an SGLT-2 inhibitor as monotherapy or in combination (including fixed-dose drug combination) with a stable dose of metformin (≥ 1500 mg or maximum tolerated dose) for at least 90 days prior to the day of screening. All medications in compliance with current local label.
- Body mass index ≥ 20 kg/m^2.

Key exclusion criteria

- 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).
- History of diabetic ketoacidosis while being treated with SGLT2 inhibitors.
- Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 60 $mL/min/1.73m^2$ as defined by KDIGO[1] classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short

term insulin treatment for a maximum of 14 days during the 90 days prior to screening is allowed.

- Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
- History or presence of pancreatitis (acute or chronic).
- Impaired liver function, defined as ALT ≥2.5 times upper normal limit at screening.
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV.

Assessments:

Efficacy

- Glucose metabolism
- Body measurements (body weight and waist circumference)

Safety

- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry, haematology and urinalysis
- Physical examination (including electrocardiogram)

Trial product(s):

Investigational medicinal products:

- Test product: Liraglutide (Victoza®) 6.0 mg/mL (3 mL prefilled pen-injector for subcutaneous injection)
- Reference therapy: Placebo (3 mL prefilled pen-injector for subcutaneous injection)

Other medicinal products:

SGLT2 inhibitors and metformin and fixed-dose combinations of the former are considered background medication (non-investigational medicinal products) and will not be provided by Novo Nordisk A/S. In countries where it is applicable, SGLT2 inhibitors may be reimbursed by Novo Nordisk A/S

2 Flow chart

Trial Periods	Protocol section	Screen-ing	Random-isation	Treatment								End of treatment (EOT)	Follow-up	Rescue medica-tion 6.4/8.1.7	Premature Discontin-uation 6.5/8.1.8
Site visit (V) **Phone contact (P)**		V	V	P	P	P	V	P	V	V	V	V	P	V	V
Visit number		1	2	3	4	5	6	7	8	9	10	11	12		
Timing of visit: Weeks		up to -2	0	1	2	3	4	6	8	14	20	26[8.1.9]	27[8.1.9]		
Visit window: Days				±3	±3	±3	±3	±5	±5	±5	±5	±5	±3		
SUBJECT RELATED INFO/ASSESSMENTS															
Informed consent	8.1.1	X													
In/exclusion criteria	6.2/6.3	X	X												
Subject compliance	8.4			X	X	X	X	X	X	X	X	X		X	X
Rescue criteria	6.4						X	X	X	X	X				
Criteria for premature discontinuation of trial product	6.5/ 8.1.7			X	X	X	X	X	X	X	X				
Withdrawal criteria	8.1.9			X	X	X	X	X	X	X	X	X			
Demography	8.2.1.1	X													
Diabetes: diagnosis, complications and treatment history	8.2.1.2	X													
Concomitant illness	8.2.1.3	X													
Medical history	8.2.1.3	X													
Concomitant medication	8.2.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Child bearing potential	8.2.1.5	X													
Tobacco use	8.2.1.6	X													
EFFICACY															
Height	8.2.2.1	X													

Trial Periods	Protocol section	Screen-ing	Random-isation	Treatment								End of treatment (EOT)	Follow-up	Rescue medica-tion 6.4/8.1.7	Premature Discontin-uation 6.5/8.1.8
Site visit (V) **Phone contact (P)**		V	V	P	P	P	V	P	V	V	V	V	P	V	V
Visit number		1	2	3	4	5	6	7	8	9	10	11	12		
Timing of visit: Weeks		up to -2	0	1	2	3	4	6	8	14	20	26[8.1.9]	27[8.1.9]		
Visit window: Days				±3	±3	±3	±3	±5	±5	±5	±5	±5	±3		
Body weight	8.2.2.1	X	X				X		X	X	X	X		X	X
BMI	8.2.2.1	X	X							X		X		X	X
Waist circumference	8.2.2.1		X							X		X		X	X
Vital signs	8.2.2.2	X	X				X		X	X	X	X		X	X
Self-measured plasma glucose (7-point profile)	8.2.2.3/ 8.2.2.4		X									X		X	X
Fasting C-peptide	8.2.2.5		X							X		X		X	X
Fasting glucagon	8.2.2.5		X							X		X		X	X
Fasting insulin	8.2.2.5		X							X		X		X	X
Fasting plasma glucose	8.2.2.5		X				X		X	X	X	X		X	X
HbA_{1c}	8.2.2.5	X	X						X	X	X	X		X	X
Lipids	8.2.2.5		X							X		X		X	X
SAFETY															
Physical examination	8.2.3.1	X										X		X	X
ECG	8.2.3.2	X										X		X	X
NYHA classification	8.2.3.3	X													
Urinalysis	8.2.3.4		X							X	X	X		X	X
Biochemistry 1	8.2.3.5	X										X		X	X
Biochemistry 2	8.2.3.5	X					X		X	X		X		X	X
Haematology	8.2.3.5	X										X		X	X
Pregnancy test	8.2.3.6	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X		X	X
Adverse events	8.2.3.7/12	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.2.3.8		X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Periods	Protocol section	Screen-ing	Random-isation	Treatment								End of treatment (EOT)	Follow-up	Rescue medica-tion 6.4/8.1.7	Premature Discontin-uation 6.5/8.1.8
Site visit (V) **Phone contact (P)**		V	V	P	P	P	V	P	V	V	V	V	P	V	V
Visit number		1	2	3	4	5	6	7	8	9	10	11	12		
Timing of visit: Weeks		up to -2	0	1	2	3	4	6	8	14	20	26[8.1.9]	27[8.1.9]		
Visit window: Days				±3	±3	±3	±3	±5	±5	±5	±5	±5	±3		
Technical complaints	12.1.6/12.4			X	X	X	X	X	X	X	X	X	X	X	X
TRIAL MATERIAL															
IWRS call	10	X	X				X		X	X	X	X		X	X
Dispensing visit	9		X				X		X	X	X				
Drug accountability	9.4/10		X				X		X	X	X	X		X	X
REMINDERS															
Hand out and instruct in diary	8.3.1	X	X				X		X	X	X				
Diary collection/review	8.3.1		X				X		X	X	X	X		X	X
Hand out and instruct in BG meter use	8.3.2	X													
Training in trial product and pen handling[a]	8.3.3		X				X		X	X	X				
Handout ID card	8.1.3	X													
Attend visit fasting	8.1.5		X				X		X	X	X	X		X	X

Footer	Description
a	Dispense directions for use

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP)[2] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[3].

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

In the case of Mexico, the above will include the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:
a) Investigation follow-up
b) Damages to health arising from the investigation development as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject
c) Timely compliance of the terms in which the authorization of a research for health in human beings had been issued
d) To present in a timely manner the information required by the Health Authority

3.1 Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease primarily characterised by abnormal glucose and lipid metabolism and associated with a high risk of cardiovascular, microvascular, and other complications. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle and genetic factors leading to chronic hyperglycaemia associated with insulin resistance and impaired insulin secretion due to abnormal beta-cell function[4-6]. Improvement of long-term glycaemic control (HbA_{1c}) is the treatment goal in patients with T2DM in order to prevent long-term complications[7, 8]. Glucose control in T2DM deteriorates progressively over time and patients require a new glucose-lowering intervention on average every 3-4 years in order to obtain or retain good control[9].

3.2 Liraglutide

Liraglutide is a once-daily human GLP-1 analogue developed by Novo Nordisk and is an active ingredient used in the authorised product Victoza® for treatment of adults with T2DM. As of up until 30 June 2016, Victoza® is approved in 106 countries/regions, including Australia, the European Union, the United States, Canada, Japan, China, Brazil, Russia and Mexico[10].

The HbA_{1c} lowering effect of liraglutide in subjects with T2DM is well established. Liraglutide has been tested in several T2DM treatment scenarios during the phase 3 and phase 4 trial programme, as monotherapy and in combination with metformin, sulfonylurea, TZD, basal insulin and

combinations hereof[11, 12]. In each of these treatment scenarios, the efficacy and safety of liraglutide has been demonstrated and a positive benefit-risk balance has been established. In addition, liraglutide has been shown to be safe and efficacious in patients with T2DM and moderate renal impairment[13]. More recently, liraglutide has shown cardiovascular benefits in patients with T2DM.

Information about liraglutide is available in the approved local product label of liraglutide (Victoza®) and in the liraglutide (NN2211) abbreviated IB, 17th edition of August 2016 or any updates hereof[14].

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

3.3 Rationale for the trial

T2DM is increasing in incidence and prevalence. Despite compliance with their treatment regimens, a large proportion of patients do not reach treatment targets[15], indicating that the current available treatment modalities are not satisfactory and more treatment options need to be explored [16, 17]. This includes establishing the benefits of combining available marketed glucose lowering agents in order to better optimise individual treatment[16, 17].

Sodium-glucose co-transporter 2 (SGLT2) inhibitors were recently established as a new class of orally administered glucose-lowering drugs (dapagliflozin, canagliflozin and empagliflozin). SGLT2 inhibitors lower blood glucose by inhibiting SGLT2 in the proximal tubule of the nephron, thereby reducing glucose reabsorption and increasing urinary glucose excretion. This action is independent of insulin. On the contrary, SGLT2 inhibitors promote secretion of glucagon, which may counteract their glucose lowering effect[18, 19]. A GLP-1 analogue such as liraglutide acts through stimulation of insulin secretion in a glucose-dependent manner. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. Given the glucagon lowering effect of liraglutide, there is scientific and therapeutic rationale that in combination with SGLT2 inhibitor, secretion of glucagon induced by the SGLT2 inhibition may be reduced. In addition for patients with T2DM who have not achieved glycaemic control on an SGLT2 inhibitor (with or without metformin), it is hypothesised that by adding liraglutide to their treatment, better glycaemic control reflected in HbA_{1c} reduction with associated decrease in body weight and no increase of hypoglycaemic events may be achieved[20].

Although reports of the use of GLP-1 receptor agonists in combination with SGLT2 inhibitors exist[20], there is still no clinical evidence available to guide clinical decision making. Liraglutide is not approved for use in combination with SGLT2 inhibitors and the efficacy and safety of liraglutide as add-on to a SGLT2 inhibitor has not been established. Therefore, there is an unmet medical need to assess the benefits and risks of liraglutide, a GLP-1 analogue, used in combination with SGLT2 inhibitors.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To compare the effect of liraglutide 1.8 mg/day versus placebo as add-on to an SGLT2 inhibitor ± metformin on glycaemic control in subjects with type 2 diabetes mellitus.

4.1.2 Secondary objective

To compare the effect of liraglutide 1.8 mg/day versus placebo as add-on to an SGLT2 inhibitor ± metformin in subjects with type 2 diabetes mellitus with regards to:

- Body weight related parameters
- Selected cardiovascular risk factors
- Safety

To compare the effect of liraglutide 1.8 mg/day versus placebo as add-on to an SGLT2 inhibitor ± metformin in subjects with type 2 diabetes mellitus with regards to:

- selected glucose metabolism parameters

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline to week 26 in HbA_{1c}

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Change from baseline to week 26 in body weight

4.2.2.2 Supportive secondary endpoints

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

Supportive secondary efficacy endpoints

Change from baseline to week 26 in:

- Fasting plasma glucose*
- Self-measured plasma glucose 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increments (over all meals)

- Fasting blood lipids (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triglycerides and free fatty acids)
- Body mass index and waist circumference
- Systolic and diastolic blood pressure*

Subjects who after 26 weeks achieve (yes/no):

- HbA_{1c} <7.0% (53 mmol/mol), American Diabetes Association target*
- HbA_{1c} ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists target*
- Weight loss ≥3%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain*
- HbA_{1c} <7.0% (53 mmol/mol) and no weight gain
- HbA_{1c} <7.0% (53 mmol/mol), no weight gain and systolic blood pressure <140 mmHg
- HbA_{1c} reduction ≥1% (11mmol/mol)
- HbA_{1c} reduction ≥1% (11mmol/mol) and no weight gain
- HbA_{1c} reduction ≥1% (11mmol/mol) and weight loss ≥3%*

Change from baseline to weeks 14 and 26 in:

- Glucagon, C-peptide and insulin (all fasting)

Supportive secondary safety endpoints

- Number of treatment emergent adverse events during 26 weeks
- Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during 26 weeks*
- Treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes during 26 weeks (yes/no)

Change from baseline to week 26 in:

- Haematology: haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes
- Biochemistry: creatinine, creatine kinase, urea, albumin, bilirubins (total), estimated glomerular filtration rate, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium, calcium (corrected), calcium (total), amylase and lipase
- Pulse
- Electrocardiogram category
- Physical examination
- Urine albumin creatinine ratio

5 Trial design

5.1 Type of trial

This is a 26-week, confirmatory, randomised, double-blind, placebo-controlled, multicentre, multinational, two-arm, parallel-group trial, investigating the effect and safety of adding liraglutide 1.8 mg/day to pre-trial treatment with any SGLT2 inhibitor (as monotherapy or in combination with metformin) in subjects with T2DM who have not achieved adequate glycaemic control despite stable treatment with SGLT2 inhibitor ± metformin for at least 90 days prior to trial participation.

Subjects will be randomised in a 2:1 manner to receive a once daily dose of liraglutide 1.8 mg or placebo applying the standard dose escalation for liraglutide with weekly increments of 0.6 mg/day. The trial medication will be added-on to the subject's stable pre-trial SGLT2 inhibitor ± metformin. Randomisation will be stratified by metformin use at baseline (yes vs. no).

Subjects will continue their participation in the trial regardless of premature discontinuation of trial product or initiation of rescue medication. Efforts will be made to encourage subjects to continue the visit schedule.

The maximum overall duration of the trial participation including screening and follow-up will be 29 weeks: the trial includes a 2-week screening period, followed by 26 weeks of treatment and a 1-week follow-up period after end of treatment. See Figure 5–1.

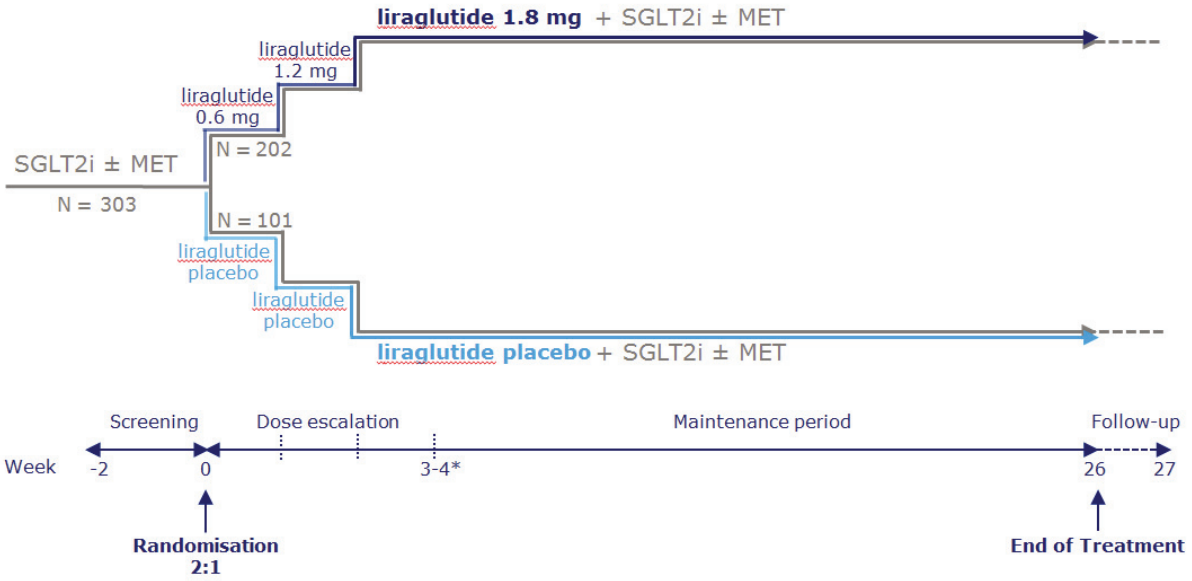


Figure 5–1 Schematic overview of the trial design

5.2 Rationale for trial design

Parallel treatment groups and a randomised double-blind, placebo controlled design were chosen in accordance with the trial objectives.

In order to evaluate the safety and effect of liraglutide as add-on to SGLT2 inhibitor ± metformin, use of any one of three currently marketed SGLT2 inhibitors: Invokana® (canagliflozin)[21], Farxiga® (dapagliflozin)[22] and Jardiance® (empagliflozin)[23] at any approved dose as monotherapy or in fixed dose-combination together with metformin, will be allowed as pre-trial therapy. Stable pre-trial treatment with metformin is ≥1500 mg/day or at the maximum tolerated dose. To ensure equal distribution and avoid bias arising from difference in metformin usage, randomisation will be stratified by metformin use (yes vs. no) at baseline. Randomisation 2:1 was chosen to have as few subjects as possible on placebo.

A trial duration of 26 weeks is considered adequate in terms of establishing superiority of liraglutide treatment versus placebo on glycaemic control and body weight in subjects with T2DM. This duration is in accordance with regulatory guidelines on diabetes[9, 24]. Furthermore, a 26 week trial period has previously been shown to be sufficient to identify the liraglutide safety profile

including tolerability and risk of hypoglycaemia. In the liraglutide phase 3b trials NN2211-1842 and 1860, both safety and efficacy observations from the first 26 weeks of treatment were generally confirmed during the extension periods up to 52 weeks (trial 1842[25-28], trial 1860[27]). The trial design is in accordance with the draft CHMP Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus[9].

The follow-up period is 1 week to allow for wash-out of liraglutide.

5.3 Treatment of subjects

After screening, the subjects will be randomised in a 2:1 manner to receive treatment with liraglutide + SGLT2 inhibitor ± metformin or placebo + SGLT2 inhibitor ± metformin. Subjects on a fixed dose combination of SGLT2 inhibitor and metformin are allowed to continue this fixed dose combination throughout the trial.

5.3.1 Liraglutide and placebo

Liraglutide and placebo are considered investigational medicinal products (IMPs) and will be blinded throughout the trial. Liraglutide and placebo will be provided by Novo Nordisk.

Liraglutide will be available at a concentration of 6 mg/mL, and supplied in a 3 mL prefilled pen-injector. Liraglutide vehicle will be used as placebo in equivalent volumes.

Liraglutide/placebo should be injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen. Injections can be done at any time of the day and irrespective of meals. It is recommended that the time of injection is consistent throughout the trial once the most convenient timing is established.

When initiating liraglutide treatment, subjects will follow a dose escalation regimen. Liraglutide/placebo will be initiated with a starting dose of 0.6 mg/day, with subsequent weekly dose escalations of 0.6 mg/day in accordance with the approved dose escalation for liraglutide until the maintenance dose of 1.8 mg/day in this trial is reached. Escalation from 0.6 to 1.2 then 1.8 mg/day can be extended by 7 days in total if subjects do not tolerate an increase in dose during dose escalation, at the discretion of the investigator. The liraglutide maintenance dose of 1.8 mg/day should remain unchanged throughout the remainder of the trial. In rare situations where a dose of 1.8 mg/day despite all efforts is not tolerated (e.g, using extra time for dose escalation and discussing with/informing the subject that gastrointestinal AEs in general are transient and subside over time), the dose can be reduced to 1.2 mg/day at the discretion of the investigator.

5.3.2 Background medication

SGLT2 inhibitors and metformin

After signing the informed consent, subjects must continue their anti-diabetic background medication (SGLT2 inhibitor +/-metformin) throughout the entire trial. Fixed dose combinations of SGLT2 inhibitors and metformin are allowed. The background medication should be maintained at the same dose level as given at trial entrance and with the same frequency during the entire treatment period unless rescue medication is needed or a safety concern (e.g., diabetic ketoacidosis, lactic acidosis, hospitalisation for surgery or acute serious medical illness) arises, qualifying for changes to the background medication.

In addition, all background medication:

- is considered to be non-investigational medicinal product (NIMP)
- will not be provided by Novo Nordisk A/S, except if required by local regulations. In countries where it is applicable, SGLT2 inhibitors may be reimbursed by Novo Nordisk A/S
- should be used in accordance with standard of care and current approved label in the individual country
- should not exceed the maximum approved dose in the individual country

5.3.2.1 SGLT2 inhibitors

Three SGLT2 inhibitors (dapagliflozin,[22] canagliflozin[21] and empagliflozin[23]) are currently approved for use either as monotherapy in metformin intolerant patients or in combination with metformin, sulfonylurea (SU), thiazolidinedione (TZD) or insulin. In addition, dapagliflozin is approved for use in combination with DPP-4 inhibitors[22]. There is however, currently no approval for any SGLT2 inhibitors to be used in combination with a GLP-1 receptor agonist.

SGLT2 inhibitors may be used at any stage of T2DM provided renal function is adequate. Besides lowering blood glucose, treatment with SGLT2 inhibitors also induces weight loss and lowering of systolic and diastolic blood pressure. Additionally, cardiovascular benefits of empagliflozin treatment have been shown previously in patients with T2DM [29].

As SGLT2 inhibitors possess a diuretic effect, hypotension and symptoms related to volume depletion may occur. Therefore they should be used with caution in the elderly, in any patient already on a diuretic and in anyone with a tenuous intravascular volume status. Initial increases in serum creatinine occur with SGLT2 inhibitors, but generally these are small, reversible changes. Due to their MOA, SGLT2 inhibitors are less effective when the eGFR is between 45-60 mL/min1.73 m^2 [30]. The FDA and EMA have added warnings to the three SGLT2 inhibitors' labels regarding diabetic ketoacidosis (normoglycemic), urosepsis and pyelonephritis.

Information about SGLT2 inhibitors including any benefits and/or any side effects, is available in the approved local label documents[31].

5.3.2.2 Metformin

Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator. Metformin dose may only be increased at the discretion of the investigator if used as rescue treatment (see Section 6.4).

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore, the risk of hypoglycemia under normal circumstances is low. Metformin may act via 3 mechanisms:

1. reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
2. in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
3. delay of intestinal glucose absorption.

In humans, independent of its action on glycaemia, metformin has a favourable effect on lipid metabolism. Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment) metabolic complication that can occur due to metformin hydrochloride accumulation. Reported cases of lactic acidosis in patients on metformin hydrochloride have occurred primarily in diabetic patients with significant renal failure. Information about metformin including any benefits and/or any side effects, is available in the approved local label documents [32].

5.3.3 Rescue medication

Rescue criteria (see Section 6.4) for subjects experiencing persistent and unacceptable hyperglycaemia have been implemented to ensure subjects' safety and in attempt to improve the retention of randomised subjects in the trial and thereby obtain additional safety data.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of treatment visit (visit 11, see Section 2) or if trial product is discontinued prematurely, the subject should be switched to a suitable marketed product at the discretion of the investigator and in accordance with ADA/European Association for the Study of Diabetes.

For Brazil only: At the end of the trial, all subjects will be assured access to the best proved prophylactic, diagnostic and therapeutic methods identified during the study (national Council of Health Resolution 466/12).

5.5 Rationale for treatment

In this trial, any locally approved SGLT2 inhibitor dosed at any locally approved dose and dosage as individually required is applicable. A range of SGLT2 inhibitor types and dosages is selected to establish the effect and safety of liraglutide as "add-on treatment" to SGLT2 inhibitors (with or without metformin) in general.

For metformin treated subjects a minimum dose of metformin of 1500 mg/day or maximum tolerated dose has been applied in order to establish the effect and safety of liraglutide as add-on treatment to SGLT2 inhibitors with or without metformin for the two metformin strata (metformin y/n at screening).

Administration of liraglutide will be similar to previous phase 3 and 4 T2DM trials and in accordance with locally approved labels. The liraglutide dose selected for the trial (1.8 mg/day) is the maximum recommended human dose for T2DM. In previous clinical trials, more subjects on this dose reached the American Diabetes Association (ADA) glycaemic target of HbA_{1c} <7.0% and experienced weight reduction in comparison to subjects treated with lower doses. The use of liraglutide 1.8 mg/day maintenance dose in this trial will ensure the safe use of liraglutide in combination with SGLT2 inhibitors with or without metformin.

The duration (26 weeks) and the dose of the randomised treatment are considered adequate for obtaining meaningful information on effect and safety in accordance with the trial objectives[14].

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 551

Number of subjects planned to be randomised: 303

For Mexico only: Approximately 40 subjects are planned to be randomized/started on trial product(s) in Mexico.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.

2. Male or female, age ≥ 18 years at the time of signing informed consent.

3. Diagnosed with type 2 diabetes mellitus.

4. HbA_{1c} of 7.0-9.5% (53-80 mmol/mol) (both inclusive).

5. Stable dose of an SGLT-2 inhibitor as monotherapy or in combination (including fixed-dose drug combination) with a stable dose of metformin (≥ 1500 mg or maximum tolerated dose) for at least 90 days prior to the day of screening. All medications in compliance with current local label.

6. Body mass index ≥ 20 kg/m^2.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.

2. Previous participation in this trial. Participation is defined as signed informed consent.

3. 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).

Brazil: According to resolution 466/12: Regarding exclusion criterion: 'Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice). For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.'

4. Receipt of any investigational medicinal product within 90 days before screening.

5. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short term insulin treatment for a maximum of 14 days during the 90 days prior to the day of screening is allowed.

6. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

7. History of diabetic ketoacidosis while being treated with SGLT2 inhibitors.

8. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.

9. History or presence of pancreatitis (acute or chronic).

10. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 60 mL/min/1.73m^2 as defined by KDIGO[1] classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.

11. Impaired liver function, defined as ALT ≥2.5 times upper normal limit at screening.

12. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.

13. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.

14. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.

15. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening.

16. Proliferative retinopathy or maculopathy requiring acute treatment according to the investigator's opinion.

17. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.

18. Known or suspected abuse of alcohol or drugs.

19. Mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with trial procedures.

20. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.

21. *Brazil; According to Resolution 251/97, item III.2.j. Participation in other trials within one year prior to screening visit (visit 1) unless there is a direct benefit to the research subject at the Investigator's discretion.*

6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. If any fasting plasma glucose (FPG) value measured by the central laboratory exceeds the limits below and no intercurrent cause of the hyperglycaemia can be identified, the subject must be called in for an unscheduled visit and a confirmatory FPG as soon as possible:

- 15.0 mmol/L (270 mg/dl) from week 4 (+/-3 days see Section 2) to end of week 7
- 13.3 mmol/L (240 mg/dl) from start of week 8 to end of week 13
- 11.1 mmol/L (200 mg/dl) from start of week 14 to end of treatment

If the confirmatory FPG (analysed by the central laboratory) exceeds the values described above and no intercurrent cause can be identified, the subject should attend a rescue medication visit (see Sections 2, 6.4 and 8.1.7) as soon as possible. After the completion of the rescue medication visit, the subject should be offered rescue medication at the discretion of the investigator and in accordance with ADA/European Association for the Study of Diabetes[16, 17]. Rescue medication excludes any GLP-receptor agonists, DPP-4 inhibitors and/or amylin analogues. Rescue medication can include intensification of existing background medication and/or initiation of suitable marketed treatment(s). The rescue treatment must be as add-on to the trial products during the remainder of the trial and does not constitute discontinuation criteria.
The randomised treatment should be continued and the subject should continue to follow their protocol-specified visit schedule (see Section 8.1.7). The rescue medication (including changes in

background medication) and any changes hereto must be captured on the concomitant medication form in the eCRF. Rescue medication will not be provided by Novo Nordisk.

6.5 Criteria for premature discontinuation of trial product

Efforts must be made so that the subject attends and completes all scheduled visit procedures. The subject should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be 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 any of the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

The primary reason for discontinuation of trial product must be specified in the eCRF. If a criterion for premature discontinuation of trial product is met, trial product should not be re-initiated but the subject should continue with the protocol-specified visit schedule.

See Section 2 for procedures to be performed for subjects discontinuing trial product prematurely.

6.6 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected.

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.

Only subjects who withdraw consent should be considered as withdrawn from trial.

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

6.7 Subject replacement

Subjects who are withdrawn or discontinue trial product prematurely will not be replaced.

6.8 Rationale for trial population

The trial population will include subjects with T2DM who have not achieved adequate glycaemic control despite at least 90 days' treatment with any SGLT2 inhibitor as monotherapy or in combination with metformin and for whom additional intensification of treatment is therefore necessary. Subjects with renal impairment defined as eGFR < 60 mL/min/1.73m^2 and/or history of diabetic ketoacidosis while being treated with SGLT2 inhibitors are excluded due to the background medications and limitations in their use.

Stable treatment prior to trial enrolment prevents differential effect on trial endpoints, while only serious concomitant conditions (e.g., NYHA class IV, history of recent serious cardiac event, neoplastic disease, pancreatitis, renal or hepatic impairment in accordance with the current Victoza® labelling) which could interfere with trial procedures preclude subjects from entering into the trial. The inclusion/exclusion criteria have been chosen to allow for enrolment of a trial population as broad as possible to ensure generalisability of trial results to the general population of patients with T2DM. The upper limit of HbA_{1c} of 9.5% was chosen due to inclusion of the placebo arm in order to avoid increased safety risks for those subjects who are at the higher range out of glycaemic control.

7 Milestones

Planned duration of recruitment period (FSFV-LSFV): 36 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 in 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 Disclosure[33], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[34], the Food and Drug Administration Amendment Act (FDAAA)[35], European Commission Requirements[36, 37] 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. Refer to the flow chart (Section 2) for visit numbers, timing of site visits and phone contacts, visit windows and assessments during the trial period.

8.1.1 Informed consent

Informed consent must be obtained before any trial related activity, see Section 18.2.

8.1.2 Investigator site logs

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

8.1.3 Screening (visit 1)

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. At screening, the subject 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. The subject should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Screening failures: For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section 12.

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

8.1.4 Re-screening

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria; this includes re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters (e.g., HbA_{1c} or ALT).

8.1.5 Fasting visits

The subject should attend fasting visits in a fasting state (see Section 2 for relevant visits). Fasting is defined as having consumed only water within the last 8 hours prior to the visit. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed, but other prescribed medication should be taken according to prescription.

If the subject does not attend the visit in a fasting state, completion of procedures except blood sampling can be performed. Blood sampling should be re-scheduled, preferably within the visit window.

8.1.6 Missed visits

Should a visit be missed, every effort should be made to re-schedule the visit within the allowed visit window. If this is not possible, the visit should be re-scheduled at the earliest possible date before the next visit.

8.1.7 Rescue medication visit

A subject eligible to receive rescue medication (see Section 6.4) will be requested to attend the rescue medication visit (Section 2) prior to initiating any rescue medication (Section 6.4). Hereafter, the subject will continue the planned visit schedule including visit 11 (EOT) and visit 12 (Follow-up) (see Section 2).

8.1.8 Premature discontinuation of trial product visit

A subject who discontinues trial product prematurely (Section 6.5) will be requested to attend the premature discontinuation visit (Section 2) prior to discontinuing treatment. Hereafter, the subject will continue the planned visit schedule including visit 11 (EOT) and visit 12 (Follow-up) (see Section 2).

The subject will be prescribed suitable marketed treatment(s) at the discretion of the investigator after discontinuation of trial products. The prescribed medication must be captured on the concomitant medication form in the eCRF. The primary reason for premature discontinuation of trial product must be specified in the end of treatment form in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS (see Section 10).

If after discontinuation of trial product the subject is not willing to attend one or more of the scheduled visits, it should be documented in the subject's medical record. In such case, site visits can be replaced by phone contacts in order to retain the subject in the trial.

8.1.9 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake the same procedures as visit 11 (EOT; Section 2) as soon as possible. The subject is asked to return the diaries and remainder of the trial products. The end-of-trial form and the end of treatment form must be completed and final drug accountability must be performed even if the subject is not able to come to the trial site. The end-of-trial form question regarding whether the subject has completed the trial period should be marked as 'No' and the date of withdrawal completed. 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. A treatment discontinuation session must be performed in the IWRS (Section 10) and the case book must be signed by the investigator in the eCRF. If the subject agrees, the follow-up visit 12 (Section 2) must be completed 1 week after visit 11.

8.2 Assessments

Review of diaries, laboratory reports, electrocardiograms (ECG's) and the results of physical examinations must be documented with the investigator's or delegated person's dated signature either on the front page of the documents or in the subject's medical record. The signed documents must be retained at the trial site as source documentation.

If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

8.2.1 Subject related information/assessments

8.2.1.1 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)

8.2.1.2 Diabetes history and diabetes complications

Diabetes history and diabetes complications will be recorded in the eCRF at screening (visit 1) and consists of:

- Date of diagnosis of T2DM
- Information regarding diabetes complications including date of onset of:
  - Diabetic retinopathy (if 'Yes' and includes macular oedema, this is to be entered in 'Further description of the complication, if applicable' in the eCRF)
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease) (if 'Yes' and includes foot ulcers, this is to be entered in 'Further description of the complication, if applicable' in the eCRF)

8.2.1.3 Concomitant illness and medical history

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

history is a medical event that the subject has experienced in the past. Procedures and assessments performed at visit 1 and/or visit 2 are considered as screenings procedures.

The information collected for concomitant illness and medical history should be recorded in the eCRF and includes the diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE (Section 12).

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

8.2.1.4 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 (screening visit; see Section 2). Changes in concomitant medication, including antidiabetic treatment and rescue medication, must be recorded at each visit as they occur. The eCRF must be updated accordingly.

The information collected for each concomitant medication includes trade name or generic name, indication, start date (only start year is applicable if more than one year) and stop date or continuation. The total daily dose is only applicable for antidiabetic medication.

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

No other treatment with anti-diabetic medication other than those listed in the inclusion criteria is allowed for subjects participating in the trial, with the exception of short term insulin treatment (≤ 7 days in total) in connection with intercurrent illness. If anti-diabetic medication is deemed as necessary, this will be considered rescue medication (see Sections 6.4 and 8.1.7).

8.2.1.5 Childbearing potential

It must be recorded in the subject's medical records by the investigator and 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 8.2.3.5. 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

8.2.1.6 Tobacco use

Details of use of tobacco must be recorded at the first visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily.

- Smoking status: Never smoked, Previous smoker, Current smoker

8.2.2 Efficacy assessments

8.2.2.1 Body measurements

Height should be assessed without shoes on, in centimetres (cm) or inches (in) and recorded to the nearest one decimal place.

Body weight should be assessed without shoes on, wearing only light clothing and is measured and recorded as either kilograms (kg) or pounds (lb) to the nearest one decimal place, preferably using the same scale throughout the trial.

Body mass index (BMI) will be calculated automatically in the eCRF once the height and weight are entered.

Waist circumference
The waist circumference is defined as the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest. It should be recorded to the nearest one decimal place using the same non-stretchable measuring tape provided by Novo Nordisk throughout the trial.

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

8.2.2.2 Vital signs

Blood Pressure
At site visits (see Section 2), systolic and diastolic blood pressure should be measured in a sitting position after the subject has been resting for at least 5 minutes. Blood pressure must be measured at the trial site using a calibrated digital blood pressure monitoring device.

Pulse, resting
Pulse (beats per minute) should be recorded at site visits (see Section 2) after resting for 5 minutes in a sitting position.

8.2.2.3 Self-measured plasma glucose (SMPG)

At visit 1 (see Section 2), the subject will be provided with a blood glucose meter including auxiliaries (e.g., lancets, plasma calibrated test strips and control solutions) as well as instructions for use. The subject will be instructed on how to use the device, including the performance of regular calibrations according to the manufacturer's instructions. As necessary, sites should repeat the directions for use to the subject at subsequent visits.

The blood glucose meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, as will be shown on the display. Only the blood glucose meter provided by Novo Nordisk should be used for the measurements required in the protocol.

The subject should be instructed how to record the results of the SMPG values in the provided diaries in case of hypoglycaemic episodes and in order to complete the 7 point profile. The record of each SMPG measurement should include the date, time and value. Occasional review by the investigator of the values stored in the memory of the blood glucose meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the trial database.

8.2.2.4 7-point self-measured plasma glucose profile

The subject will be instructed to perform a 7-point SMPG profile two times during the trial, preferably within one week prior to site visit 2 and site visit 11 (see Section 2), on a day where the subject does not anticipate unusual strenuous exercise.

The plasma glucose levels should be measured and recorded in the diary (including date, time and value) at the following time points always starting with the first measurement before breakfast.

Time points for 7-point SMPG profile:

- Before breakfast
- 90 min after start of breakfast
- Before lunch
- 90 min after start of lunch
- Before dinner
- 90 min after start of dinner
- At bedtime

8.2.2.5 Glucose metabolism and lipids

Blood samples will be drawn at the site at the time points specified in Section 2 and analysed at the central laboratory in order to determine levels of the following laboratory parameters:

Glucose metabolism

- fasting C-peptide
- fasting glucagon
- fasting insulin
- FPG
- HbA_{1c}

Fasting plasma glucose

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

Low plasma or blood glucose values reported by a laboratory in relation to specific protocol assessments should be assessed case by case and should not per default be reported as a hypoglycaemic episode on the usual hypoglycaemic episode forms. These should be reported as AEs related to the procedure.

Lipids

- cholesterol
- free fatty acids (FFA)
- high density lipoprotein (HDL) cholesterol
- low density lipoprotein (LDL) cholesterol
- very low density lipoprotein (VLDL) cholesterol
- triglycerides

8.2.3 Safety assessments

8.2.3.1 Physical examination

A physical examination must be performed and include the following:

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

In addition to the above, the lower left and lower right extremities will be assessed with regards to diabetes complications where the evaluation is normal if the subject has no leg or foot ulcers, and abnormal if the subject has one or more leg or foot ulcers. If reporting an abnormality, it should be specified if the ulcer appears infected or not.

For physical examinations, the evaluations based on investigator's or delegate's judgment, must follow the categories:

- Normal
- Abnormal (any abnormality should be specified in the eCRF free text)
  - Was the result clinically significant? (Yes/No)

8.2.3.2 ECG-12 lead

A 12-lead ECG must be performed (see Section 2) and interpreted locally by the investigator or assigned delegate. The evaluations based on the investigator's or delegate's judgment, must follow the categories:

- Normal
- Abnormal (any abnormality should be specified in the eCRF free text)

Was the result clinically significant? (Yes/No)

An ECG performed for any reason unrelated to this trial within 30 days prior to the first visit is acceptable providing no clinical signs or symptoms suggestive of cardiac disease have occurred in the meantime. If the ECG 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 is not related to this trial.

It is allowed to perform the visit 1 ECG between visit 1 and visit 2. The results must be available prior to randomisation. An ECG performed within 30 days before either the rescue medication visit, premature discontinuation visit or visit 11 (EOT) is acceptable as data for the respective visit, providing no clinical signs or symptoms suggestive of cardiac disease have occurred after visit 1.

8.2.3.3 NYHA

The functional capacity of subjects with heart disease should be assessed at screening (see Section 2) according to the NYHA classification[38] and either class I, II, III, IV or 'none' should be captured in the eCRF Table 8–1.

Table 8–1 NYHA criteria for functional capacity

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

8.2.3.4 Urinalysis

Urinalysis will be performed at visits specified in Section 2. For these visits, it is preferable that the subject collects a morning urine sample on the day of the visit and provides this to the site staff. If the subject does not take their sample with them to the site, the urine sample can then be collected while at site. Urine samples will be analysed at the central laboratory to determine levels of the following safety laboratory parameters:

- Albumin
- Creatinine
- Urine albumin creatinine ratio (UACR).

8.2.3.5 Biochemistry and Haematology

Blood samples will be drawn at site at the time points specified in Section 2 and analysed at the central laboratory in order to determine levels of the following laboratory parameters:

Biochemistry 1

- Albumin
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Amylase
- Lipase
- Bilirubins
- Calcium (total)
- Calcium corrected
- Creatine kinase

Biochemistry 2

- Potassium
- Sodium
- Urea
- Creatinine, used by central laboratory for calculation of eGFR according to the CKD-EPI creatinine equation for adults[1].

Haematology

- Erythrocytes
- Haemoglobin
- Haematocrit
- Leucocytes
- Thrombocytes

8.2.3.6 Pregnancy test

For females of child bearing potential; see Sections 2 and 8.2.1.5:

– presence or absence of serum beta-human chorionic gonadotropin (hCG)

At visits 1 and 11, a blood pregnancy test will be performed for women of child-bearing potential.

In Section 2 for the period between visits 1 and 11 where marked as (X): for women of childbearing potential, a urine-stick pregnancy test must be performed if a menstrual period is missed or according to local requirements. If during the phone contact the subject reports a missing menstrual period, the subject will have to attend the site for an unscheduled visit as soon as possible to have a urine-stick pregnancy test performed.
US only: At the last scheduled visit, male subjects must be asked if their female partner has become pregnant (see Section 12.5.2).

Pregnancy testing will not be required (unless required by local law) for women of non-childbearing potential (see Section 8.2.1.5).

8.2.3.7 Adverse events

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

- **Medication error**

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

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episode and/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.

- **Adverse events requiring additional data collection**

For some AEs additional data collection is required and a specific event form (Renal Event) must be completed in addition to the AE form. If a renal event is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms of renal failure (acute kidney injury (AKI), acute kidney disease (AKD)[39] or chronic kidney disease (CKD)[1])
- Specific laboratory tests supporting the diagnosis
- Imaging performed supporting the diagnosis
- Kidney biopsy results
- Risk or confounding factors identified including exposure to nephrotoxic agents

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

8.2.3.8 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 recorded by the subject in the diary. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 2 to visit 12.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines.[40]

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

In case of several low SMPG values within the 60 minutes interval, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode but the start time of the episode will remain as the time of 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 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 concentration[41].

Oral carbohydrates should 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), other factors not listed or unknown
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[41]?
  - 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.

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 [42-44]. The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

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

8.2.4 Laboratory assessments

The laboratory analyses (see Sections 8.2.3.4, 8.2.3.5, 8.2.3.6) will be performed by a central laboratory. Descriptions of 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 a central laboratory (for central laboratory details, see attachment I).

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units. Laboratory results will be sent by the central laboratory to the investigator on an on-going basis. For laboratory report values outside the reference range, the investigator must document whether the value is clinically significant or not. The investigator must sign and date the reports from the central laboratory or document the review in the subject's medical record on the day of the evaluation.

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 8.2.3.7 and Section 12.

Laboratory samples will be destroyed no later than the finalisation of the clinical trial report or as required according to local regulations.

8.3 Subject training

8.3.1 Diaries

The subject must be provided with diaries at the specified visits (Section 2). It is the responsibility of the investigator to review the diary for the subject's notes regarding possible AEs, hypoglycaemic episodes and concomitant medication (see Sections 8.2.1.4, 8.2.3.8, 8.2.3.7 and 12). All relevant data must be transcribed into the eCRF during or following the contact with the subject. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected. Each diary dispensed to a subject should be collected at the next clinic visit and retained as source data.

The subject should be instructed in recording the following data in the diary according to the provided diary instructions:

- Date of first liraglutide/placebo injection
- Date and dose of liraglutide/placebo, SGLT2 inhibitor and metformin (if applicable) on the day prior to each visit
- 7-point SMPG profile including date, actual clock time and SMPG value of all measurements
- Details on hypoglycaemic episodes
- Any medical condition(s) and concomitant medication(s)

8.3.2 Blood glucose meter

See Section 8.2.2.3.

8.3.3 Training in the prefilled pen-injector

The subject must be trained in how to handle the prefilled pen-injector for liraglutide/placebo, the s.c. administration and the gradual increase of the dose at weekly intervals to reach 1.8 mg/day, when the pre-filled pen injector is handed out (see Section 2 and Section 9.2). Training should be repeated during the trial at the investigators discretion based on the subjects needs 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
- Always perform an air shot before the first use of a new prefilled pen
- The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection.

8.4 Subject compliance

Throughout the trial, the investigator will remind the subject to follow the trial procedures and requirements to ensure subject compliance. The investigator must assess the compliance of the subject at each visit based on a review of glycaemic control, adherence to the visit schedule and completion of the subject's diary including the 7-point SMPG profiles. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance: The doses of metformin (if applicable), SGLT2 inhibitor, liraglutide and liraglutide placebo should be reviewed at each site visit by reviewing the previous day's dose of drug in the diary and by monitoring of drug accountability. If a subject is discovered to be noncompliant, the investigator must inform the subject of the importance of taking IMP and other diabetes treatments as prescribed.

9 Trial supplies

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

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

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

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Delivery device
Liraglutide (IMP, test product)	6 mg/mL	Solution for injection	Subcutaneous injection (s.c.)	3 mL, prefilled pen-injector
Liraglutide placebo (IMP, reference therapy)	N/A			

Liraglutide and placebo are visually identical.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[43], 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, see section 2) and at all subsequent dispensing visits.

9.3 Storage

Table 9–2 Storage conditions

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

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

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

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

9.4 Drug accountability and destruction

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

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

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

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

Subjects must be 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.

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.

The accountability for the NIMP (SGLT2 inhibitor and metformin if applicable) consists of the recording of the dose and dose frequency at every visit to the site. Dose information must be source data verifiable and must be entered in the eCRF.

9.5 Auxiliary supplies

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

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

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

10 Interactive voice/web response system

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Dispensing verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Code break
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.
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.

If a subject requires additional trial product between dispensing visits, the site must perform an additional dispensing session in the IWRS.

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blinded trial. A randomisation session will be carried out for all subjects using the IWRS. At the randomisation visit (V2), subjects meeting all eligibility criteria will be randomised to one of two parallel treatment arms as described in Section 5.1.

Randomisation will be stratified based on baseline metformin use (yes vs. no) to ensure a 2:1 distribution of the two treatment arms within the two strata.

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 is allowed to continue in the trial. If the subject must be withdrawn from the trial, a withdrawal 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 clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form (see Section 8.2.3.8).

The following three definitions are used when assessing an AE:

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

  Relationship between an AE and the relevant trial products:
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.

– **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

12.1.2 Serious adverse event

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

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

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

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

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

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

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

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

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x 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 an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug or use of wrong device.
  - Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. 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.

Medication errors must be reported on an AE form and a specific event form, see Section 8.2.3.7.

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. In this trial, details for AEs requiring additional data collection and the completion of specific event form (Renal Event) in the eCRF can be found in Sections 8.2.3.7, 12.1.5 and 12.2

12.1.6 Technical complaints

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

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

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

All AEs, observed either by the investigator or the 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.

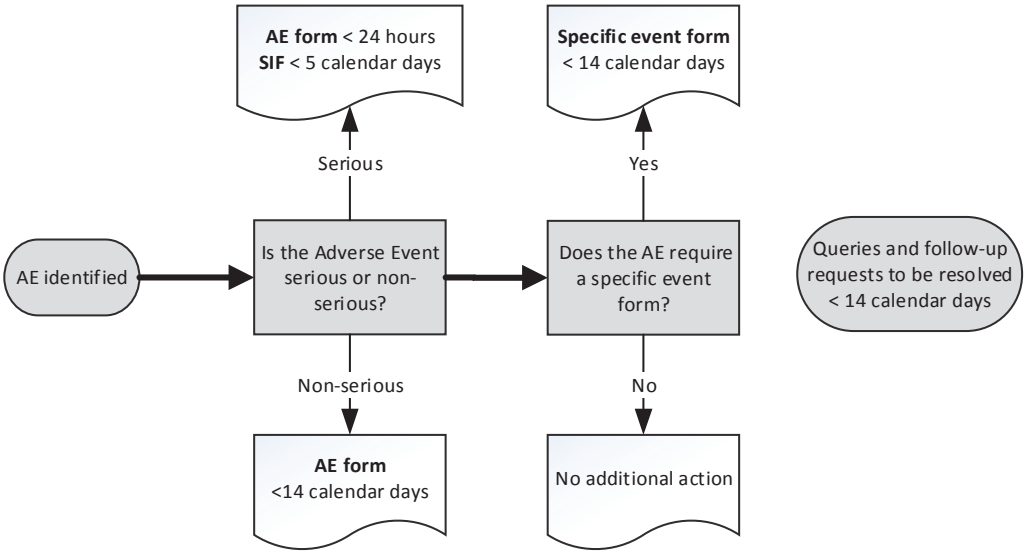
For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

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.
- **SAEs with additional data collection**: in addition to above, also the specific event form **within 14 calendar days** of the investigator's first knowledge of the AE
- **Non –serious AEs with additional data collection:** The AE form, and specific event form **within 14 calendar days** of the investigator's first knowledge of the event

If the eCRF is unavailable, the concerned AE information must be reported on 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 for the completion of forms are from the time of investigator's awareness.
AEs requiring specific event forms are descibed in Section 12.1.4 *and 12.1.5.*

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Company Core Data Sheet for Victoza® 6.0 mg/mL, 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[2]. 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[2], 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 an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- liraglutide/placebo pen injector
- Novo Nordisk needles

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk. Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

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

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

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

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

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

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

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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

1. Reporting of pregnancy information

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

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

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

2. Reporting of AE information

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

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

Non-serious AEs:

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

SAEs:

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

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

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

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

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

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

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

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

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

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

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

12.6 Precautions and/or overdose

When initiating treatment with liraglutide, the subject may, in some cases, experience loss of

fluids/dehydration, e.g., in cases of vomiting, nausea or diarrhoea sometimes with a decrease in kidney function (see Section 18.1). It is important to avoid dehydration by drinking enough fluids. From clinical trials and marketed use, overdoses of liraglutide have been reported up to 40 times the recommended maintenance dose (72 mg). Events reported included severe nausea, vomiting and diarrhoea. None of the reports included severe hypoglycaemia. All patients recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms.

12.7 Committees related to safety

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.

The investigator or delegated staff must 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.

13.2 Case report form flow

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

At the end of the trial the investigator must ensure that all remaining data has been entered into the eCRF **no later than 3 days** after last subject last visit (LSLV) at the site in order to ensure the planned lock of the database.

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

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification (SDV) and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after FSFV. 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). 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 (except for BMI).

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

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

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

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

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

- Date for obtaining informed consent.

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

15 Data management

Data management is the responsibility of Novo Nordisk. Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

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

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

16 Computerised systems

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

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

17 Statistical considerations

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis. No interim analyses or other analyses of unblinded data will be performed before the database is locked.

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, anti-diabetic background medication at screening (metformin use: yes vs no) will be included based on the actual information collected through the eCRF. In case of missing eCRF information concerning the stratification, the information collected from the IWRS will be used.

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Laboratory values below the lower limit of quantification (LLoQ) will be set to ½LLoQ. The number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

Results from a statistical analysis will, at a minimum be presented by the estimated treatment contrasts for the comparison between liraglutide and placebo with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

Primary and secondary estimands

Two estimands addressing different aspects of the trial objective will be defined; a primary de-facto (effectiveness) estimand and a secondary de-jure (efficacy) estimand:

1. Primary estimand

   - de-facto treatment difference at week 26 for all randomised subjects

The primary de-facto estimand assesses the average glycaemic benefit in a future population with T2DM with inadequate glycaemic control that results from adding treatment with liraglutide to a stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin including potential rescue medication(s) as compared to a continuing stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin including potential rescue medication(s). Generalisation of this estimand depends among other things on the extent to which the use of rescue medication and treatment adherence in this trial reflects clinical practice. All post-baseline scheduled visit data will be included in the analysis, including data collected after discontinuation of trial product or initiation of rescue medication(s).

2. Secondary estimand

   - de-jure treatment difference at week 26 for all randomised subjects if all subjects adhered to treatment and did not initiate rescue medication

The secondary de-jure estimand assesses the glycaemic benefit a future subject with inadequate glycaemic control is expected to achieve if adding treatment with liraglutide to a stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin as compared to a stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of liraglutide compared to placebo for purposes of treating individual subjects. Generalisation of this estimand depends among other things on the extent to which the compliance to trial product administration in this trial reflects clinical practice. Only post-baseline scheduled visit data collected prior to discontinuation of trial product or initiation of rescue medication will be included in the analysis. This will avoid confounding from rescue medication.

Missing data considerations at week 26

When estimating the primary estimand, the proportion of missing data, (i.e., data that do not exist even though subjects are intended to stay in the trial regardless of treatment status and initiation of rescue medication(s)), is expected to be at a maximum 10% based on previous experience in T2DM trial NN2211-4059[45]. Missing data will mainly be due to withdrawal from trial or loss to follow-up.

The proportion of missing data when estimating the secondary estimand is expected to be higher (25%), since data collected after discontinuation of trial product or initiation of rescue medication(s) will be set to missing. This assumption of 25% missing data is based on previous observations in the T2DM trial NN2211-4059[45]. Across treatment arms, the main reasons for missing data are

expected to be: early treatment discontinuation due to GI AEs and initiation of rescue medication. Initiation of rescue medication is expected to be more frequent in the placebo arm, whereas a higher proportion of subjects are expected to discontinue treatment due to AEs in the liraglutide arm when compared to the other treatment arm. Overall, the frequency of missing data is expected to be similar across treatment arms.

To document the extent and reason for missing data, descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

17.1 Sample size calculation

The primary endpoint is change from baseline to week 26 in HbA_{1c}. The confirmatory secondary endpoint is change from baseline to week 26 in body weight.

The sample size has been determined in order to demonstrate superiority of liraglutide vs. placebo both as add-on to SGLT2 inhibitor +/- metformin, with respect to both the primary and confirmatory secondary endpoints. The two pre-specified confirmatory tests are assumed to be independent. Since the tests are expected to be positively correlated, the assumption of independence is viewed as conservative. The hypotheses and testing procedure are described in Section 17.2.

The sample size assumptions for treatment effects, adjusted treatment effects and the standard deviations (SD) are given in Table 17–1. These are based on results from previous trials in the liraglutide Phase 3a clinical development program[46-51], and are supported by trial NN2211-4059[45].

They are as follows:

- Change in HbA_{1c}: a minimal treatment effect (TE) of 0.5% for liraglutide vs. placebo both as add-on to SGLT2i +/- metformin; standard deviation (SD) assumed to be 1.1%.

- The proportion of subjects either discontinuing treatment, initiating rescue medication, or not completing the week 26 HbA_{1c} assessment is expected to be 25% equally distributed among the two treatment arms. The TE among these 25% of subjects is expected to be 0.25%, leading to an adjusted TE of 0.4375% in the entire trial population.

- Change in body weight: a minimal treatment effect of 2.0 kg for liraglutide vs. placebo both as add-on to SGLT2i +/- metformin; SD assumed to be 4.0 kg.

- Similarly as for HbA_{1c}, the TE among the 25% of subjects either discontinuing treatment, initiating rescue medication, or not completing the week 26 body weight assessment is

expected to be reduced to 1.0 kg, leading to an adjusted TE of 1.75 kg in the entire trial population.

Table 17–1 Assumptions used in the sample size calculation

Liraglutide vs. placebo	HbA_{1c}	Body weight
TE	-0.50%	-2.0 kg
Adjusted TE	-0.4375%	-1.75 kg
SD	1.1%	4.0 kg

* TE: treatment effect

Based on these assumptions, the sample size is set to 202 in the liraglutide arm and 101 in the placebo arm for the full analysis set in order to achieve 90% power to confirm superiority in reducing HbA_{1c} of liraglutide vs. placebo. Marginal powers for individual hypotheses are presented in Table 17–2. The planned total sample size in the trial will be 303 subjects.

Table 17–2 Marginal powers for meeting individual hypothesis

Statistical test	HbA_{1c} superiority	Body weight superiority
Power (%)	90%	95%

17.2 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): includes all randomised subjects. Subjects in the FAS will contribute to evaluation “as randomised”.

Safety analysis set (SAS): includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the period they were on treatment. This will be referred to as contributing to the evaluation “as treated”.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Data selections and observation periods

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as up to and including the follow-up visit (visit 12).

Subjects and data to be used in an analysis will be selected in a two-step manner.

- Firstly, subjects will be selected based on the specified analysis set
- Secondly, data points on the selected subjects from first step will be selected based on the specified observation period

Definition of the observation periods:

In-trial: This observation period represents the time period where subjects are considered to be in the trial, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in the IWRS) and ends at the date of:

- the last direct subject-site contact, which is scheduled to take place 7 days after planned last dose of trial product at the follow-up visit (visit 12) for subjects completing the trial
- withdrawal for subjects who withdraw their informed consent
- the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- death for subjects who die before any of the above

On-treatment: This observation period represents the time period where subjects are considered treated with the trial product. The observation period is a subset of the in-trial observation period. It starts at the date of first dose of trial product. Three slightly different end dates will be needed to cover all assessments appropriately:

For AEs, the observation period ends at the first date of:

- the follow-up visit (visit 12)
- the last date on trial product + 1 day (hypoglycaemic episodes only)
- the last date on trial product + 10 days (all AEs excluding hypoglycaemic episodes). The follow-up visit is scheduled to take place 7 days after the last date on trial product. The visit window for the follow-up visit is +/-3 days.
- the end-date for the in-trial observation period

A different end date is specified for hypoglycaemic episodes to ensure specificity of reversible effects of treatment, as well as to ensure consistency across the liraglutide phase 3b clinical development programme.

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product + 3 days. This will be used in order to ensure specificity of reversible effects of treatment.

On-treatment without rescue medication: This observation period is a subset of the on-treatment observation period, where subjects are considered treated with trial product, but have not initiated any rescue medications. Specifically it starts at date of first dose of trial product and the observation period ends at the first date of:

- the last dose of trial product + 3 days
- initiation of rescue medication

The in-trial observation period will be the primary observation period when estimating the primary estimand. The on-treatment without rescue observation period will be the primary observation period when estimating the secondary estimand. The on-treatment observation period will be considered supportive for evaluating efficacy. Safety will be evaluated based on the in-trial and the on-treatment observation periods. For hypoglycaemic episodes, a sensitivity analysis will also be performed using the on-treatment period specified for all other AEs (last date on trial product + 10 days).

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period.

Confirmatory hypotheses

For the primary HbA_{1c} endpoint and the secondary confirmatory body weight endpoint, the following hypotheses are planned to be tested:

- Superiority in reducing HbA_{1c} of liraglutide 1.8 mg/day vs. placebo after 26 weeks
- Superiority in reducing body weight of liraglutide 1.8 mg/day vs. placebo after 26 weeks

A hierarchical testing procedure is used to control the overall type-1 error at a nominal two-sided 5% level. The primary endpoint and the confirmatory secondary endpoint will be analysed in the following order:

A. Primary endpoint (HbA_{1c})

B. Confirmatory secondary endpoint (Body weight)

In order to be able to conclude significance for the confirmatory secondary endpoint, a significant difference in favour of the liraglutide group must be found both for the primary endpoint and the confirmatory secondary endpoint.

17.3 Primary endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c}.

17.3.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation. Imputation of missing data at week 26 will be done within 4 groups of subjects defined by randomised treatment arm, and whether subjects at week 26; (i) have discontinued treatment or initiated rescue medication or (ii) are still on treatment and have not initiated rescue medication. It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 26 are similar in terms of randomised treatment arm and treatment adherence/rescue status.

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with country and the stratification factor (metformin use at baseline: yes vs no) as categorical fixed effects and baseline HbA1c measurement as a covariate will be fitted to observed values of the change from baseline at week 26 in HbA1c.
- The estimated parameters for location and dispersion, as well as the variability of these estimates, will be used to impute values for each subject with missing week 26 data based on stratification factor and country and baseline HbA1c. Thus, 1000 complete data sets will be generated including observed and imputed values.

Analysis used for confirming superiority versus placebo at week 26:

For each of the 1000 (now complete) imputed data sets the change in HbA_{1c} from baseline to week 26 will be analysed using an ANCOVA with treatment, country and the stratification factor (metformin use at baseline: yes vs. no) as categorical fixed effects and baseline HbA_{1c} as covariate.

The results obtained from analysing the datasets will be combined using Rubin's rule[52] to draw inference.

From this analysis the estimated treatment difference between liraglutide and placebo together with two-sided 95% CI and p-value for the test of no difference in effect will be presented.

17.3.2 Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the on-treatment without rescue observation period. The primary analysis for the secondary estimand will be performed using a Mixed Model for Repeated Measurements (MMRM). A restricted maximum likelihood (REML) will be used in fitting this model. The model will include change from baseline in HbA_{1c} measurements collected at scheduled visits up to and including week 26 as dependent variables. The independent effects included in the model will be treatment, country and the stratification factor (metformin use at baseline: yes vs. no) as categorical fixed effects and baseline HbA_{1c} as a covariate, all nested within visit. An unstructured covariance matrix for HbA_{1c} measurements within the same subject will be employed, assuming measurements from different subjects are independent.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is MAR. Under this assumption the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be the same as for the observed data.

17.3.3 Sensitivity Analysis

To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary and secondary estimand. In line with the European Medicines Agency (EMA) recommendations[53], and the US National Research Council[54] data.

The evaluation of the robustness of the primary analysis results will primarily be based on a pattern mixture model approach using multiple imputation. An overview of the sensitivity analyses for each of the estimands are specified below followed by a more detailed description of the three different pattern mixture models used.

Sensitivity analyses for the primary estimand

The estimation of the primary estimand will be repeated using the following sensitivity analyses:

- A placebo multiple imputation analysis based on FAS using the in-trial observation period.
- A placebo multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the in-trial observation period.

- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period.

- An MMRM analysis (the primary analysis for the secondary estimand) based on FAS using the in-trial observation period.

Sensitivity analyses for the secondary estimand

The estimation of the secondary estimand will be repeated using the following sensitivity analyses:

- A placebo multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.

- A placebo multiple imputation analysis based on FAS using the on-treatment observation period. This sensitivity analysis aims to compare liraglutide versus placebo for subjects who adhere to treatment regardless of whether or not rescue medication has been initiated.

- A placebo multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the on-treatment without rescue medication observation period.

- A tipping-point multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.

17.3.3.1 Pattern mixture models

All three pattern mixture model sensitivity analyses aim to stress-test the primary HbA_{1c} results by changing the assumptions for part or all missing data in the liraglutide treatment arm, while maintaining the missing at random data assumption for the placebo arm:

- Placebo multiple imputation analysis: In this sensitivity analysis, missing data at week 26 for subjects in both treatment arms will be imputed to resemble the distribution of the week 26 values observed in the placebo arm. In effect, this imputation approach removes the treatment difference between liraglutide and placebo for subjects randomised to liraglutide with missing data at week 26, given that liraglutide is better in reducing HbA_{1c} than placebo.
- Placebo multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely: In this sensitivity analysis, only missing data at week 26 for subjects who discontinue liraglutide treatment due to treatment related AE(s) will be imputed to resemble the distribution of the week 26 values observed in the placebo arm. For subjects who discontinue liraglutide treatment for reasons other than treatment related AE(s), missing data at week 26 will be imputed as in the primary analysis. Treatment related AEs are defined as AEs classified as possible or probable related to trial product as reported by the investigator. In effect, this imputation approach removes the treatment difference between

liraglutide and placebo for this selected group of subjects randomised to liraglutide. This sensitivity analysis is less conservative as compared to the above sensitivity analysis.

- Tipping-point multiple imputation analysis: In this sensitivity analysis, missing data will first be imputed according to the primary analysis. Second, for the liraglutide arm a penalty will be added to the imputed values at week 26. The approach is to gradually increase this penalty until the confirmed HbA_{1c} conclusion from the primary analysis is reversed. For each hypothesis tested the specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the primary analysis results.

17.3.3.2 Assessment of sensitivity analyses

The results from the sensitivity analyses will be collectively used to interpret the robustness of the trial results for HbA_{1c}. Due to the inherent conservative nature of the sensitivity analyses, it will not be a requirement that all confirmatory hypotheses are consistently confirmed across the sensitivity analyses. Thus, no absolute success criteria will be pre-defined for each sensitivity analysis. The sensitivity results in totality will be used to substantiate the credibility of the trial results.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

Change from baseline to week 26 in body weight will be a confirmatory secondary endpoint.

The primary and secondary estimands will be estimated using the same approaches as described for the primary HbA_{1c} endpoint. Baseline body weight will be used as a covariate instead of baseline HbA_{1c} in both the imputation and analysis model. From the analyses, the estimated treatment differences between liraglutide and placebo will be presented together with associated two-sided 95% CIs and p-values for testing no difference from zero. Sensitivity analyses similar to the ones pre-specified for testing superiority for the primary HbA_{1c} endpoint will be made to evaluate the robustness of the body weight results.

17.4.2 Supportive secondary endpoints

The below supportive secondary efficacy endpoints will be evaluated for:

- the primary estimand based on FAS using the in-trial observation period
- the secondary estimand based on FAS using the on-treatment without rescue medication observation period

No sensitivity analyses are planned for these.

17.4.2.1 Efficacy endpoints

Continuous efficacy endpoints

Change from baseline to week 26 in:

- Fasting Plasma Glucose (FPG)
- Self-Measured Plasma Glucose (SMPG): 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increments (over all meals)
- Fasting blood lipids (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triglycerides and free fatty acids)
- BMI and waist circumference
- Systolic and diastolic blood pressure

BMI will be calculated based on body weight and height based on the formulae:

BMI kg/m2 = body weight (kg)/(height (m) × height (m)) or (kg/m2 = [lb/in2 × 703])

Change from baseline to weeks 14 and 26 in:

- Glucagon, C-peptide and insulin (all fasting)

The above continuous endpoints will be analysed separately using similar modeling approaches as for the primary endpoint with the associated baseline response as a covariate. Fasting lipid profile endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Binary efficacy endpoints

Subjects who after 26 weeks achieve (yes/no):

- HbA_{1c} <7.0% (53 mmol/mol), American Diabetes Association target
- HbA_{1c} ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists target
- Weight loss ≥3%

- HbA_{1c} <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} <7.0% (53 mmol/mol) and no weight gain
- HbA_{1c} <7.0% (53 mmol/mol), no weight gain and systolic blood pressure <140 mmHg
- HbA_{1c} reduction ≥1% (11mmol/mol)
- HbA_{1c} reduction ≥1% (11mmol/mol) and no weight gain
- HbA_{1c} reduction ≥1% (11mmol/mol) and weight loss ≥3%

Handling of missing data for the response status of the above binary endpoints will be determined from the imputed continuous responses. A total of 1000 imputed data sets will be created based on the same models as used to analyse HbA_{1c} and body weight. For the secondary estimand the MMRM based analysis will be implemented in a multiple imputation setting. The imputed complete data sets will be analysed using a logistic regression model with treatment, stratification factor and country as categorical fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for binary weight endpoints and both baseline HbA_{1c} and body weight for the binary endpoints that combines both parameters). Inference comparing treatments will be drawn using Rubin's rule[52].

17.4.2.2 Safety endpoints

- Number of treatment emergent AEs during 26 weeks

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

A treatment emergent AE is defined as an AE with onset in the on-treatment observation period (see definition of observation periods in Section 17.2).

Treatment emergent AEs will be summarised 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 1000 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period. The development over time in gastrointestinal AEs will be evaluated by the use of graphical methods.

Other safety endpoints

Change from baseline to week 26 in:

- Haematology: haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes
- Biochemistry: creatinine, creatine kinase, urea, albumin, bilirubins (total), estimated glomerular filtration rate, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium, calcium (corrected), calcium (total), amylase and lipase
- Pulse
- ECG category
- Physical examination
- UACR

The above safety endpoints will be summarised descriptively by treatment arm and visit. Categorical safety endpoints will be summarised as counts and relative frequencies.

Classification of Hypoglycaemia:
Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period only.

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs within the on-treatment observation period (see definition of observation periods in Section 17.2).
Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05.59 both inclusive.

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

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[55]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

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

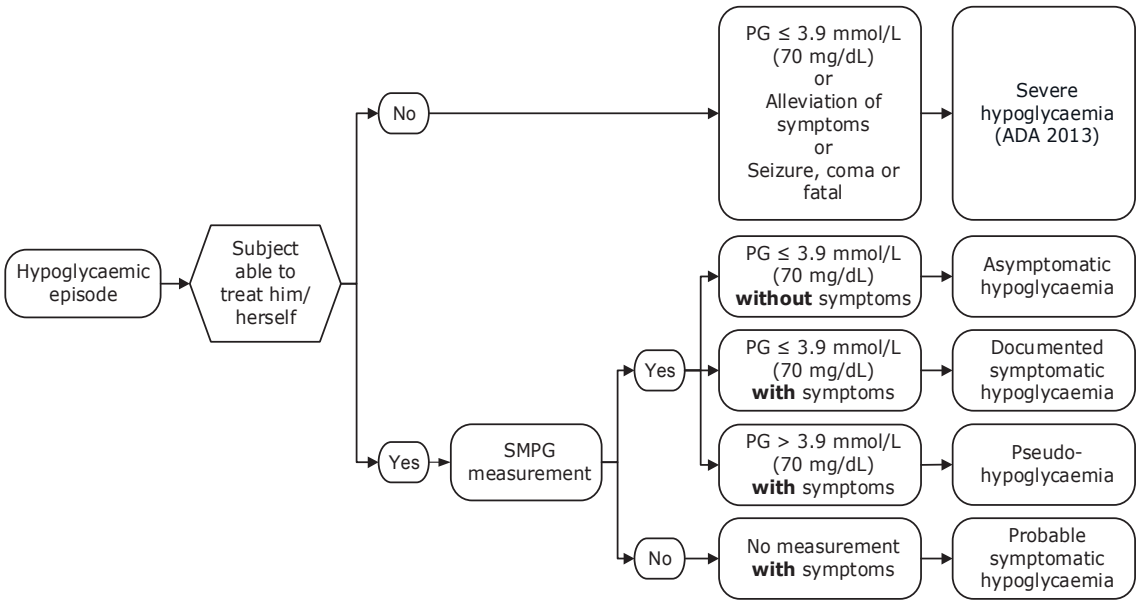
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[40] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

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

ADA classification[40] 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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–1 ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes will be presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 patient years of observation time.

Analysis of severe or BG confirmed symptomatic hypoglycaemic endpoints

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include factors for treatment, stratification factor and country as fixed factors and baseline HbA_{1c} as covariate.

The binary endpoint showing whether a subject has at least one treatment emergent severe or BG confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment, stratification factor and country as fixed factors and baseline HbA_{1c} as covariate.

18 Ethics

The trial will be conducted in compliance with ICH GCP[2] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[3].

18.1 Benefit-risk assessment of the trial

Inclusion and exclusion criteria have been defined in order to ensure that subjects are eligible for trial participation. Subjects will be treated within a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial. It is expected that all subjects participating in the trial will benefit from participation through close contact to the trial site, frequent visits and thereby an intensified evaluation of their diabetes.

Two thirds of the subjects will be randomised to receive liraglutide 1.8 mg/day. As liraglutide has been shown to be effective in lowering blood glucose levels, it can be expected that these subjects will experience improved glucose control during the trial. Subjects may benefit from the effect of treatment on weight, as has been previously demonstrated for liraglutide.

Hyperglycaemic rescue criteria have been defined to ensure that subjects will be offered additional glucose lowering rescue treatment should the level of glycaemic control exceed acceptable limits during trial participation. Treatment discontinuation criteria have been defined in order to ensure subject safety throughout the trial.

The trial drugs may be associated with AEs, however relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of trial participation. Furthermore, subjects will be fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

Acute kidney injury is a focus with regards to safety of trial products:

- In subjects treated with GLP-1 analogues including liraglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute kidney injury.
- SGLT2 inhibitors have also been associated with volume depletion related to AEs, and ketoacidosis as a result of severe dehydration has been reported during treatment with SGLT2 inhibitors.
- Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 analogues are co-administered with metformin.

The investigator should encourage subjects with gastrointestinal AEs to drink plenty of fluids in order to avoid volume depletion and to monitor renal function for signs and symptoms of fluid loss during therapy. As a precaution, serum creatinine and other markers of kidney function will be

measured regularly. In subjects treated with metformin who experience prolonged or severe nausea and vomiting, the investigator should monitor serum creatinine, and if clinically indicated, withhold metformin until resolution of renal dysfunction.

Safety information on Victoza® can be found in the approved local label for Victoza® and in the liraglutide (NN2211) abbreviated IB, 17th edition of August 2016 or any updates hereof[14]. Safety information of any oral antidiabetic drug (OAD(s)) used in this trial can be found in the approved local label of the individual OAD.

The subject has the right to withdraw from the trial at any time, without giving a specific reason. Novo Nordisk will be entitled to retain any data that was collected.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[2] and the requirements in the Declaration of Helsinki[3].

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.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

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

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

18.3 Data handling

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

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

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

18.4 Information to subjects during trial

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

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

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

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

19.2 Prevention of missing data

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

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

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

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)

- Signed receipt of Investigator's brochure (if applicable), signed receipt of Victoza® SmPC or similar labelling (according to local regulations)
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)
- **For US trial sites:** verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- **For US trial sites:** FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

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

For sites outside the US:

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

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

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP[2] applicable regulatory requirements and the Declaration of Helsinki[3].

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

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-

related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

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

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

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

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

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

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

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

23 Reports and publications

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information

obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

Two investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigators) on behalf of all participating investigators. The signatory investigators will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[57].

23.1 Communication of results

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[33].

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

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

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

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[57] (sometimes referred to as the Vancouver Criteria).

Novo Nordisk will appoint investigator(s) to prepare publications in collaboration with Novo Nordisk.

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

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation

24.1 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems 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, or Victoza® SmPC or similar labelling, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

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

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

Regulatory Authorities:

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

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

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.

Russia: Federal Law of 12 April 2010 No. 61-FZ "On Medicinal Drugs' Circulation" and the Civil Code of the Russian Federation.

27 References

1. KDIGO. 2012 Clinical Practive Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements. 2013;3(1).
2. Guideline IHT. Guideline for Good Clinical Practice E6(R1). 10 Jun 1996.
3. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
4. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787-835, ix.
5. International Diabetes Federation. IDF Diabetes Atlas 7th edition. 2015.
6. Introduction. Diabetes Care. 2016;39 Suppl 1:S1-2.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.
8. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-86.
9. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1). Adoption by CHMP. 14 May 2012.
10. Novo Nordisk A/S. Victoza® (liraglutide), Periodic Safety Update Report (PSUR), Current version and any updates hereof.
11. Novo Nordisk A/S. Victoza® (liraglutide), US label information. 22 Apr 2016.
12. Novo Nordisk A/S. Summary of Product Characteristics, Victoza (liraglutide). 23 March 2015.
13. Davies MJ, Bain SC, Atkin SL, Rossing P, Scott D, Shamkhalova MS, et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. Diabetes Care. 2016;39(2):222-30.
14. liraglutide (NN2211) abbreviated IB, 17th edition of August 2016.
15. Centers for Disease Control and Prevention A, GA: U.S.Department of Health and Human Services. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. 2014 2014.
16. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care. 2012;35(6):1364-79.
17. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58(3):429-42.

18. Muscelli E, Astiarraga B, Barsotti E, Mari A, Schliess F, Nosek L, et al. Metabolic consequences of acute and chronic empagliflozin administration in treatment-naive and metformin pretreated patients with type 2 diabetes. Diabetologia. 2016;59(4):700-8.
19. Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thévenet J, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med. 2015;21(5):512-7.
20. Fulcher G, Matthews DR, Perkovic V, de Zeeuw D, Mahaffey KW, Mathieu C, et al. Efficacy and safety of canagliflozin when used in conjunction with incretin-mimetic therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2016;18(1):82-91.
21. Janssen-Cilag International N.V. Invokana (canagliflozin) EU prescribing information (SmPC). January 2016.
22. Astrazeneca AB. Forxiga (dapagliflozin) EU prescribing information (SmPC). May 2015.
23. Boehringer Ingelheim International GmbH. Jardiance (empagliflozin) EU prescribing information (SmPC). December 2015.
24. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, Draft Guidance. 2008.
25. DeVries JH, Bain SC, Rodbard HW, Seufert J, D'Alessio D, Thomsen AB, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. Diabetes Care. 2012;35(7):1446-54.
26. Rosenstock J, Rodbard HW, Bain SC, D'Alessio D, Seufert J, Thomsen AB, et al. One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target. J Diabetes Complications. 2013;27(5):492-500.
27. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010;375(9724):1447-56.
28. Pratley R, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. International Journal of Clinical Practice. 2011;65(4):397-407.
29. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28.
30. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38(1):140-9.
31. Current local SmPC for any SGLT2 inhibitor and any updates hereof.
32. Local SmPC for metformin, current version. 2008.

33. Novo Nordisk Code of Conduct for Clinical Trial Disclosure. Avaliable from: http://novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx. 11 Jan 2015.
34. 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.
35. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007.
36. 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.
37. 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.
38. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Boston: Mass: Little, Brown & Co; 1994 1994. p. 253-6.
39. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney international supplements. 2012;2(1):1-138.
40. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245-9.
41. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med. 2001;18(9):690-705.
42. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin. 2009;25(4):929-42.
43. European Commission. The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products (ENTR/F/2/AM/an D(2010) 3374). 3 February 2010.
44. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Avaliable from: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. 2009.
45. Bailey T TR, Tinahones FJ, Rao P, Tsoukas GM, Thomsen AB, Kaltoft MS aMM. Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH™): a randomized, double-blind, double-dummy, active-controlled 26-week trial. Diabetes, Obesity and Metabolim 2016.

46. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009;26(3):268-78.
47. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and Safety Comparison of Liraglutide, Glimepiride, and Placebo, All in Combination With Metformin, in Type 2 Diabetes The LEAD (Liraglutide Effect and Action in Diabetes)-2 study. Diabetes Care. 2009;32(1):84-90.
48. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373(9662):473-81.
49. Zinman B, Gerich J, Buse J, et al. Efficacy and safety of the human GLP-1 analog liraglutide in combination with metformin and TZD in patients with type 2 diabetes mellitus (LEAD-4 Met + TZD). Diabetes Care. 2009;32:1224-30.
50. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009;52(10):2046-55.
51. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374(9683):39-47.
52. Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.
53. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). 2 Jul 2010.
54. National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press. 2010.
55. 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.
56. 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.
57. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 01
to Protocol, final version 1.0
dated 16 September 2016

Trial ID:NN2211-4315

LIRA-ADD2SGLT2i – liraglutide versus placebo as add-on to SGLT2 inhibitors

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted]

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 "Double click to update Table of Content"

Page

1 Introduction including rationale for the protocol amendment 3

2 Changes 4

2.1 Section 4.2.2.2: Supportive secondary endpoints (Page 19 of 94) 4
2.2 Section 8.2.3.5: Biochemistry and Haematology (Page 41 of 94) 4
2.3 Section 17.4.2.2: Safety endpoints (Page 76 of 94) 4
2.4 Section 17.4.2.2: Safety endpoints (Page 77 of 94) 4
2.5 Section 17.4.2.2: Safety endpoints (Page 79 of 94) 5

1 Introduction including rationale for the protocol amendment

Rationale for the changes:

1. 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, where the SGLT2 inhibitor is background medication. There is no safety risk for those subjects who do not have the bicarbonate assay performed during their treatment.
2. Minor changes in the statistical section have been made in order to ensure clarity and alignment across trials.

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 4.2.2.2: Supportive secondary endpoints (Page 19 of 94)

Supportive secondary safety endpoints

Change from baseline to week 26 in:

- Haematology: haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes
- Biochemistry: *serum bicarbonate*, creatinine, creatine kinase, urea, albumin, bilirubins (total), estimated glomerular filtration rate, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium, calcium (corrected), calcium (total), amylase and lipase

2.2 Section 8.2.3.5: Biochemistry and Haematology (Page 41 of 94)

Biochemistry 2

- *Serum bicarbonate*
- Potassium
- Sodium
- Urea
- Creatinine

2.3 Section 17.4.2.2: Safety endpoints (Page 76 of 94)

The safety endpoints will be evaluated based on SAS using the on-treatment and in-trial observation periods unless otherwise stated. The following endpoints are used to support the safety objective:

Adverse events

- Number of treatment emergent AEs during 26 weeks

2.4 Section 17.4.2.2: Safety endpoints (Page 77 of 94)

Other safety endpoints

Change from baseline to week 26 in:

- Haematology: haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes
- Biochemistry: *serum bicarbonate*, creatinine, creatine kinase, urea, albumin, bilirubins (total), estimated glomerular filtration rate, alanine aminotransferase, aspartate aminotransferase,

alkaline phosphatase, sodium, potassium, calcium (corrected), calcium (total), amylase and lipase
- Pulse
- ECG category
- Physical examination
- UACR

~~The above safety endpoints will be summarised descriptively by treatment arm and visit. Categorical safety endpoints will be summarised as counts and relative frequencies.~~

The above safety endpoints will be evaluated based on SAS using the on-treatment and in-trial observation periods. Continuous endpoints will be summarised descriptively by treatment arm and visit. Categorical safety endpoints will be summarised as counts and relative frequencies.

Hypoglycaemia

- *Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during 26 weeks**
- *Treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes during 26 weeks (yes/no)*

2.5 Section 17.4.2.2: Safety endpoints (Page 79 of 94)

Analysis of severe or BG confirmed symptomatic hypoglycaemic endpoints

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed *for the on-treatment period* using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include factors for treatment, stratification factor and country as fixed factors and baseline HbA_{1c} as covariate.

Protocol Amendment

no 02

to Original Protocol, version 1.0, dated 16 September 2016 and Global Protocol Amendment 01, version 1.0, dated 26 October 2016 (All countries) and Protocol final version 2.0 dated 26 October 2016

Trial ID:NN2211-4315

LIRA-ADD2SGLT2i – liraglutide versus placebo as add-on to SGLT2 inhibitors

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted]

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 "Double click to update Table of Content"

Page

1 Introduction including rationale for the protocol amendment 3

2 Changes 4

2.1 Section 2: Flow Chart (page 14 of 94) 4
2.2 Section 2: Flow Chart (page 15 of 94) 5
2.3 Section 5.3.2: Background medication (page 23 of 94) 6
2.4 Section 5.3.2.1: SGLT2 inhibitors (page 23 of 94) 6
2.5 Section 8.2.2.4: 7-point self-measured plasma glucose profile (page 37 of 94) 7
2.6 Section 8.3.1: Diaries (page 45 of 94) 7
2.7 Section 17: Statistical considerations (page 65 of 94) 8
2.8 Section 17.3.1: Primary analysis for the primary estimand (page 71 of 94) 9
2.9 Section 17.3.3: Sensitivity Analysis (page 72 of 94) 9

1 Introduction including rationale for the protocol amendment

Rationale for the changes:

1. Parentheses added around the flowchart 'Pregnancy test' assessment 'X' at premature discontinuation of trial product visit and rescue medication visit (X) to indicate that for women of childbearing potential, a urine-stick pregnancy test must be performed if a menstrual period is missed or according to local requirements.
2. 'X' removed from the flowchart rescue medication visit 'IWRS call' as IWRS is not used for this in this protocol.
3. Minor change in the background medication section (5.3.2), removing the bullet describing reimbursement of background medication as is already described in the summary section 1, so as not to be repetitive and to avoid ambiguity.
4. Information is added regarding SGLT2 inhibitor lower limb amputation warnings in section 5.3.2.1 to ensure comprehensive information is provided after recent label updates.
5. Addition of the description of the requirement for 7-point self-measured plasma glucose profiles at the rescue medication and premature discontinuation of trial product visits included in section 8.2.2.4 as previously described only in the flowchart (section 2).
6. Removed the capture of date and dose of background medication in diary section 8.3.1 as this is not collected in the diaries but only in the eCRF concomitant medications form so as to avoid collecting the same information twice.
7. Minor change in statistical section 17 has been made in order to ensure clarity.
8. The imputation of missing data has been modified such that missing values for all patients will be modelled after patients who discontinue or initiated rescue therapy.
9. An ANCOVA allowing for unequal variances has been included as a sensitivity analysis to evaluate the robustness of the primary analysis, in particular, the assumption of equal variances between treatment groups.

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 (page 14 of 94)

Trial Periods	Protocol section	Screen-ing	Random-isation	Treatment								End of treatment (EOT)	Follow-up	Rescue medica-tion 6.4/8.1.7	Premature Discontin-uation 6.5/8.1.8
Site visit (V) Phone contact (P)		V	V	P	P	P	V	P	V	V	V	V	P	V	V
Visit number		1	2	3	4	5	6	7	8	9	10	11	12		
Timing of visit: Weeks		up to -2	0	1	2	3	4	6	8	14	20	26[8.1.9]	27[8.1.9]		
Visit window: Days				±3	±3	±3	±3	±5	±5	±5	±5	±5	±3		
SUBJECT RELATED INFO/ASSESSMENTS															
SAFETY															
Physical examination	8.2.3.1	X										X		X	X
ECG	8.2.3.2	X										X		X	X
NYHA classification	8.2.3.3	X													
Urinalysis	8.2.3.4		X							X	X	X		X	X
Biochemistry 1	8.2.3.5	X										X		X	X
Biochemistry 2	8.2.3.5	X					X		X	X		X		X	X
Haematology	8.2.3.5	X										X		X	X
Pregnancy test	8.2.3.6	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X		*(X)*	*(X)*
Adverse events	8.2.3.7/12	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.2.3.8		X	X	X	X	X	X	X	X	X	X	X	X	X

2.2 Section 2: Flow Chart (page 15 of 94)

Trial Periods	Protocol section	Screen-ing	Random-isation	Treatment								End of treatment (EOT)	Follow-up	Rescue medica-tion 6.4/8.1.7	Premature Discontin-uation 6.5/8.1.8
Site visit (V) **Phone contact (P)**		V	V	P	P	P	V	P	V	V	V	V	P	V	V
Visit number		1	2	3	4	5	6	7	8	9	10	11	12		
Timing of visit: Weeks		up to -2	0	1	2	3	4	6	8	14	20	26[8.1.9]	27[8.1.9]		
Visit window: Days				±3	±3	±3	±3	±5	±5	±5	±5	±5	±3		
SUBJECT RELATED INFO/ASSESSMENTS															
Technical complaints	12.1.6/12.4			X	X	X	X	X	X	X	X	X	X	X	X
TRIAL MATERIAL															
IWRS call	10	X	X				X		X	X	X	X		~~X~~	X
Dispensing visit	9		X				X		X	X	X				
Drug accountability	9.4/10		X				X		X	X	X	X		X	X

2.3 Section 5.3.2: Background medication (page 23 of 94)

SGLT2 inhibitors and metformin

After signing the informed consent, subjects must continue their anti-diabetic background medication (SGLT2 inhibitor +/-metformin) throughout the entire trial. Fixed dose combinations of SGLT2 inhibitors and metformin are allowed. The background medication should be maintained at the same dose level as given at trial entrance and with the same frequency during the entire treatment period unless rescue medication is needed or a safety concern (e.g., diabetic ketoacidosis, lactic acidosis, hospitalisation for surgery or acute serious medical illness) arises, qualifying for changes to the background medication.

In addition, all background medication:

- is considered to be non-investigational medicinal product (NIMP)
- ~~will not be provided by Novo Nordisk A/S, except if required by local regulations. In countries where it is applicable, SGLT2 inhibitors may be reimbursed by Novo Nordisk A/S~~
- should be used in accordance with standard of care and current approved label in the individual country
- should not exceed the maximum approved dose in the individual country

2.4 Section 5.3.2.1: SGLT2 inhibitors (page 23 of 94)

Three SGLT2 inhibitors (dapagliflozin,[22] canagliflozin[21] and empagliflozin[23]) are currently approved for use either as monotherapy in metformin intolerant patients or in combination with metformin, sulfonylurea (SU), thiazolidinedione (TZD) or insulin. In addition, dapagliflozin is approved for use in combination with DPP-4 inhibitors[22]. There is however, currently no approval for any SGLT2 inhibitors to be used in combination with a GLP-1 receptor agonist.

SGLT2 inhibitors may be used at any stage of T2DM provided renal function is adequate. Besides lowering blood glucose, treatment with SGLT2 inhibitors also induces weight loss and lowering of systolic and diastolic blood pressure. Additionally, cardiovascular benefits of empagliflozin treatment have been shown previously in patients with T2DM [29].

As SGLT2 inhibitors possess a diuretic effect, hypotension and symptoms related to volume depletion may occur. Therefore they should be used with caution in the elderly, in any patient already on a diuretic and in anyone with a tenuous intravascular volume status. Initial increases in

serum creatinine occur with SGLT2 inhibitors, but generally these are small, reversible changes. Due to their MOA, SGLT2 inhibitors are less effective when the eGFR is between 45-60 mL/min1.73 m^2 [30]. The FDA and EMA have added warnings to the three SGLT2 inhibitors' labels regarding diabetic ketoacidosis (normoglycemic), urosepsis and pyelonephritis. *The FDA has added a warning only to the canagliflozin label regarding lower limb amputation, while EMA has added this warning to all three SGLT2 inhibitors' labels.*

Information about SGLT2 inhibitors including any benefits and/or any side effects, is available in the approved local label documents[31].

2.5 Section 8.2.2.4: 7-point self-measured plasma glucose profile (page 37 of 94)

~~The~~ *All* subject*s* will be instructed to perform a 7-point SMPG profile two times during the trial, preferably within one week prior to site visit 2 and site visit 11 (see Section 2), on a day where the subject does not anticipate unusual strenuous exercise.
Subjects who attend a rescue medication visit or a premature discontinuation of trial product visit, will also be instructed to perform a 7-point SMPG profile within one week prior to the visit.

The plasma glucose levels should be measured and recorded in the diary (including date, time and value) at the following time points always starting with the first measurement before breakfast.

Time points for 7-point SMPG profile:

- Before breakfast
- 90 min after start of breakfast
- Before lunch
- 90 min after start of lunch
- Before dinner
- 90 min after start of dinner
- At bedtime

2.6 Section 8.3.1: Diaries (page 45 of 94)

The subject must be provided with diaries at the specified visits (Section 2). It is the responsibility of the investigator to review the diary for the subject's notes regarding possible AEs, hypoglycaemic episodes and concomitant medication (see Sections 8.2.1.4, 8.2.3.8, 8.2.3.7 and 12). All relevant data must be transcribed into the eCRF during or following the contact with the subject. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

Each diary dispensed to a subject should be collected at the next clinic visit and retained as source data.

The subject should be instructed in recording the following data in the diary according to the provided diary instructions:

- Date of first liraglutide/placebo injection
- Date and dose of liraglutide/placebo~~, SGLT2 inhibitor and metformin (if applicable)~~ on the day prior to each visit
- 7-point SMPG profile including date, actual clock time and SMPG value of all measurements
- Details on hypoglycaemic episodes
- Any medical condition(s) and concomitant medication(s)

2.7 Section 17: Statistical considerations (page 65 of 94)

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis. No interim analyses or other analyses of unblinded data will be performed before the database is locked.

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, anti-diabetic background medication at ~~screening~~ *randomisation* (metformin use: yes vs no) will be included based on the actual information collected through the eCRF. In case of missing eCRF information concerning the stratification, the information collected from the IWRS will be used.

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Laboratory values below the lower limit of quantification (LLoQ) will be set to ½LLoQ. The number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

Results from a statistical analysis will, at a minimum be presented by the estimated treatment contrasts for the comparison between liraglutide and placebo with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

2.8 Section 17.3.1: Primary analysis for the primary estimand (page 71 of 94)

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation. ~~Imputation of missing data at week 26 will be done within 4 groups of subjects defined by randomised treatment arm, and whether subjects at week 26; (i) have discontinued treatment or initiated rescue medication or (ii) are still on treatment and have not initiated rescue medication.~~ *Imputation of missing data at week 26 for all subjects will be based on patients who discontinue or initiate rescue therapy within each randomised treatment arm, respectively.* It is hereby assumed that the ~~likely~~ values of what the missing data would have been if available are ~~best~~ *reasonably* described by information from subjects *on the same treatment arm* who at week 26 *had discontinued or initiated rescue therapy.* ~~are similar in terms of randomised treatment arm and treatment adherence/rescue status.~~

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with country and the stratification factor (metformin use at baseline: yes vs no) as categorical fixed effects and baseline HbA1c measurement as a covariate will be fitted to observed values of the change from baseline at week 26 in HbA1c.
- The estimated parameters for location and dispersion, as well as the variability of these estimates, will be used to impute values for each subject with missing week 26 data based on stratification factor and country and baseline HbA1c. Thus, 1000 complete data sets will be generated including observed and imputed values.

2.9 Section 17.3.3: Sensitivity Analysis (page 72 of 94)

To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary and secondary estimand. In line with the European Medicines Agency (EMA) recommendations[53], and the US National Research Council[54] data.

The evaluation of the robustness of the primary analysis results will primarily be based on a pattern mixture model approach using multiple imputation. An overview of the sensitivity analyses for each of the estimands are specified below followed by a more detailed description of the three different pattern mixture models used.

Sensitivity analyses for the primary estimand

The estimation of the primary estimand will be repeated using the following sensitivity analyses:

- A placebo multiple imputation analysis based on FAS using the in-trial observation period.

- A placebo multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the in-trial observation period.
- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period.
- An MMRM analysis (the primary analysis for the secondary estimand) based on FAS using the in-trial observation period.
- *A multiple imputation analysis similar to the primary analysis, but instead using ANCOVA allowing for unequal variances between the two treatment groups based on FAS using the in-trial observation period. This sensitivity analysis aims to evaluate the assumption of equal variances implicit in the ANCOVA model for the primary analysis.*