

## Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03136484
Sponsor trial ID:	NN9535-4270
Official title of study:	Efficacy and Safety of Semaglutide Versus Canagliflozin as add-on to Metformin in Subjects With Type 2 Diabetes
Document date:	03 June 2019

## 16.1.1 Protocol and protocol amendments

### List of contents

<b>Protocol .....</b>	<a href="#">Link</a>
<b>Appendix A .....</b>	<a href="#">Link</a>
<b>Appendix B.....</b>	<a href="#">Link</a>
<b>Protocol amendment 1 .....</b>	<a href="#">Link</a>
<b>Attachment I and II.....</b>	<a href="#">Link</a>

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

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date: 17 October 2016  
Version: 2.0  
Status: Final  
Page: 1 of 118

**Novo Nordisk**

## **Protocol**

**Trial ID: NN9535-4270**

**SUSTAIN 8 – semaglutide versus canagliflozin**

**Efficacy and safety of semaglutide versus canagliflozin as add-on to metformin in subjects with type 2 diabetes**

**Trial phase: 3b**

**Protocol originator**



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 ~~No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk.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

## Table of Contents Page

<b>Table of Contents</b> .....	<b>2</b>
<b>Table of Figures</b> .....	<b>7</b>
<b>Table of Tables</b> .....	<b>7</b>
<b>List of abbreviations</b> .....	<b>8</b>
<b>1 Summary</b> .....	<b>12</b>
<b>2 Flow chart</b> .....	<b>15</b>
<b>3 Background information and rationale for the trial</b> .....	<b>18</b>
3.1 Background information.....	18
3.1.1 Type 2 diabetes.....	18
3.1.2 Glucagon-like peptide-1.....	18
3.1.3 Semaglutide.....	19
3.1.4 Non-clinical data.....	19
3.1.4.1 Semaglutide.....	19
3.1.5 Clinical data – semaglutide.....	20
3.1.5.1 Pharmacokinetics.....	20
3.1.5.2 Efficacy.....	21
3.1.5.3 Safety.....	21
3.1.6 Canagliflozin.....	22
3.2 Rationale for the trial.....	22
<b>4 Objective(s) and endpoint(s)</b> .....	<b>24</b>
4.1 Objective(s).....	24
4.2 Endpoint(s).....	24
4.2.1 Primary endpoint.....	24
4.2.2 Secondary endpoints.....	24
4.2.2.1 Confirmatory secondary endpoints.....	24
4.2.2.2 Supportive secondary efficacy endpoints.....	24
4.2.2.3 Supportive secondary safety endpoints.....	25
<b>5 Trial design</b> .....	<b>27</b>
5.1 Type of trial.....	27
5.2 Rationale for trial design.....	28
5.3 Treatment of subjects.....	28
5.3.1 Background medication.....	29
5.4 Injection site.....	29
5.5 Missed dose.....	29
5.6 Treatment after discontinuation of trial product.....	29
5.7 Rationale for treatment.....	29
<b>6 Trial population</b> .....	<b>31</b>
6.1 Number of subjects.....	31
6.2 Inclusion criteria.....	31
6.3 Exclusion criteria.....	31
6.4 Randomisation criteria (only applicable for the DXA scan sub-population).....	33
6.5 Rescue criteria.....	33

6.6	Criteria for premature discontinuation of trial product.....	34
6.7	Withdrawal from trial .....	34
6.8	Subject replacement.....	35
6.9	Rationale for trial population.....	35
<b>7</b>	<b>Milestones.....</b>	<b>36</b>
<b>8</b>	<b>Methods and assessments .....</b>	<b>37</b>
8.1	Visit procedures .....	37
8.1.1	Investigator site log.....	37
8.1.2	Screening, Visit 1.....	37
8.1.3	Screening failures .....	37
8.1.4	Re-screening .....	38
8.1.5	Fasting visits .....	38
8.1.6	Unscheduled visits .....	38
8.1.7	Phone contacts .....	38
8.1.8	Premature discontinuation of trial product .....	39
8.1.9	Withdrawal from trial .....	39
8.1.10	Investigator assessment.....	40
8.2	Subject related information/assessments .....	40
8.2.1	Demography.....	40
8.2.2	Diabetes history and diabetes complications .....	41
8.2.3	Hypoglycaemia unawareness.....	41
8.2.4	Concomitant illness and medical history .....	41
8.2.5	Concomitant medication .....	41
8.2.6	Childbearing potential.....	42
8.2.7	Tobacco use .....	43
8.3	Efficacy assessments.....	43
8.3.1	Height, body weight and BMI .....	43
8.3.2	Waist circumference .....	43
8.3.3	Systolic and diastolic blood pressure.....	44
8.3.4	Self-measured plasma glucose (SMPG) .....	44
8.3.5	7-point profile .....	44
8.3.6	DXA scan (sub-population only).....	45
8.4	Safety assessments.....	46
8.4.1	Physical examination .....	46
8.4.2	Pulse.....	46
8.4.3	Electrocardiogram – 12 lead .....	46
8.4.4	Eye examination .....	47
8.4.5	Adverse events.....	47
8.4.5.1	Medication error.....	47
8.4.5.2	Adverse events requiring additional data collection .....	48
8.4.6	Hypoglycaemic episodes .....	48
8.5	Laboratory assessments .....	51
8.5.1	Laboratory assessments for efficacy.....	52
8.5.2	Laboratory assessments for safety .....	52
8.6	Other assessments .....	53
8.6.1	Subject diary .....	53
8.6.2	Electronic patient reported outcome questionnaires .....	54
8.6.2.1	SF-36v2 .....	54

8.6.2.2	DTSQs.....	54
8.6.2.3	Control of Eating Questionnaire (CoEQ).....	54
8.6.3	Training in the PDS290 pen-injector.....	55
8.6.4	Training in blood glucose meter use.....	55
8.7	Subject compliance.....	55
<b>9</b>	<b>Trial supplies.....</b>	<b>56</b>
9.1	Trial products.....	56
9.2	Labelling.....	57
9.3	Storage.....	57
9.4	Drug accountability and destruction.....	58
9.5	Auxiliary supplies.....	58
<b>10</b>	<b>Interactive voice/web response system.....</b>	<b>59</b>
<b>11</b>	<b>Randomisation procedure and breaking of blinded codes.....</b>	<b>60</b>
11.1	Breaking of blinded codes.....	60
<b>12</b>	<b>Adverse events, technical complaints and pregnancies.....</b>	<b>61</b>
12.1	Definitions.....	61
12.1.1	Adverse event.....	61
12.1.2	Serious adverse event.....	62
12.1.3	Non-serious adverse event.....	63
12.1.4	Medication errors.....	63
12.1.5	Adverse events requiring additional data collection.....	63
12.1.6	Technical complaints.....	64
12.2	Reporting of adverse events.....	65
12.3	Follow-up of adverse events.....	67
12.4	Technical complaints and technical complaint samples.....	68
12.4.1	Reporting of technical complaints.....	68
12.4.2	Collection, storage and shipment of technical complaint samples.....	69
12.5	Pregnancies.....	69
12.5.1	Pregnancies in female subjects.....	69
12.6	Precautions and/or overdose.....	71
12.7	Committees related to safety.....	71
12.7.1	Novo Nordisk safety committee.....	71
12.7.2	Event adjudication committee.....	71
<b>13</b>	<b>Case report forms.....</b>	<b>74</b>
13.1	Corrections to case report forms.....	74
13.2	Case report form flow.....	75
13.3	Electronic collection of questionnaires.....	75
<b>14</b>	<b>Monitoring procedures.....</b>	<b>76</b>
<b>15</b>	<b>Data management.....</b>	<b>78</b>
<b>16</b>	<b>Computerised systems.....</b>	<b>78</b>
<b>17</b>	<b>Statistical considerations.....</b>	<b>79</b>
17.1	General considerations.....	79
17.1.1	Data transformations.....	79
17.1.2	Definition of baseline.....	80

17.1.3	Primary estimand .....	80
17.1.4	Trial completion.....	80
17.1.5	Missing data considerations at week 52.....	80
17.2	Sample size calculation.....	81
17.2.1	Sample size for the sub-study (DXA scan).....	83
17.3	Definition of analysis sets.....	84
17.3.1	Data selections and observation periods .....	84
17.4	Primary endpoint.....	86
17.4.1	Primary analysis for the primary estimand .....	86
17.4.2	Primary hypotheses.....	87
17.4.3	Multiplicity and criteria for confirming hypotheses .....	87
17.4.4	Statistical subgroup analyses of HbA <sub>1c</sub> .....	88
17.4.5	Sensitivity analyses.....	88
17.4.5.1	Sensitivity analyses for the primary estimand.....	88
17.4.5.2	Other sensitivity analyses.....	89
17.5	Secondary endpoints.....	89
17.5.1	Confirmatory secondary endpoints .....	89
17.5.2	Supportive secondary endpoints .....	91
17.5.2.1	Efficacy endpoints.....	91
17.5.2.2	Safety endpoints .....	92
17.6	Health economics and/or patient reported outcomes (PROs) .....	97
<b>18</b>	<b>Ethics .....</b>	<b>98</b>
18.1	Benefit-risk assessment of the trial .....	98
18.1.1	Risk and precautions.....	98
18.1.2	Identified risk.....	98
18.1.3	Potential risks.....	98
18.1.4	Other safety considerations.....	99
18.1.5	Benefits.....	101
18.2	Risk and benefit conclusion.....	102
18.3	Informed consent .....	102
18.4	Data handling.....	103
18.5	Information to subjects during trial.....	103
18.6	Premature termination of the trial and/or trial site.....	103
<b>19</b>	<b>Protocol compliance.....</b>	<b>104</b>
19.1	Protocol deviations .....	104
19.2	Prevention of missing data.....	104
<b>20</b>	<b>Audits and inspections .....</b>	<b>104</b>
<b>21</b>	<b>Critical documents .....</b>	<b>105</b>
<b>22</b>	<b>Responsibilities .....</b>	<b>107</b>
<b>23</b>	<b>Reports and publications.....</b>	<b>108</b>
23.1	Communication of results.....	108
23.1.1	Authorship .....	109
23.1.2	Site-specific publication(s) by investigator(s) .....	109
23.2	Investigator access to data and review of results .....	109
<b>24</b>	<b>Retention of clinical trial documentation.....</b>	<b>111</b>

24.1	Retention of clinical trial documentation.....	111
<b>25</b>	<b>Institutional Review Boards/Independent Ethics Committees and regulatory authorities.....</b>	<b>112</b>
<b>26</b>	<b>Indemnity statement .....</b>	<b>113</b>
<b>27</b>	<b>References .....</b>	<b>114</b>

Appendix A Monitoring of Calcitonin

Appendix B Adverse events requiring additional data collection

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

	<b>Page</b>
Figure 5–1 Trial design .....	27
Figure 12–1 Reporting of AEs .....	66
Figure 17–1 Graphical illustration of the closed testing procedure. ....	83
Figure 17–2 Novo Nordisk classification of hypoglycaemia .....	94
Figure 17–3 ADA classification of hypoglycaemia .....	95

## Table of Tables

	<b>Page</b>
Table 9–1 Trial products .....	56
Table 9–2 Storage conditions .....	57
Table 12–1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication .....	64
Table 12–2 Adverse events for adjudication .....	72
Table 17–1 Assumptions used in the sample size calculation .....	82
Table 17–2 Calculated powers for meeting individual hypotheses .....	82

## List of abbreviations

ADA	American Diabetes Association
AACE	American Association of Clinical Endocrinologists
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
BMI	body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
CoEQ	Control of Eating Questionnaire
CVOT	Cardio Vascular Outcome Trial
DFU	direction for use
DPP-4	ubiquitous dipeptidyl peptidase
DTSQs	Diabetes Treatment Satisfaction Questionnaire, short form
DKA	Diabetic Ketoacidosis
DUN	dispensing unit number
DXA	dual X-ray absorptiometry
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ePRO	electronic patient reported outcome
EMA	European Medicines Agency

Exenatide ER	exenatide extended release
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA <sub>1c</sub>	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IgE	immunoglobulin E
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
i.v.	Intravenous
LDL	low-density lipoprotein

LLOQ	lower limit of qualification
LOCF	Last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
MACE	major adverse cardiac events
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	Multipel endokrin neoplasi typ 2
MI	Myocardial infarction
MMRM	Mixed Model for Repeated Measurements
NIMP	non-investigational medicinal products
NOAEL	no observable adverse event effect level
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OW	Once weekly
P	phone contact
PG	plasma glucose
PK	Pharmacokinetics
PMM	Pattern mixture model
PP	per protocol

PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis set
s.c.	subcutaneous(ly)
SF-36v2™	Short form healthy survey
SDV	source data verification
SIF	safety information form
SGLT-2	Sodium-glucose co-transporter-2
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2D	Type 2 diabetes mellitus
TMM	Trial Materials Manual
UNL	upper normal limit
UNR	upper normal range
UTN	Universal Trial Number

# 1 Summary

## Objective(s) and endpoint(s):

### Primary objective

To compare the effect of once-weekly (OW) dosing of subcutaneous semaglutide (1.0 mg) versus once-daily dosing of oral canagliflozin (300 mg) on glycaemic control in subjects with type 2 diabetes (T2D) on a background treatment of metformin.

### Secondary objectives

To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus canagliflozin 300 mg once-daily after 52 weeks of treatment in subjects with T2D with regards to:

- Weight management
- Other parameters of effect, safety and Patient Reported Outcomes

### Endpoint(s)

#### Primary endpoint

- Change from baseline to week 52 in HbA<sub>1c</sub>

#### Supportive secondary efficacy endpoints

Change from baseline to week 52 in:

- Fasting Plasma Glucose (FPG)\*
- Systolic and diastolic blood pressure\*
- Diabetes Treatment Satisfaction Questionnaire (DTSQ)\*: Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately

### Trial design:

This is a 52-week, confirmatory, randomised, double-blind, double dummy, active-controlled, multicentre, multinational, two-arm, parallel-group trial.

Subjects with type 2 diabetes inadequately controlled with metformin alone will after approximately 2 weeks screening period be randomised in a 1:1 manner to receive either a dose of 1.0 mg semaglutide once-weekly or 300 mg canagliflozin once-daily.

After a period of approximately 52 weeks in total, all subjects enter a follow up period of 5 weeks ended by a follow-up visit. Total trial duration for the individual subjects will be approximately 59 weeks.

### Trial population:

A planned total number of 784 subjects will be randomised in a 1:1 manner.

### **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  $\geq 18$  years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus (T2D).
4. HbA<sub>1c</sub> of 7.0-10.5% (53-91 mmol/mol, both inclusive).
5. Stable daily dose of metformin ( $\geq 1500$  mg or maximum tolerated dose as documented in the subject medical record and in compliance with current local label) for at least 90 days prior to the day of screening.

### **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).
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days prior to the day of screening.
5. Any disorder which in the investigator’s opinion might jeopardise subject’s safety or compliance with the protocol.
6. Subject with alanine aminotransferase (ALT)  $> 2.5$  x upper normal limit (UNL).
7. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
8. History or presence of pancreatitis (acute or chronic).
9. History of diabetic ketoacidosis (DKA).
10. Any of the following: myocardial infarction (MI), stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
13. Renal impairment measured as eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> as defined by Kidney Disease Improving global outcomes (KDIGO 2012)<sup>1</sup> classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.
14. 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 prior to the day of screening is allowed.

15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated funduscopy performed within the past 90 days prior to randomisation.
16. 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 is allowed.

**Assessments:**

- Glucose metabolism (HbA<sub>1c</sub>, fasting plasma glucose)
- Body measurements (weight (kg), body mass index (BMI), waist circumference, total fat mass (kg) and total lean mass measured by DXA in a sub-population)
- Blood pressure
- Fasting blood lipids (total cholesterol, LDL, HDL and triglycerides)
- Self-measured plasma glucose (7-point profile)
- Patient reported outcomes
- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry and haematology
- Pulse
- Calcitonin and creatinine
- Physical examination
- Electrocardiogram
- Dilated funduscopy/fundophotography

**Trial product(s):**

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

Investigational medicinal products:

- Test product: Semaglutide 1.34mg/ml, solution for injection, 1.5 mL prefilled PDS290 pen-injector
- Reference therapy: Canagliflozin 100 mg/300 mg, tablets

## 2 Flow chart

Trial Periods	Screening	Randomisation	Treatment								End of Treatment	Follow-up	End of treatment, Premature discontinuation	Follow-up
			V3	V4	P5	V6	V7	V8	V9	V10				
Visit (V)/ phone contact (P)	V1	V2	V3	V4	P5	V6	V7	V8	V9	V10	P11	V10A	P11A	
Timing of visit (weeks)	-2	0	4	8	10	12	16	28	40	52	57			
Visit window (days)	±7		±3	±3	±3	±7	±7	±7	±7	±7	±7			
<b>SUBJECT RELATED INFO/ASSESSMENTS</b>	<b>Section</b>													
Informed consent	<a href="#">18.3</a>	x												
In/exclusion criteria	<a href="#">6.2, 6.3</a>	x	x											
Randomisation	<a href="#">6.4</a>		x											
Withdrawal criteria	<a href="#">6.7</a>			x	x	x	x	x	x	x	x	x		
Concomitant illness	<a href="#">8.2.4</a>	x												
Concomitant medication	<a href="#">8.2.5</a>	x	x	x	x	x	x	x	x	x	x	x	x	
Demography	<a href="#">8.2.1</a>	x												
Hypoglycaemia unawareness	<a href="#">8.2.3</a>	x												
Diagnosis of diabetes	<a href="#">8.2.2</a>	x												
Diabetes history and diabetes complications	<a href="#">8.2.2</a>	x												
Medical history	<a href="#">8.2.4</a>	x												
Tobacco use	<a href="#">8.2.7</a>	x												
<b>EFFICACY</b>														
Height	<a href="#">8.3.1</a>		x											
Body weight	<a href="#">8.3.1</a>		x	x	x		x	x	x	x	x	x	x	
BMI	<a href="#">8.3.1</a>		x	x	x		x	x	x	x	x	x	x	
Waist circumference	<a href="#">8.3.1</a>		x						x		x		x	
PRO questionnaires	<a href="#">8.6.2</a>		x						x		x		x	

Trial Periods	Screening	Randomisation	Treatment							End of Treatment	Follow-up	End of treatment, Premature discontinuation	Follow-up
			V3	V4	P5	V6	V7	V8	V9				
Visit (V)/ phone contact (P)	V1	V2	V3	V4	P5	V6	V7	V8	V9	V10	P11	V10A	P11A
Timing of visit (weeks)	-2	0	4	8	10	12	16	28	40	52	57		
Visit window (days)	±7		±3	±3	±3	±7	±7	±7	±7	±7	+7		
<b>SUBJECT RELATED INFO/ASSESSMENTS</b>													
<b>EFFICACY cont.</b>	<b>Section</b>												
Systolic blood pressure	<a href="#">8.3.3</a>	x	x	x	x		x	x	x	x	x		x
Diastolic blood pressure	<a href="#">8.3.3</a>	x	x	x	x		x	x	x	x	x		x
Fasting plasma glucose	<a href="#">8.5.1</a>		x	x	x		x	x	x	x	x		x
HbA <sub>1c</sub>	<a href="#">8.5.1</a>	x	x	x	x		x	x	x	x	x		x
Lipids	<a href="#">8.5.1</a>		x						x		x		x
7-point profile	<a href="#">8.3.5</a>		x						x		x		x
DXA scan	<a href="#">8.3.6</a>	x								x			x
<b>SAFETY</b>													
Hypoglycaemic episodes	<a href="#">8.4.6</a>		x	x	x	x	x	x	x	x	x	x	x
ECG	<a href="#">8.4.3</a>		x						x		x		x
Eye examination	<a href="#">8.4.4</a>		x								x		x
Physical examination	<a href="#">8.4.1</a>	x							x		x		x
Pulse, sitting	<a href="#">8.4.2</a>	x	x	x	x		x	x	x	x	x		x
Biochemistry	<a href="#">8.5.2</a>	x	x	x	x		x	x	x	x	x		x
Creatinine (including eGFR)	<a href="#">8.5.2</a>	x	x	x	x		x	x	x	x	x		x
Haematology	<a href="#">8.5.2</a>		x	x	x		x	x	x	x	x		x
Pregnancy test	<a href="#">8.5.2</a>	x	x						x		x		x
Adverse events	<a href="#">12.1.1</a>		x	x	x	x	x	x	x	x	x	x	x
Calcitonin	<a href="#">8.5.2</a>		x						x		x		x

Trial Periods		Screening	Randomisation	Treatment							End of Treatment	Follow-up	End of treatment, Premature discontinuation	Follow-up
Visit (V)/ phone contact (P)		V1	V2	V3	V4	P5	V6	V7	V8	V9	V10	P11	V10A	P11A
Timing of visit (weeks)		-2	0	4	8	10	12	16	28	40	52	57		
Visit window (days)		±7		±3	±3	±3	±7	±7	±7	±7	±7	+7		
<b>SUBJECT RELATED INFO/ASSESSMENTS</b>														
<b>TRIAL MATERIAL cont.</b>	<b>Section</b>													
Dispensing visit			x	x	x		x	x	x	x				
Drug accountability				x	x		x	x	x	x	x		x	
IWRS call	<a href="#">10</a>	x	x	x	x		x	x	x	x	x		x	
<b>REMINDERS</b>														
Fasting visits	<a href="#">8.1.5</a>		x	x	x		x	x	x	x	x		x	
Hand-out direction for use (DFU)			x											
End of treatment											x		x	
End of trial												x <sup>a</sup>		
Hand-out and instruct on BG meter use		x												
Re-training on the BG meter use			x											
Training in trial product and pen handling			x	x										
Hand out ID card		x												
Hand out and instruct in diary	<a href="#">8.6.1</a>	x	x	x	x		x	x	x	x				
Collect and review diary			x	x	x		x	x	x	x	x		x	

<sup>a</sup> If premature discontinuation, End of Treatment form must be filled-in when the discontinuation happens and End of Trial form at scheduled visit P11. If a subject completes both the treatment and the trial at scheduled time, the End of Treatment form must be filled at V10 and End of Trial form to be filled in at P11. In case of subject withdrawal, both End of Treatment form and End of Trial form must be filled-in at the time they withdraw from the trial.

### 3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP<sup>2</sup> and applicable regulatory requirements, and in accordance with the Declaration of Helsinki<sup>3</sup>.

*For Mexico only: 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

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

#### 3.1 Background information

##### 3.1.1 Type 2 diabetes

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver<sup>4</sup>.

Optimal glycaemic control is the treatment goal in subjects with T2D in order to prevent long-term complications associated with chronic hyperglycaemia<sup>5</sup>. Despite the availability of several antidiabetic drugs, a significant proportion of subjects with T2D do not achieve the recommended blood glucose (BG) target levels<sup>6,7</sup>.

##### 3.1.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets<sup>8,9</sup>. Subjects with T2D have a decreased incretin effect<sup>10-13</sup>. However, the insulinotropic action of GLP-1 and thus, the ability to lower blood glucose (BG) levels, is preserved when GLP-1 is administered at supraphysiological levels<sup>14</sup>. In addition, supraphysiological levels of GLP-1 induce reduction in body weight<sup>15</sup>. GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation<sup>16,17</sup>. Physiologically, GLP-1 also has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish

upon chronic stimulation of the GLP-1 receptor<sup>15-17</sup>. These mechanisms of action make glucagon-like peptide-1 receptor agonists (GLP-1RAs) an attractive pharmacological treatment for T2D<sup>18-20</sup>.

### 3.1.3 Semaglutide

Semaglutide is a potent human GLP-1 analogue with a pharmacokinetic (PK) profile suitable for once-weekly subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza<sup>®</sup>), a once-daily GLP-1RA developed by Novo Nordisk and approved worldwide for the treatment of T2D. The extended half-life of the semaglutide molecule is primarily obtained due to binding to albumin, which is facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone to increase stability against DPP-4, and a change in position 34 from a lysine to an arginine to limit the options for acylation to the one remaining lysine in the sequence; 2) a large hydrophilic spacer between the lysine in position 26 and the gamma glutamate where the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group<sup>21, 22</sup>. The spacer and the fatty acid both contribute to increased albumin binding, which results in a prolonged half-life of approximately 1 week, making semaglutide suitable for once weekly (OW) s.c. administration.

### 3.1.4 Non-clinical data

#### 3.1.4.1 Semaglutide

The nonclinical programme for semaglutide was designed according to the ICH M3<sup>23</sup> guideline to support the clinical development. The standard nonclinical data package required to support phase 3 clinical trials has been completed. In addition, 2-year carcinogenicity studies and a pre- and postnatal development toxicity study have been completed.

Semaglutide is generally well tolerated with expected GLP-1 effects on food intake and body weight being dose limiting in mice, rats and cynomolgus monkeys. Two potential safety issues have been identified and are detailed below.

#### Thyroid C-cell tumours in rodents

Thyroid C-cell neoplasia was seen in mice and rat 2-year carcinogenicity studies. Proliferative C-cell changes in rodents are a known effect following GLP-1 receptor activation by GLP-1 receptor agonists. The finding in rodents is caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid, and accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low<sup>24</sup>.

#### Embryo–foetal development toxicity

Semaglutide adversely affected embryo–foetal development in the rat by a GLP-1 receptor-mediated impaired function of the inverted yolk sac placenta during a period of gestation when the

rat embryo is entirely dependent on the inverted yolk sac placenta for its nutrient supply. In primates, the yolk sac does not invert to fully enclose the embryo, and it does not come in direct contact with the uterine wall to form a placenta as in rodents. Accordingly, the mechanism by which semaglutide adversely affects embryo-foetal development in the rat, is not likely to be of relevance to humans. Studies in cynomolgus monkeys confirmed that maternal dosing of semaglutide does not affect embryo-foetal development in this species. However, the initial maternal body weight loss caused by the pharmacological effect of semaglutide coincided with increased early pregnancy loss in one of three studies. In cynomolgus monkeys, the overall developmental no observable adverse event effect level (NOAEL) was determined to be 0.015 mg/kg/3 days, which provides an exposure equivalent to the human exposure at 1.0 mg/week based on area under the curve (AUC).

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide (NN9535) Investigator's Brochure (IB),<sup>25</sup> or any updates hereof.

### **3.1.5 Clinical data – semaglutide**

As of 1 August 2016, 16 clinical pharmacology trials (trials 1820, 3679, 3633, 3616, 3819, 4010, 3789, 3652, 3685, 3634, 3687, 3817, 3818, 3684, 3651 and 3635) and 1 phase 2 trial (trial 1821) and 8 phase 3a trials (NN9535-3623, 3624, 3625, 3626, 3627, 3744, 4091, 4092) have been completed with semaglutide s.c.OW.

Clinical pharmacology trials were conducted in healthy subjects, in subjects with T2D, in subjects with obesity and in subjects with renal- and hepatic impairment. Semaglutide phase 3a programme evaluated the efficacy and safety of semaglutide in a broad T2D population and covered the continuum of T2D care. The programme evaluated mono- and combination therapy with antiglycaemic therapies and compared semaglutide with the most important comparators at the time of initiating the phase 3a programme. In addition, the phase 3a programme included a long-term (104-week) cardiovascular outcomes trial (trial 3744) in a T2D population at high risk of cardiovascular events.

#### **3.1.5.1 Pharmacokinetics**

The results from the completed clinical pharmacology trials confirm that semaglutide has PK properties compatible with once-weekly administration, having a flat concentration profile over time, with a median time to maximum concentration ( $t_{max}$ ) of 36–60 hours post-dosing and an elimination half-life ( $t_{1/2}$ ) of approximately 1 week (149–165 hours). The absolute bioavailability of semaglutide s.c. was estimated to be 89%. The PK properties of semaglutide appear comparable between healthy subjects, subjects with T2D and subjects with renal failure.

Results from drug-interaction studies with warfarin, metformin, atorvastatin and digoxin indicate that no dose adjustment of the co-administered drugs is warranted when administered together with semaglutide. In addition, semaglutide does not decrease the exposure of oral contraceptives and hence, is not anticipated to decrease the effectiveness of oral contraceptives.

### **3.1.5.2 Efficacy**

Based on results from the clinical pharmacology trials, semaglutide treatment, compared to placebo, reduced both fasting and postprandial plasma glucose by improving multiple aspects of beta-cell function and by reducing both fasting and postprandial glucagon concentrations, all in a glucose dependent manner. The body weight loss observed with semaglutide was primarily from fat tissue and was considered to be explained by lowered appetite, both in the fasting and postprandial state, and lowered energy intake. In addition, semaglutide improved control of eating and reduced food cravings. Similar to other GLP-1 receptor agonists, semaglutide caused a minor delay of early postprandial gastric emptying.

Both as monotherapy and as combination therapy, semaglutide significantly reduced HbA<sub>1c</sub> and body weight in all phase 3a trials when compared with the trial-specific comparator, including the active comparators sitagliptin, exenatide extended release (exenatide ER) and insulin glargine. In the 5 global phase 3a trials (3623, 3624, 3625, 3626 and 3627), reductions in HbA<sub>1c</sub> and body weight of up to 1.85 %-point and 6.42 kg, respectively, were obtained with semaglutide 1.0 mg. Significantly more subjects with semaglutide versus comparators reached the ADA and AACE-defined treatment targets of an HbA<sub>1c</sub> <7% and ≤6.5%, respectively, and weight loss responses of ≥5% and ≥10%. The superior and clinically relevant beneficial effects of semaglutide on glycaemic control as estimated by change in HbA<sub>1c</sub> were substantiated by improvements in secondary glycaemia-related supportive endpoints.<sup>26-29</sup>

### **3.1.5.3 Safety**

Data from the 5 global phase 3a clinical trials (NN9535-3623, 3624, 3625, 3626 and 3627) showed that the safety and tolerability of semaglutide at doses up to 1.0 mg per week and administered for up to 56 weeks of treatment were consistent with other GLP-1RAs. Commonly reported adverse events (AEs) included nausea and vomiting, most of which were mild to moderate in severity. The escalation regimen utilized was associated with good tolerability and low numbers of discontinuation due to AEs. Accordingly, the most frequently reported AEs in subjects with T2D were gastrointestinal (e.g., nausea and vomiting), as were the most frequent AEs leading to premature treatment discontinuation.

Hypoglycaemia occurred infrequently in subjects receiving semaglutide and the events were mainly non-severe. Hypoglycaemic episodes have mainly been observed when semaglutide is combined with SU or insulin. In line with findings for other GLP-1RAs, an increase in heart rate and serum levels of lipase and amylase has also been observed in subjects exposed to semaglutide. As with all protein based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. However, only few subjects administered semaglutide experienced allergic reactions and injection site reactions. These have mainly been mild and transient of nature; however, more generalised reactions may occur.

The effect of semaglutide on major adverse cardiovascular events (MACE) was evaluated in a T2D population at high risk for CV events, in the cardiovascular outcome trial, SUSTAIN 6 (NN9535-3744)<sup>30</sup>. SUSTAIN 6 trial achieved its primary objective by showing non-inferiority of once-weekly s.c. semaglutide versus placebo on cardiovascular outcomes; moreover, s.c. semaglutide statistically significantly reduced cardiovascular risk versus placebo<sup>30</sup>. In addition, results from the recently completed LEADER® trial (EX2211-3748) showed that treatment with the once daily liraglutide does not increase the risk of MACE as compared to placebo. In fact, treatment with liraglutide reduced the risk of the primary composite outcome consisting of death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke by 13% versus placebo<sup>31</sup>. A post-marketing cardiovascular outcomes trial on canagliflozin (CANVAS) is ongoing and results are expected in Q1 2017, see <https://clinicaltrials.gov/ct2/show/NC01032629>.

The overall safety profile of semaglutide in the SUSTAIN 6 trial (NN9535-3744) was consistent with previous semaglutide clinical studies. However, in this trial, the diabetic retinopathy complications were reported more frequently in the semaglutide-treated subjects compared with placebo. Please see Section [18](#) for more details.

Please see the current edition of semaglutide s.c. (NN9535) IB or any updates hereof for further details<sup>25</sup>.

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

### **3.1.6 Canagliflozin**

The selected active comparator in this trial is canagliflozin, a selective inhibitor of the sodium-glucose co-transporter-2 (SGLT-2), which is the predominant transporter responsible for glucose reabsorption from the glomerular filtrate back into the circulation. Inhibition of SGLT-2 reduces BG levels by blocking renal glucose reabsorption, thereby increasing urinary glucose excretion. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on the BG concentration and renal function. Canagliflozin was developed by Janssen Pharmaceuticals and approved in 2013 in the US to improve glycaemic control in adults with T2D.

For further details, please see the current approved label for canagliflozin<sup>32</sup>.

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

## **3.2 Rationale for the trial**

The currently available treatment modalities for T2D are still not satisfactory and there is a significant proportion of patients not reaching the treatment targets<sup>6</sup>.

The aim for the present trial is to compare the effect of semaglutide versus canagliflozin, in subjects with T2D inadequately controlled with metformin, in terms of glycaemic control, weight

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date: 17 October 2016  
Version: 2.0  
Status: Final  
Page: 23 of 118

**Novo Nordisk**

management and other efficacy parameters. This trial is also designed to compare safety profile, tolerability and patient satisfaction.

In order to further investigate the effects of semaglutide vs canagliflozin on body weight, a sub-study on body composition has been implemented in this trial, which will allow collection of information on changes in body fat and lean mass.

## 4 Objective(s) and endpoint(s)

### 4.1 Objective(s)

#### Primary objective

To compare the effect of once-weekly dosing of subcutaneous semaglutide (1.0 mg) versus once-daily dosing of oral canagliflozin (300 mg) on glycaemic control in subjects with T2D on a background treatment of metformin.

#### Secondary objective

To compare the effect of semaglutide s.c. 1.0 mg once-weekly versus canagliflozin 300 mg once-daily after 52 weeks of treatment in subjects with T2D with regards to:

- Weight management
- Other parameters of effect, safety and Patient Reported Outcomes (PRO)

### 4.2 Endpoint(s)

#### 4.2.1 Primary endpoint

- Change from baseline to week 52 in HbA<sub>1c</sub>

#### 4.2.2 Secondary endpoints

##### 4.2.2.1 Confirmatory secondary endpoints

##### Change from baseline to week 52 in

- body weight (kg)

In a sub-set of subjects assessed through dual X-ray absorptiometry (DXA):

- Total fat mass (kg)

##### 4.2.2.2 Supportive secondary efficacy endpoints

##### Change from baseline to week 52 in:

- Fasting Plasma Glucose (FPG)\*
- Self-Measured Plasma Glucose (SMPG), 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides)
- Systolic and diastolic blood pressure\*
- Body Mass Index (BMI) and waist circumference
- Body weight (%)
- Scores for selected patient reported outcomes:

- SF-36v2™ Short Form health survey: Total scores (physical component and mental component) and scores from the 8 domains
- Diabetes Treatment Satisfaction Questionnaire (DTSQ)\*: Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately
- Control of Eating Questionnaire (CoEQ): Scores from the 4 domains and scores from 19 individual items

In a sub-set of subjects, assessed through DXA, change from baseline to week 52 in:

- Total fat mass (%)
- Total lean mass (kg)
- Total lean mass (%)
- Visceral fat mass (kg)<sup>a</sup>
- Visceral fat mass (%)<sup>a</sup>
- Ratio between total fat mass and total lean mass

<sup>a</sup>analyses marked with an 'a' will be performed based on specific DXA equipment and software availability.

**Subjects who after 52 weeks treatment achieve (yes/no):**

- HbA<sub>1c</sub> <7.0% (53 mmol/mol), American Diabetes Association (ADA) target
- HbA<sub>1c</sub> ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists (AACE) target\*
- Weight loss ≥3%
- Weight loss ≥5%
- Weight loss ≥10%
- HbA<sub>1c</sub> <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA<sub>1c</sub> reduction ≥1%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥3%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥5%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥10%

**4.2.2.3 Supportive secondary safety endpoints**

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

**Change from baseline to week 52 in:**

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Electrocardiogram (ECG) category
- Physical examination category
- Eye examination category

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

## 5 Trial design

### 5.1 Type of trial

This is a 52-week, confirmatory, randomised, double-blind, double dummy, active-controlled, multicentre, multinational, two-arm, parallel-group trial.

Subjects with T2D inadequately controlled on metformin alone, will after approximately 2 weeks screening period, be randomised in a 1:1 manner to receive either semaglutide 1.0 mg once-weekly and canagliflozin placebo once-daily, or canagliflozin 300 mg once-daily and semaglutide placebo once-weekly after a dose escalation phase of 8 weeks, see [Figure 5-1](#).

Subjects continue participation in the trial regardless of premature discontinuation of trial product or the initiation of rescue medication.

After the treatment period of approximately 52 weeks in total, all subjects enter a follow-up period of 5 weeks which ends by a follow-up visit. Total trial duration for the individual subjects is approximately 59 weeks.

The randomisation will be stratified according to the participation in the sub-study (yes or no) in order to ensure balanced treatment allocation within the sub-study.

The trial design is summarised schematically in [Figure 5-1](#).

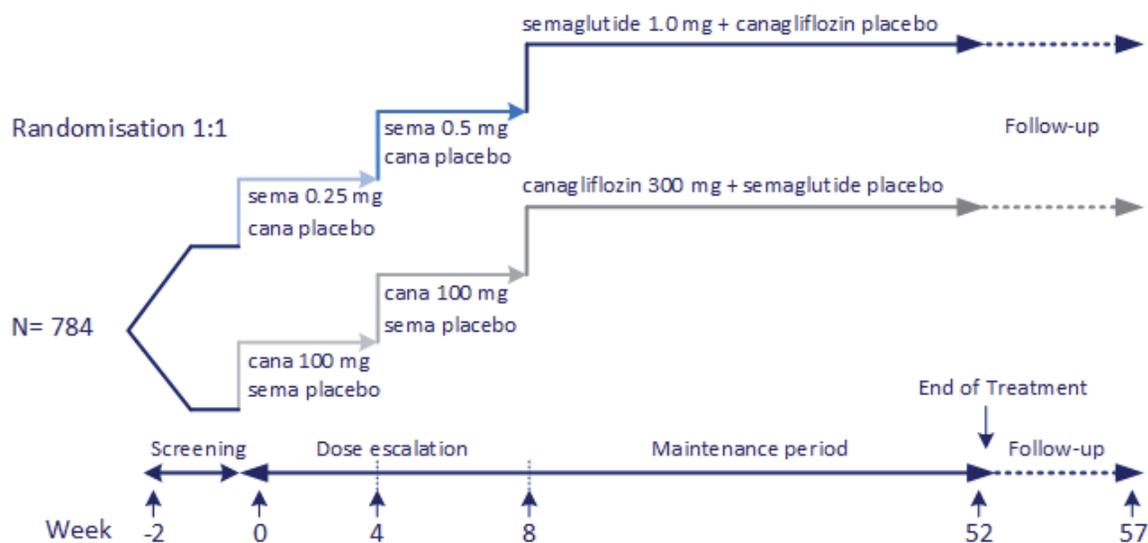


Figure 5-1 Trial design

## 5.2 Rationale for trial design

This trial has been designed as a double-blind, two-arm, parallel-group trial to compare the effect of semaglutide s.c. 1.0 mg once-weekly versus canagliflozin 300 mg once-daily, as add-on to metformin, in terms of glycaemic control, weight management and other effect parameters. Furthermore, the trial is designed to address and compare safety, tolerability, patient well-being and treatment satisfaction. Body composition will be measured using dual energy x-ray absorptiometry (DXA) in a subset of 174 subjects (87 subjects per treatment arm) at V1 and V10 or V10A.

Semaglutide is administered as s.c. injections and canagliflozin as oral tablets. In order to fulfil blinding of the trial, a double-dummy design has been implemented. Accordingly, all subjects randomised to semaglutide s.c. will also receive canagliflozin placebo tablets, while subjects randomised to canagliflozin will also receive semaglutide placebo s.c. injections.

The treatment duration is 52 weeks, considered adequate for assessment of effect, safety, tolerability and patient satisfaction.

The follow-up period is 5 weeks to allow for wash-out of semaglutide.

## 5.3 Treatment of subjects

### Semaglutide treatment arm

Treatment with semaglutide, once-weekly must follow a fixed dose escalation. The maintenance dose of semaglutide 1.0 mg is reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg. During the final maintenance period (V4-V10, see Table 5–1), doses must not be changed. In addition, all subjects randomised to semaglutide will receive canagliflozin placebo once-daily.

### Canagliflozin treatment arm

Treatment with canagliflozin, once-daily must follow a fixed dose escalation. The maintenance dose of canagliflozin 300 mg is reached after 56 doses (8 weeks) of 100 mg. After the maintenance dose of 300 mg is reached the dose must not be changed during the course of the trial unless the eGFR falls  $<45\text{ mL}/\text{min}/1.73\text{ m}^2$ , see below. In addition, all subjects randomised to canagliflozin will receive semaglutide placebo once-weekly.

Treatment with canagliflozin must be in compliance with current local prescribing information. Canagliflozin should be taken orally once a day, preferably before the first meal of the day. Tablets should be swallowed whole. Treatment with canagliflozin or canagliflozin placebo should be temporarily stopped in subjects who are hospitalized for major surgical procedures or acute serious medical illnesses. In subjects whose eGFR falls persistently  $<60\text{ mL}/\text{min}/1.73\text{ m}^2$ , the dose of canagliflozin or canagliflozin placebo should be reduced to 100 mg once-daily. The dose can be re-escalated to 300 mg once-daily in case the renal function improves (eGFR  $\geq 60\text{ mL}/\text{min}/1.73\text{ m}^2$ )

during the trial. If the eGFR falls  $<45 \text{ mL/min/1.73 m}^2$ , treatment with all trial products should be discontinued (see section [6.6](#))<sup>1</sup>.

### **5.3.1 Background medication**

The only allowed diabetes background medication is metformin. After signing the informed consent, subjects must continue pre-trial dose ( $\geq 1500 \text{ mg}$  or maximum tolerated dose as documented in the subject medical record and in accordance with current local label) of metformin throughout the entire treatment period, at the same dose level as given at trial entrance and with the same frequency, unless rescue criteria (see section [6.5](#)) are met.

#### **Metformin**

Metformin is considered non-investigational medicinal product (NIMP) and will not be provided by Novo Nordisk, except if required by local regulations. Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator and in compliance to the current local label.

### **5.4 Injection site**

Semaglutide (and semaglutide placebo) is administered subcutaneously by injections in the thigh, abdomen or upper arm, at any time of the day irrespective of meals. Injections should be administered on the same day of the week during the trial. Injections should not be administered intravenously or intramuscularly.

### **5.5 Missed dose**

If a semaglutide dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours) away. If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing time of the week.

If a canagliflozin dose is missed it should be taken as soon as the subject remembers; however, a double dose should not be taken on the same day.

### **5.6 Treatment after discontinuation of trial product**

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued prematurely, the subject should be switched to a suitable marketed product at the discretion of the investigator, while taking into consideration the long half-life of semaglutide.

*For Brazil only: At the end of the trial, all participant subjects should be assured the access to the best proved prophylactic, diagnostic and therapeutic methods identified during the trial.*

### **5.7 Rationale for treatment**

Semaglutide has been developed for s.c. administration. The dose of 1.0 mg once-weekly has been chosen based on careful evaluation to strike a satisfactory balance of efficacy and safety that would satisfy the majority of subjects. Hence, the duration and the dose of the randomised treatments are considered adequate for obtaining meaningful information on effect and safety in accordance with the trial objectives. Subjects will be enrolled for a treatment period of 52 weeks in order to enable evaluation of the full effect and durability of the primary and secondary endpoints as well as reasonable safety assessment.

For semaglutide, the three dose levels (0.25, 0.5 and 1.0 mg), have been chosen based on data from the phase 2 dose-finding trial. This regimen has shown the optimal benefit-risk profile for further development for treatment of T2D in the SUSTAIN programme<sup>25</sup>.

Canagliflozin has been chosen as active comparator since it is an established OAD within the drug class of SGLT-2 inhibitors and treatment will be initiated with 100 mg in accordance with the current approved EU-PI<sup>32</sup>.

Both s.c. semaglutide and oral canagliflozin will be dose escalated to their highest respective maintenance doses to investigate and compare the maximum efficacy of the two medications when added to metformin.

The duration of randomised treatments is considered adequate to collect sufficient data on effect and safety in accordance with the trial objectives.

## 6 Trial population

### 6.1 Number of subjects

Number of subjects planned to be screened (meaning the number of subjects providing informed consent):	1307
Number of subjects planned to be randomised in a 1:1 manner:	784
Number of subjects planned to be randomised in sub-study on body composition:	174
Number of subjects planned to complete the trial on randomised trial product without rescue medication.	549

*For Mexico only: Approximately 75 subjects are planned to be screened and 45 subject are planned to be randomised in Mexico.*

### 6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age above or equal to 18 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus (T2D).
4. HbA<sub>1c</sub> of 7.0-10.5% (53-91 mmol/mol, both inclusive).
5. Stable daily dose of metformin ( $\geq$ 1500 mg or maximum tolerated dose as documented in the subject medical record and in compliance with current local label) for at least 90 days prior to the day of screening.

### 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.

*For Brazil Only: 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.*

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).

*For Brazil only: 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.*

*For EU countries only:*

*The following contraceptive measures are considered adequate:*

- *Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
  - *Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
  - *Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)*
  - *Bilateral tubal occlusion*
  - *Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository). (Not applicable for Sweden and the UK).*
  - *Vasectomised partner (where partner is sole partner of subject) and that the vasectomised partner has received medical assessment of the surgical success.*
  - *True sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days prior to the day of screening.
  5. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
  6. Subjects with ALT >2.5 x upper normal limit (UNL).
  7. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
  8. History or presence of pancreatitis (acute or chronic).
  9. History of diabetic ketoacidosis (DKA).
  10. Any of the following: myocardial infarction (MI), stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
  11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
  12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
  13. Renal impairment measured as eGFR <60 ml/min/1.73 m<sup>2</sup> as defined by Kidney Disease Improving global outcomes (KDIGO 2012)<sup>1</sup> classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening. .

14. 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 prior to the day of screening is allowed.
15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.
16. 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.

#### **6.4 Randomisation criteria (only applicable for the DXA scan sub-population)**

To be randomised, all randomisation criteria must be answered “yes”.

1. The quality evaluation of the baseline DXA scan needs to be performed and found acceptable by the imaging laboratory prior to randomisation.

#### **6.5 Rescue criteria**

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification and the conclusion of the consideration to be documented in the medical records. If any of the FPG values (see section [8.5.1](#)) (including protocol scheduled fasting SMPG, see section [8.6.1](#)) exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG (at central laboratory) should be obtained by calling the subject for a re-test.

- 13.3 mmol/L (240 mg/dL) from week 8 to end of week 13
- 11.1 mmol/L (200 mg/dL) from week 14 to end of treatment

In addition, subject should be offered rescue medication if:

- HbA<sub>1c</sub> (at central laboratory) >8.5 % (69.4 mmol/mol) from week 26 to end of treatment.

If the confirmatory FPG also exceeds the value described above, the subject should be offered rescue medication (i.e. intensification of anti-diabetic background medication and/or initiation of new anti-diabetic medication).

It is important for trial integrity that only subjects actually needing treatment intensification (as defined above) are started on rescue medication. Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule. Rescue medication should be prescribed at the investigator’s discretion as add-on to randomised treatment and according to American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines<sup>33,34</sup> (excluding GLP-1RAs, DPP-4 inhibitors, amylin analogues and SGLT-2).

Rescue medication and any changes hereto should be captured on the concomitant medication form in the electronic case report form (eCRF), see Section [13](#). Rescue medication is considered to be

NIMP and will not be provided by Novo Nordisk, unless required by the country's Health Authority or IEC/IRB.

## 6.6 Criteria for premature discontinuation of trial product

All efforts should be made to keep the subject on trial product. However, the subject might be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

If so, all efforts must be made to ensure the subjects attend and complete all scheduled visit procedures. Subjects 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 [6.7](#)).

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Safety concern related to trial product or unacceptable intolerability at the discretion of the investigator
3. Pregnancy\*
4. Intention of becoming pregnant\*
5. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
6. If the eGFR falls persistently  $<45 \text{ mL/min/1.73m}^2$ , treatment with any trial product should be discontinued (see section [5.3](#))
7. Calcitonin  $\geq 100 \text{ ng/L}$  (see [appendix A](#))

\*No DXA scans can be performed on these subjects.

See Section [8.1.8](#) for procedures to be performed for subjects discontinuing trial product prematurely.

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 subjects should continue with protocol-specified visit schedule.

## 6.7 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. 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.

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

## **6.8 Subject replacement**

Subjects who discontinue trial product prematurely will not be replaced.

## **6.9 Rationale for trial population**

The trial population will include subjects with T2D treated with stable doses of metformin for at least 90 days prior to screening as changes in the background medication shortly before trial participation may potentially impact data interpretation. The HbA<sub>1c</sub> limits of 7.0-10.5% (53-91 mmol/mol) have been chosen to include subjects needing intensification of their anti-diabetic medication. FPG and HbA<sub>1c</sub> will be monitored throughout the trial and rescue medication should be initiated in subjects with persistent, unacceptable hyperglycaemia. No BMI or blood pressure restrictions are applied. Subjects with liver test abnormalities (ALT >2.5 x UNL) are excluded to avoid potential confounding of liver safety assessments. In addition, subjects with mild, moderate, severe or end-stage renal impairment are excluded due to restrictions in the labels of canagliflozin and metformin. As SGLT-2 inhibitors have been associated with diabetic ketoacidosis, subjects with a history of diabetic ketoacidosis are also excluded from this trial. Overall, the eligibility criteria will allow for enrolment of a relatively broad trial population resembling the target population in common practice while taking relevant safety precautions.

## 7 Milestones

Planned duration of recruitment period 24 weeks.

Planned date for FPFV: 15-Mar-2017

Planned date for LPLV: 24-Oct-2018

End of trial (P11) is defined as LPLV.

### **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 included in the screening period and eligible for randomisation can be randomised.

### **Trial registration:**

Information of the trial will be disclosed at [clinicaltrials.gov](http://clinicaltrials.gov) and [novonordisk-trials.com](http://novonordisk-trials.com). According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure<sup>35</sup>, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)<sup>36</sup>, the Food and Drug Administration Amendment Act (FDAAA)<sup>37</sup>, European Commission Requirements<sup>38,39</sup> and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

## **8 Methods and assessments**

### **8.1 Visit procedures**

The following sections describe the assessments and procedures. These are also included in the flow chart (see Section [2](#)) as well as visit numbers, timing of site and phone visits and windows during the trial period.

Informed consent must be obtained before any trial related activity, see Section [18.3](#).

For each Dispensing visit; interact with IWRS to obtain allocation of trial products, confirm dispensing of allocated trial products and, except for the randomisation visit, confirm trial products returned unused or lost.

A treatment completion session must be performed in the IWRS after completion of V10.

#### **8.1.1 Investigator site log**

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

In addition, the investigator must keep a log of staff and a delegation of task(s) list at the trial site. Investigator must sign the log of staff and the delegation of task(s) at the trial site prior to the delegation of tasks.

#### **8.1.2 Screening, Visit 1**

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

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

#### **8.1.3 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 (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events must be carried out according to Section [12](#).

A screening failure session must be made in the IWRS and the screening failure form completed in the eCRF. 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 or randomisation criteria; this includes re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters.

#### **8.1.5 Fasting visits**

The subjects should attend site visits in a fasting state (see section [2](#) for details). Fasting is defined as having consumed only water within the last 6 hours prior to the visit.

If the subject does not attend the visit in a fasting state, the subject should be asked to attend a re-scheduled visit within the visit window to have the fasting assessments performed.

Glucose lowering agents and trial product should not be taken until after blood sampling has been performed but other prescribed medication should be taken according to prescription.

#### **8.1.6 Unscheduled visits**

Unscheduled visits can be performed at the investigators discretion if an AE requires additional follow-up or if required by the Novo Nordisk department responsible for safety. Unscheduled visits can take place at any time during the trial from screening until the last visit in the trial. Further, unscheduled visits for re-sampling can take place if laboratory samples are lost or damaged before arriving at the analysing laboratory. This re-sampling will be at the discretion of the Novo Nordisk medically responsible person in collaboration with the investigator.

All assessments performed at any time during the trial can be performed during unscheduled visits with the exception of DXA body composition scan (only permitted if required due to DXA technical reasons), waist circumference and ePROs.

Visits/contacts to the site not related to the trial do not need to be reported as an unscheduled visit. Contacts for re-dispensing of trial drug as replacement for lost or damaged trial drug do not need to be recorded as unscheduled visits but need to be recorded in the IV/WRS.

#### **8.1.7 Phone contacts**

The phone contacts should be conducted as outlined in the flow chart (see Section [2](#)).

At V2, and V3 the investigator should instruct the subject how to dose escalate semaglutide/semaglutide placebo up to 1.0 mg once-weekly and also how to dose escalate canagliflozin up to 300 mg daily. At the planned phone contact (P5), the investigator should follow-up on any symptoms associated with diabetic ketoacidosis (DKA), any AEs as well as compliance and potential technical issues in regards to the dose escalation.

At the phone contacts at P11 and P11A occurring at least 5 weeks after V10 or V10A the investigator should follow up on any new concomitant medication, hypoglycaemic episodes or any AEs.

### **8.1.8 Premature discontinuation of trial product**

If a subject prematurely discontinues trial product, the investigator must undertake procedures described for V10A as soon as possible (preferably the same day), which are similar to those at V10. P11A should be scheduled at least 5 weeks after the last date on trial product.

If premature discontinuation of trial product is decided during a scheduled visit, the visit will be converted into a V10A and trial procedures must be performed accordingly.

Subjects should continue with the originally scheduled site contacts after P11A and up to and including P11. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after P11A. However, all attempts should be made to ensure that V10 is performed as a site visit and includes all planned assessments.

In summary, subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or trial product discontinuation for any reason. Only subjects who decline any further contact with the site in relation to the trial should be considered as withdrawn from the trial (for withdrawal procedures see Section [8.1.9](#)).

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 made. A treatment discontinuation session must be performed in the IWRS at V10A (see Section [10](#)).

### **8.1.9 Withdrawal from trial**

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for V10A (End of treatment) as soon as possible. If a subject has already prematurely discontinued from trial product and previously attended visit V10A and visit P11A, no further visits should be attended.

For withdrawn subjects the end-of-trial form and end-of-treatment form must be completed, including the primary reason for premature discontinuation of trial product, and final drug accountability must be performed even if the subject is not able to come to the trial site.

A treatment discontinuation session must be made in the IWRS, however if a subject has already prematurely discontinued from trial product and a treatment discontinuation session in IWRS has been done, no IWRS session should be completed. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

Where the reasons are obtained, the primary reason for withdrawing consent must be specified in the end-of-trial form in the eCRF.

### **8.1.10 Investigator assessment**

Review of diaries, ePROs, laboratory reports, ECGs, dilated funduscopy/fundus photography, physical examinations etc. must be documented with the investigator's or delegate's dated signature either on the front page of the documents and/or in the subjects medical record. The signed documents must be retained at the trial site as source documentation.

For ECGs, physical examinations and dilated funduscopy/fundus photography the evaluations must follow the categories:

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

The evaluation should be based on the investigator's or delegate's judgement.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or clinically non-significant. All laboratory printouts must be signed and dated by the investigator on the day of evaluation. The signed laboratory report is retained at the site as source documentation.

In case of abnormal clinical significant findings found as a result of screening procedures conducted at visit 1 or assessments revealing baseline conditions at visit 2, the investigator must state a comment in the subject's medical record and record this in the concomitant illness form in the eCRF. At subsequent visits, any clinically significant changes or new clinically significant findings must be reported as an AE according to section [12](#).

Investigator or trial site staff must review the diary to ensure that AEs, including overall changes in health and concomitant medication, are reported.

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 Subject related information/assessments**

### **8.2.1 Demography**

Demography will be recorded at screening and consists of:

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

### **8.2.2 Diabetes history and diabetes complications**

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

- Date of diagnosis of type 2 diabetes
- Information regarding diabetes complications including date of onset
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease)

### **8.2.3 Hypoglycaemia unawareness**

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8<sup>40</sup>.

The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always. Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.

### **8.2.4 Concomitant illness and medical history**

A **concomitant illness** is any illness that is present at the start of the trial as described in section [8.1.10](#).

**Medical history** is a medical event that the subject has experienced in the past. Only relevant medical history as judged by the investigator should be reported.

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

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

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

### **8.2.5 Concomitant medication**

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

Details of any concomitant medication must be recorded at the first visit (screening visit). Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes:

- trade name or generic name,
- indication, start date (only start year is applicable if more than one year) and stop date or continuation.
- total daily dose (only applicable for anti-diabetic 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.

### **8.2.6 Childbearing potential**

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

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section [8.5.2](#). Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 5 weeks after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation or are postmenopausal (e.g. women above the age of 50, who have been without menstrual period for at least 1 year).
- Other medical reasons preventing childbearing potential

*For Argentina only: Birth control methods will be reimbursed by Novo Nordisk Pharma Argentina S.A.*

*For Brazil only: 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.*

*For EU countries only:*

*The following contraceptive measures are considered adequate:*

- *Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
- *Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)*
- *Bilateral tubal occlusion*
- *Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository). (Not applicable for the Sweden and UK).*
- *Vasectomised partner (where partner is sole partner of subject) and that the vasectomised partner has received medical assessment of the surgical success.*
- *True sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*

### **8.2.7 Tobacco use**

Details of tobacco use must be recorded at the screening visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

Smoking status:

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

## **8.3 Efficacy assessments**

### **8.3.1 Height, body weight and BMI**

Height is measured without shoes in cm or inches and recorded to nearest ½ cm or ¼ inch.

Body weight should be measured and recorded in the eCRF in kilogram or pound (kg or lb), with one decimal, without shoes and only wearing light clothing.

BMI will be calculated in the eCRF every time the weight is measured using the equation:

$$\text{BMI} = \text{body weight (kg)} / (\text{height (m)} \times \text{height (m)}) \text{ or } [\text{kg/m}^2 = \text{lb/in}^2 \times 703]$$

### **8.3.2 Waist circumference**

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

The measurement of waist circumference should be performed and recorded in the eCRF. The

waist circumference will be measured using a non-stretchable measuring tape. It should be recorded to the nearest ½ cm or ¼ inch using the same measuring tape throughout the trial.

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

### **8.3.3 Systolic and diastolic blood pressure**

Systolic and diastolic blood pressure should be measured in a sitting position after the subject has been resting for at least 5 minutes and by using standard clinical practice at the trial site.

### **8.3.4 Self-measured plasma glucose (SMPG)**

At the screening visit, subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The blood glucose meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

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

Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

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.

### **8.3.5 7-point profile**

The subject will be asked to perform a 7-point SMPG profile, preferably within one week prior to site visit according to the flow chart, on days where the subject does not anticipate unusual strenuous exercise.

Time points, including date and time, for the 7-point 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 bed time

### **8.3.6 DXA scan (sub-population only)**

Body composition will be measured using dual energy x-ray absorptiometry (DXA) whole body scans. These scans will be performed in a sub-set of 174 randomised subjects (approximately 87 subjects per treatment arm). The overall process of image acquisition, transfer, central analysis, reporting of results and archiving is described in an **Imaging Charter** prepared by the laboratory. The baseline DXA scan will be performed at screening (V1+5 days), this to allow the imaging laboratory to confirm the quality of the scan, prior randomisation. It is recommended the site confirms patient eligibility prior performing the DXA scans. At the end of treatment visit (V10 or V10A), the scans must be performed  $\pm$  5 calendar days.

The quality of the baseline DXA scan obtained at V1 must be confirmed by the imaging laboratory before the subject can be randomised. The quality of the DXA scans will be evaluated by the imaging laboratory designated by Novo Nordisk for reading in a blinded manner. If a subject withdraws prematurely from the trial, an end of trial DXA scan should preferably be performed.

Process for image acquisition is outlined in an **Image acquisition guideline (IAG)**. Besides the two scans per subject described in this protocol a limited number of repeat scans might be acquired if required due to technical reasons. Repeated scans should not be performed if the subject has prematurely discontinued trial medication due to pregnancy or intention of becoming pregnant.

A cross calibration using cross calibration phantom will be performed at least once at each site prior to the database lock (DBL) of the trial.

Each trial site participating in the sub-study will receive an **imaging manual** prepared and distributed by the imaging laboratory which will include machine specific instructions for acquiring DXA scans. The manual will serve as reference tool for use during the trial and when training technologists. DXA technologist training will occur at the start of the trial and at any time deemed necessary to assure proper scan acquisition.

Following DXA scan acquisition each trial site will be responsible for transferring each DXA scan to the imaging laboratory for quality review and analysis. DXA analysis data will include:

- Total fat mass (kg)
- Total fat mass (%)
- Total lean mass (kg)

- Total lean mass (%)
- Visceral fat mass (kg)\*
- Visceral fat mass (%)\*
- Ratio between total fat mass and total lean mass

\*analyses marked with an asterisk will be performed based on specific DXA equipment and software availability.

DXA analysis data will be transferred from the imaging laboratory to Novo Nordisk immediately prior to the DBL of the trial. The investigators will receive the results from the analysis only after LPLV in order to avoid un-blinding.

## **8.4 Safety assessments**

### **8.4.1 Physical examination**

A physical examination must be performed at V1, V8 and V10/V10A and include the following:

- General appearance
- Skin
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Central and peripheral nervous system
- Lymph node palpation

### **8.4.2 Pulse**

Pulse (beats per minute) should be recorded at the site of visits after resting for 5 minutes in a sitting position.

### **8.4.3 Electrocardiogram – 12 lead**

A 12-lead ECG must be performed and interpreted locally by the investigator as described in section [8.1.10](#)

It is allowed to perform the baseline ECG between the screening visit and the randomisation visit. The result should be available prior to randomisation. An ECG performed for any reason unrelated to this trial within 7 days prior to the screening visit is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime.

If the ECG was performed as part of a routine clinical practice on/before the date when the subject has signed the informed consent, it must be documented in the medical records that the reason for performing the procedure is not related to this trial.

#### **8.4.4 Eye examination**

The eye examination will be performed as per flowchart (see section 2).

It is allowed to perform the baseline fundus photography or dilated fundoscopy between the screening visit and the randomisation visit. Results of the baseline fundus photography or dilated fundoscopy must be available and evaluated by the investigator before randomisation. If the subject had a fundus photography or dilated fundoscopy performed within 90 days prior to randomisation, the investigator may base their evaluation upon the results of that examination. However, the examination must be repeated before randomisation if the subject experienced worsening of visual function since the last examination. If the subject did not have a fundus photography or dilated fundoscopy performed within 90 days prior to randomisation, such examination must be performed by the investigator or other qualified health care professional prior to randomisation. If the applicable fundus photography or dilated fundoscopy was performed before the subject signed the informed consent form, it must be documented in the medical records that the reason for performing the examination was not related to this trial.

In addition, dilated fundoscopy/fundus photography must be performed at V10. In the case of premature discontinuation, the assessments must be performed both at V10A and at V10. The assessments at V10A and V10 can be performed in the period between V10A and P11A, and between V10 and P11, respectively but the results should be available no later than at P11A and P11, respectively.

The investigator should indicate whether the outcome of the eye examination was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of this screening procedure must be recorded as concomitant illness/medical history in accordance with section [8.2.4](#).

#### **8.4.5 Adverse events**

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

##### **8.4.5.1 Medication error**

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

- Trial 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](#).

#### **8.4.5.2 Adverse events requiring additional data collection**

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

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack)
- Heart failure
- Hypersensitivity reaction
- Neoplasm (excluding thyroid neoplasm)
- Pancreatitis
- Renal Event
- Thyroid disease (including thyroid neoplasm)
- Hepatic event
- Diabetic retinopathy
- Laboratory outlier

See [appendix B](#) for details about the additional information to report.

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

#### **8.4.6 Hypoglycaemic episodes**

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

All plasma glucose values:

- $\leq 3.9$  mmol/L (70 mg/dL) or
- $>3.9$  mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms

should be reported in the diary according to the instructions below in section [8.6.1](#) throughout the trial from visit 1 to visit 10/10A. For the follow-up visit (P11/P11A) the hypoglycaemic episode(s) should be documented in the subject's medical record.

All information must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 1 to visit 11/11A.

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<sup>41</sup>.

An SMPG value  $\leq 3.9$  mmol/L (70 mg/dL) or hypoglycaemic symptoms will be recorded in the diary in the hypoglycaemic episode form by the subject. Repeated SMPG measurements and/or symptoms, will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is  $>3.9$  mmol/dL (70 mg/dL) and/or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurement and/or symptoms.

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

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- Stop date and time of the hypoglycaemic episode (stop time is the first time plasma glucose value is  $>3.9$  mmol/L (70 mg/dL) and/or symptoms have been resolved).
- If a stop date and time is not reported, a hypoglycaemic episode will cover a period of 60 minutes.
- The PG 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 and time of last trial product administration and other anti-diabetic medications 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. PG 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<sup>41</sup>.

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms (layman term used in the diary is specified in brackets if different from the protocol term)?<sup>41</sup>
  - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
  - General malaise: headache or malaise (feeling discomfort/unease)
- Other symptoms

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

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data<sup>42, 43</sup>.

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

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

## 8.5 Laboratory assessments

The laboratory assessments will be performed by a central laboratory. If collected, anti-semaglutide IgE antibody samples will be analysed by Novo Nordisk (for further details see Section [18.1.1](#)). The central laboratory may utilise sub-contractors.

In the events described in section [8.4.5.2](#), a local laboratory must be used.

Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storage and shipping of samples, will be described in the laboratory manual provided by the central laboratory.

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

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window stated in the flow chart. For some of the samples drawn during the trial, subjects will be asked to attend the relevant site visits fasting (see section [8.1.5](#)).

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis and the investigator must review all laboratory results for signs of concomitant illness and AEs and report these according to this protocol (see section [12](#)).

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.

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

*For Brazil only: All laboratory results will be communicated to the investigators.*

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

All laboratory samples will be destroyed at the latest at the completion of the clinical trial report or according to local regulations.

*For Brazil only: Biological samples from Brazil will be destroyed at the end of the trial.*

### **8.5.1 Laboratory assessments for efficacy**

Blood samples will be drawn according to flow chart and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

- Glucose metabolism:
- HbA<sub>1c</sub>
- FPG
- Lipids (all fasting):
  - Total cholesterol
  - LDL cholesterol
  - HDL cholesterol
  - Triglycerides

#### **Fasting plasma glucose**

FPG is measured at central laboratory in order to evaluate glycaemic control. The subject must attend these visits fasting (see Section [8.1.5](#)).

A central FPG result obtained at the central laboratory of  $\leq 3.9$  mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section [12.1.1](#)).

### **8.5.2 Laboratory assessments for safety**

Blood samples will be drawn and analysed at the central laboratory to determine levels of the following laboratory parameters:

Biochemistry:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Albumin, bilirubin (total)
- Alkaline phosphatase,
- Potassium,
- Sodium
- Calcium (total)
- Amylase
- Lipase
- Calcitonin
- Creatinine, including eGFR (per CKD-EPI)<sup>1</sup>

#### Haematology:

- Haemoglobin
- Haematocrit
- Erythrocytes
- Thrombocytes
- Leucocytes

#### Pregnancy test (females of child bearing potential):

- Serum beta-human chorionic gonadotropin (V1, V8, V10/V10A)
- Urine dip stick (V2)

#### **Calcitonin**

Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart (see section [2](#)). In case any calcitonin value at any time of the trial is  $\geq 10$  ng/L, the algorithm in [appendix A](#) should be followed.

#### **Pregnancy testing**

Females of childbearing potential will have a serum pregnancy test performed. At the randomisation visit, a urine pregnancy test must be performed prior to randomisation.

In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subject should be instructed not to dose trial product before pregnancy has been ruled out.

Pregnancy testing will not be required (unless required by local law) for women of non-childbearing potential, such as but not limited to women who have undergone a hysterectomy, bilateral oophorectomy, bilateral tubal ligation or are postmenopausal (e.g. women above the age of 50, who have been without menstrual period for at least 1 year), see section [8.2.6](#).

### **8.6 Other assessments**

#### **8.6.1 Subject diary**

The subject must be provided with paper diaries at visits described in the flow chart. If a subject prematurely discontinues trial product, diaries, should be not be dispensed and completed by the subject after follow-up-premature discontinuation visit (P11A). Entries in the diaries are only to be made by the subject, unless otherwise specified.

The investigator should instruct the subject in recording the following data in the diary:

- Date, time and dose of first dose of trial product
- Date and last dose of trial product prior to each visit
- SMPG 7-point profile
- Hypoglycaemic episodes
- Concomitant medication
- AEs

The diaries should be handed out/collected as indicated in the flow chart. The subject should bring the diary for review at every clinic visit up until end of treatment visit (V10). The recordings must be reviewed as described in section [8.1.10](#) and transcribed to the eCRF.

If any hypoglycaemic events are reported at P11 or P11A, the information related to the hypoglycaemic event(s) should be documented in the subject's medical record and the entry in the medical record will be considered source data.

### **8.6.2 Electronic patient reported outcome questionnaires**

The following PRO questionnaire will be used in the trial:

SF-36v2™

DTSQ

CoEQ

The questionnaires should be completed by the subject as specified in the flow chart, see section [2](#), preferably after conclusion of all fasting related activities but before any other visit-related activities. It takes approximately 15 minutes to complete the questionnaires, see Section [13.3](#). Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The assessments must be reviewed as described in Section [8.1.10](#).

#### **8.6.2.1 SF-36v2**

The SF-36v2™ questionnaire will be used to assess subjects overall health related quality of life and can also be used to estimate quality adjusted life years (QALY) which is used in cost effectiveness calculations. This questionnaire contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, body pain, general health, vitality, social functioning, role emotional and mental health.

#### **8.6.2.2 DTSQs**

The DTSQs questionnaire will be used to assess subject's treatment satisfaction. This questionnaire consists of 8 items and measures the subject's diabetes treatment (including insulin, tablets and/or diet in terms of convenience, flexibility and general feelings regarding treatment).

#### **8.6.2.3 Control of Eating Questionnaire (CoEQ)**

The CoEQ has its origin in the Food Craving Record. It comprises of 21-items designed to assess the intensity of food cravings, as well as subjective sensation of appetite and mood. For this trial a version with only 19 items will be included.

### **8.6.3 Training in the PDS290 pen-injector**

The subjects must be trained in how to handle the PDS290 pen-injector when handed out the first time. Training should be repeated during the trial at regular intervals at the discretion of the investigator in order to ensure correct use of the device. The training should be done in accordance with the directions for use.

### **8.6.4 Training in blood glucose meter use**

The subjects must be provided with a BG meter at visit 1 and instructed in how to use and handle the BG meter, in accordance with the flow chart (see section [2](#)). The subjects will be instructed in how to use the device and the instruction will be repeated at visit 2 and thereafter as necessary during the trial.

### **8.7 Subject compliance**

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

**Treatment compliance:** will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused trial products. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

## 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).

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product Dispensing Unit Number (DUN) to the subject at each dispensing or randomisation visit. The correct DUN must be dispensed to the subject.

If additional medication is needed, the IWRS must be contacted in order to have correct medication allocated.

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

Semaglutide 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	Container/delivery device
Semaglutide 1.34 mg/mL	1.34 mg/mL	Solution for injection	Subcutaneous	1.5 mL PDS290 pre-filled pen-injector
Semaglutide placebo	N/A			
Canagliflozin 100 mg	100 mg	Tablet	Oral	Blister pack
Canagliflozin placebo	N/A			
Canagliflozin 300 mg	300 mg			
Canagliflozin placebo	N/A			

Background medication is defined as antidiabetic treatment with metformin. All randomised subjects must continue their antidiabetic pre-trial background medication throughout the entire duration of the trial, unless rescue criteria are met or a safety concern arises. As metformin is considered background medication (non-investigational medicinal product), it will not be provided by Novo Nordisk. However, metformin will be reimbursed if required by the country's Health Authority or IEC/IRB.

Semaglutide 1.34 mg/mL and semaglutide placebo are visually identical and will be packed blinded.

Canagliflozin 100/300 mg drug and corresponding placebo will be packed blinded. There are 2 different placebos: 1 for each of the respective doses of canagliflozin (100 mg and 300 mg).

## 9.2 Labelling

The trial products will be labelled in accordance with Annex 13<sup>44</sup>, local regulations and trial requirements. Each box will be labelled with a unique (DUN).

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 directions for use (DFU) is given to the subject orally and in writing at the first dispensing visit (randomisation visit, V2).

*For Argentina only: Glucose-lowering background medication and rescue medication, if applicable, will be reimbursed by Novo Nordisk Pharma Argentina S.A.*

## 9.3 Storage

**Table 9–2 Storage conditions**

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time <sup>a</sup>
Semaglutide 1.34 mg/mL	Store in refrigerator (2–8°C) Do not freeze Protect from light	Store below 30°C Do not freeze Protect from light	8 weeks
Semaglutide placebo			
Canagliflozin 100 mg	Do not store above 30°C Do not freeze Protect from light	N/A	N/A
Canagliflozin placebo			
Canagliflozin 300 mg			
Canagliflozin placebo			

<sup>a</sup> In-use time starts in the subjects home when the product is taken out of the refrigerator.

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

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

#### **9.4 Drug accountability and destruction**

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

Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at End of Treatment visit (please see flow chart, section [2](#)).

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 should be performed at pen level for semaglutide/placebo, and at tablet level for Canagliflozin/placebo.

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

#### **9.5 Auxiliary supplies**

The following auxiliary supplies will be supplied by Novo Nordisk in accordance with the TMM:

- DFU for PDS290 pen-injector
- Needles for PDS290 pen-injector
- BG-meter and BG-meter related auxiliaries

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 guides and worksheets will be provided to each trial site.

## 11 Randomisation procedure and breaking of blinded codes

This is a double-blind, two-arm parallel-group trial. A randomisation session will be performed for all eligible subjects by using IWRS.

At the randomisation visit (V2), eligible subjects will be randomised to one of the two parallel treatment groups in a 1:1 manner:

- semaglutide 1.0 mg once-weekly + canagliflozin placebo
- canagliflozin 300 mg once-daily + semaglutide placebo

The randomisation will be stratified according to the participation in the DXA scan sub-study (yes or no) in order to ensure balanced treatment allocation within the sub-study.

When a subject is randomised he/she must be assigned the lowest available randomisation number.

### 11.1 Breaking of blinded codes

The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken. However, if the code is broken by Global Safety, the monitor will not be notified.

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, and sign and date the document. The reason for code break should be documented in the medical record.

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 1](#).

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

## 12 Adverse events, technical complaints and pregnancies

### 12.1 Definitions

#### 12.1.1 Adverse event

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

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section [8.4.6](#)

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<sup>a</sup> experience.
- In-patient hospitalisation<sup>b</sup> or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity<sup>c</sup>.
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening<sup>a</sup> or require hospitalisation<sup>b</sup> 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<sup>d</sup>.

<sup>a</sup> 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.

<sup>b</sup> 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.

- <sup>c</sup> 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).
- <sup>d</sup> 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 ALT or AST >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

Additional assessments should be made for events meeting the criterion of Hy's law as stated above (see [appendix B](#)).

### **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.  
Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. 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 [8.4.5.1](#).

### **12.1.5 Adverse events requiring additional data collection**

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

In this trial the following AEs require the completion of specific event forms in the eCRF, see [Table 12-1](#)

**Table 12-1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication**

Event	Specific event form	Event adjudication
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	Yes
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	Yes
Heart failure	Yes	Yes (only if requiring hospitalisation)
Hypersensitivity reaction	Yes	No
Neoplasm (excluding thyroid neoplasm)	Yes	Yes (only if malignant)
Pancreatitis	Yes	Yes (only if acute pancreatitis)
Renal Event	Yes	No
Thyroid disease (including thyroid neoplasm)	Yes	Yes, (only if malignant thyroid neoplasm or C-cell hyperplasia)
Death	No	Yes
Hepatic event defined as: ALT or AST >5 x UNL and total bilirubin ≤ 2 x UNL ALT or AST >3 x UNL and total bilirubin >2 x UNL Hepatic event leading to trial product discontinuation	Yes	No
Diabetic retinopathy	Yes	No
Laboratory outlier	Yes	No

For details about specific event forms, see [appendix B](#)

### 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 (V1) until the end of the post-treatment follow-up period (P11). 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 by the investigator or subject, must be reported by the investigator and evaluated.

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

For SAEs, a SIF must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one SIF 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.

Some events will undergo event adjudication by the Event Adjudication Committee (EAC), please refer to Section [12.7.2](#). For AEs qualifying for event adjudication, the Adjudication Form will also have to be completed in the eCRF. The Adjudication Form is a checklist of clinical data to be provided from the site.

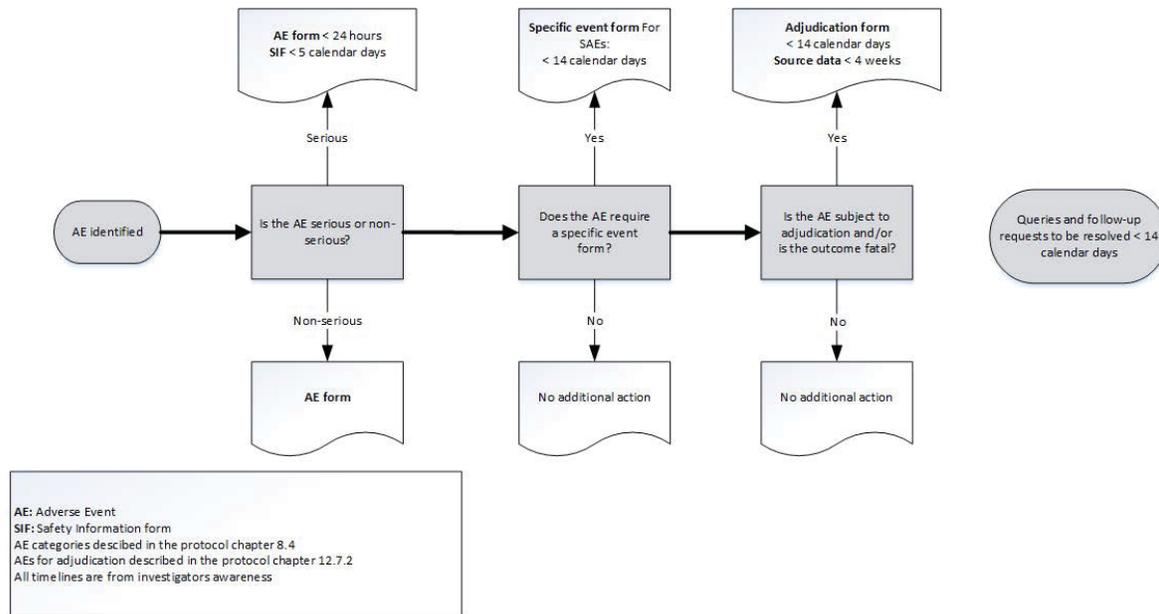
### Timelines for initial reporting of AEs:

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

- **SAEs:** The AE form **within 24 hours** and the SIF **within 5 calendar** days of the investigator’s first knowledge of the SAE.
- **For SAEs requiring reporting on a specific event form:** In addition to the above the specific event form **within 14 calendar days** from the investigator’s first knowledge of the AE.
- **Events for adjudication:** The adjudication form should be completed within 14 calendar days of investigator’s first knowledge of the AE, see Section [12.7.2](#). The investigator should preferably provide the medical documentation within 4 weeks of event identification according to instructions in the event adjudication site manual.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk 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.



**Figure 12–1 Reporting of AEs**

### **Novo Nordisk assessment of AE expectedness:**

Novo Nordisk assessment of AE expectedness is performed according to the following reference documents:

- Semaglutide: NN9535 IB<sup>25</sup> current version and any updates thereto
- Canagliflozin: Current version of the EU PI<sup>32</sup> and U.S. Food and Drug Administration (FDA) prescribing information 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<sup>2</sup>. 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<sup>2</sup>, 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:

- Semaglutide 1.34 mg/mL or placebo, 1.5 mL pen-injector
- Canagliflozin 100 mg or placebo tablets (blister pack)
- Canagliflozin 300 mg or placebo tablets (blister pack)
- Novo Nordisk needles for prefilled PDS290 pen-injector

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

Contact details (fax, e-mail and address) are provided in [attachment 1](#) 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 and forward the technical complaint form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, 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 1](#)) 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.

#### **Forms and timelines for reporting AEs:**

Non-serious AEs:

- AE form<sup>a</sup> **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<sup>a</sup> **within 24 hours** of the investigator's first knowledge of the SAE.
- SIF **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.

<sup>a</sup> 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.

## **12.6 Precautions and/or overdose**

Events of nausea, vomiting and headache have been reported in connection with accidental administration of semaglutide doses up to 4 mg. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdosage, appropriate supportive treatment should be initiated according to subject's clinical signs and symptoms.

## **12.7 Committees related to safety**

### **12.7.1 Novo Nordisk safety committee**

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

### **12.7.2 Event adjudication committee**

An independent external EAC is established to perform validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE. Pre-defined clinical data consist of copies of source documents collected and delivered by the investigational sites.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk.

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities and work processes of the committee.

The events outlined in Section [12.1.5](#) have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to Standardized Definitions<sup>45</sup>.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the event adjudication vendor.

The AEs for adjudication are listed in [Table 12–2](#)

**Table 12–2 Adverse events for adjudication**

Events	Description	Adjudication outcome
Death*	<ul style="list-style-type: none"> <li>All-cause death</li> </ul>	<ul style="list-style-type: none"> <li>Cardiovascular death (including undetermined cause of death)</li> <li>Non-Cardiovascular death</li> </ul>
Acute Coronary Syndrome	<p>Acute Coronary Syndrome conditions include:</p> <ul style="list-style-type: none"> <li>ST-elevation acute myocardial infarction (STEMI)</li> <li>Non-ST elevation acute myocardial infarction (NSTEMI)</li> <li>Silent MI</li> <li>Unstable angina pectoris (UAP) requiring hospitalisation</li> </ul>	<ul style="list-style-type: none"> <li>Acute myocardial infarction (STEMI or NSTEMI), silent MI</li> <li>Unstable angina pectoris requiring hospitalisation</li> </ul>
Cerebrovascular events	<ul style="list-style-type: none"> <li>Episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction</li> <li>Transient Ischaemic Attack (TIA) is defined as a transient episode (&lt;24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction</li> </ul>	<ul style="list-style-type: none"> <li>Ischaemic stroke</li> <li>Haemorrhagic stroke</li> <li>Undetermined stroke</li> <li>TIA</li> </ul>
Heart failure requiring hospitalisation	<ul style="list-style-type: none"> <li>Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)</li> </ul>	<ul style="list-style-type: none"> <li>Heart failure requiring hospitalisation</li> </ul>
Acute pancreatitis	<p>The diagnosis of acute pancreatitis requires two of the following three features:</p> <ul style="list-style-type: none"> <li>Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)</li> <li>Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal</li> <li>Characteristic findings of acute pancreatitis on imaging</li> </ul>	<ul style="list-style-type: none"> <li>Acute pancreatitis           <ul style="list-style-type: none"> <li>Mild</li> <li>Moderate severe</li> <li>Severe</li> </ul> </li> </ul>
Malignant neoplasm	<p>Malignant neoplasms are defined as:</p> <ul style="list-style-type: none"> <li>Neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems</li> <li>Thyroid neoplasms are excluded in this event category</li> </ul>	<ul style="list-style-type: none"> <li>Malignant neoplasm</li> </ul>
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	<ul style="list-style-type: none"> <li>Malignant thyroid neoplasms are defined as thyroid neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems</li> <li>C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland</li> </ul>	<ul style="list-style-type: none"> <li>Malignant thyroid neoplasm</li> <li>C-cell hyperplasia</li> </ul>

\*Death is not a separate event, but an outcome

There are different processes for capturing events for adjudication:

- Direct reporting by investigator:
  - All AEs need to be assessed by the investigator if any AE category is applicable. If the AE category selected is in scope for adjudication, the event specific adjudication form will be populated for sites to complete
  - AEs with fatal outcome
- Screening:
  - All AEs will be screened by NN for potential missed events for adjudication and if needed, the investigator will be asked to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.
- EAC identified events:
  - The EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

The assessment made by the EAC will be included in the clinical trial report as well as the assessments made by the investigator. However, the adjudication made by the (EAC), given its independent analysis of each event, will be attributed with greater importance of the two. The outcome of adjudication will be kept in the clinical trial database.

## 13 Case report forms

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

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

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

The pregnancy forms are paper based CRFs. Also, the AE forms, technical complaint forms, and safety information forms will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data is recorded in these forms as soon as possible after the visit.

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after Last Patient Last Visit (LPLV) 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.

### **13.3 Electronic collection of questionnaires**

Novo Nordisk will use a tablet computer at sites for electronic recording of PRO questionnaires (see Section [8.6.2](#)). The tablet computer and related support services will be supplied by an external vendor.

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

All data entered will be transferred automatically from the tablet computer to a database hosted by the supplier which is considered source data. Data entered on the devices will upon confirmation of successful backup be deleted from the devices.

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

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

## 14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after, this will include a visit at the DXA radiology unit as well. 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 LPLV at the trial site. The on-site monitoring visit interval to the DXA radiology unit must not exceed 6 months at sites with active subjects.

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

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

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

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

The original of the completed diaries and ePROs (tablets) must not be removed from the trial site, unless they form part of the CRF/eCRF and a copy is kept at the site.

All data entered will be automatically transferred from the device to the ePRO database, hosted by the supplier. This database is considered as the source. 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.
- Reason for screening failure

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

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date:	17 October 2016	<b>Novo Nordisk</b>
Version:	2.0	
Status:	Final	
Page:	77 of 118	

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

## 15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a CRO.

In cases where data management activities are delegated to external vendors, there will be regular transfer of data during the trial.

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

### 17.1 General considerations

No interim analyses or other analyses of un-blinded or between group data will be performed before the database is locked.

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.

Laboratory values below the lower limit of quantification (LLOQ) will be set to  $\frac{1}{2}$ LLOQ.

Results from a statistical analysis will be presented by the estimated treatment contrasts at week 52 with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference if not otherwise specified.

The comparison presented from a statistical analysis will be semaglutide 1.0 mg versus canagliflozin 300 mg

If no statistical analysis is specified, data will be presented using relevant summary statistics.

Data from all trial sites will be analysed and reported together.

The regions used in the statistical analyses are defined as:

- North America (USA and Canada)
- Region Europe (UK, Ireland, Italy and Sweden)
- International Operations (Lebanon, Malaysia, Argentina, Mexico, Brazil, India)

#### 17.1.1 Data transformations

A number of the continuous parameters will be log-transformed prior to statistical analysis. The output tables and figures will show the results of the analysis back-transformed to the original scale, implying that log-treatment-differences are reported as treatment ratios. Confidence intervals for the treatment ratios will be calculated as exponentiated upper and lower limits for log-treatment difference confidence intervals. The standard errors (SE) of the back-transformed mean and ratio to baseline estimates are also provided; these SEs are calculated using the delta-method (first order Taylor approximation), whereby the SE on the original scale is calculated as the product of the SE on log-scale and the exponentiated estimate of the mean (geometric mean).

### **17.1.2 Definition of baseline**

For each assessment, the baseline assessment is defined as the latest available measurement at or prior to the randomisation visit. This specifically implies that if a visit 2 assessment is missing (whether it was planned or not planned) then the screening assessment (from visit 1), if available, will be used as the baseline assessment.

### **17.1.3 Primary estimand**

To further detail the trial objective an estimand is defined which is a *de-jure* (efficacy) estimand:

#### 1. Primary estimand

- The treatment difference between semaglutide and canagliflozin at week 52 for all randomised subjects if all subjects completed treatment and did not initiate rescue medication

This primary *de-jure* estimand is considered clinically relevant as it assesses the glycaemic benefit a person with T2D is expected to achieve if initiating and continuing treatment with semaglutide compared to canagliflozin. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference. This will avoid confounding from rescue medication.

### **17.1.4 Trial completion**

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 (P11). Subjects completing the follow-up visit (P11) will be considered trial completers.

### **17.1.5 Missing data considerations at week 52**

The actual rate of missing data at week 52 is expected to be maximum 10% based on the rate of trial completers from the subcutaneous semaglutide phase 3a clinical development program. The frequency of missing data is expected to be similar in the semaglutide and the canagliflozin groups.

When estimating the primary estimand, the combined rate of missing data, subjects discontinuing treatment prematurely or initiating rescue medication on top of trial product, is expected to be maximum 30%. This is based on the results from the subcutaneous semaglutide phase 3a clinical development program. Based on these data, premature treatment discontinuation due to gastrointestinal adverse events is expected to be low but more frequent in semaglutide compared to canagliflozin. Other reasons for discontinuing treatment are assumed to be unrelated to treatment and therefore occur with similar rates, so overall the frequency of missing data or data not used at week 52 in the primary analysis is expected to be slightly larger in semaglutide as compared to canagliflozin.

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

## 17.2 Sample size calculation

The primary endpoint, change from baseline to week 52 in HbA<sub>1c</sub> (%) will be tested for non-inferiority and superiority of semaglutide vs. canagliflozin. The confirmatory secondary endpoints, change from baseline to week 52 in body weight (kg) and change from baseline to week 52 in total fat mass (kg) are planned to be tested for superiority of semaglutide vs. canagliflozin.

The sample size calculation is made to ensure a power of at least 90% for meeting HbA<sub>1c</sub> superiority of semaglutide vs. canagliflozin out of the four pre-specified confirmatory hypotheses shown in [Table 17-1](#). The closed testing procedure described in Bretz et.al. 2011<sup>46</sup> combined with a hierarchical approach is used to control the overall type-1 error at a nominal two-sided 5% level. The statistical testing strategy is built on the following principle:

- Glycaemic efficacy must be established by HbA<sub>1c</sub> non-inferiority before testing for added benefits in terms of superiority in terms of HbA<sub>1c</sub> or body weight.
- HbA<sub>1c</sub> and body weight superiority must be established before testing for added benefits in terms of superiority in terms of total fat mass.

The sample size is calculated using the calcPower function in the R package, gMCP<sup>47</sup> using 10,000 simulations. All of the four pre-specified confirmatory tests are assumed to be independent. Since some of these tests are positively correlated, the assumption of independence is viewed as conservative. The four hypotheses are:

- HbA<sub>1c</sub> non-inferiority of semaglutide 1.0 mg vs. canagliflozin 300 mg with a non-inferiority margin of 0.3
- HbA<sub>1c</sub> superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg
- Body weight superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg
- Total fat mass superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg

The sample size assumptions for efficacy based on on-treatment data without rescue medication, a treatment effect based on in-trial data (see Section [17.3.1](#)) and the standard deviations (SD) are given in [Table 17-1](#). The HbA<sub>1c</sub> and body weight assumptions are based on the efficacy results and an observed reduction of approximately 20% and 15% respectively in in-trial treatment effect compare to efficacy in the subcutaneous semaglutide phase 3a clinical development programme<sup>28, 48-52</sup>.

A similar reduction in the in-trial treatment effect compared to efficacy is assumed with canagliflozin as comparator. The total fat mass assumption is based on the relevant literature

focusing on fat mass<sup>53-55</sup>, which indicates a smaller SD for total fat mass as compared to body weight.

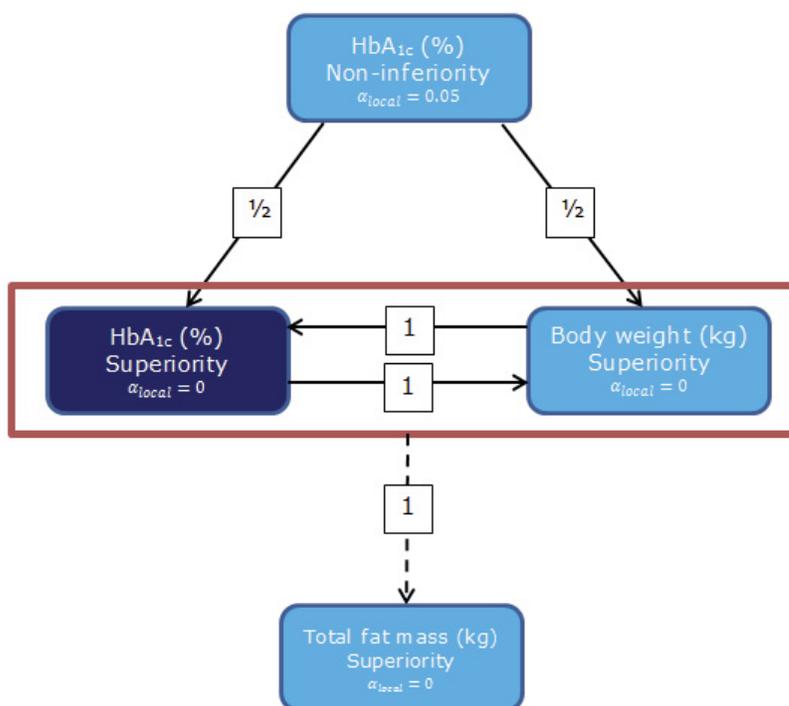
**Table 17–1 Assumptions used in the sample size calculation**

Semaglutide vs. canagliflozin	HbA <sub>1c</sub>	Body weight	Total fat mass
Efficacy	-0.32%	-2.4 kg	-1.8 kg
In-trial treatment effect	-0.256%	-2.04 kg	-1.53 kg
Standard deviation	1.1%	4.0 kg	3.5 kg

With the above assumptions, allocating 392 subjects to the semaglutide arm and the canagliflozin arm provides 90% power to confirm HbA<sub>1c</sub> superiority of semaglutide vs. canagliflozin across plausible assumptions.

**Table 17–2 Calculated powers for meeting individual hypotheses**

Statistical test	HbA <sub>1c</sub> non- inferiority	HbA <sub>1c</sub> superiority	Body weight superiority	Total fat mass superiority
Efficacy Power (%)	>99%	90%	>99%	91%
In-trial effect power (%)	>99%	90%	>99%	74%



**Figure 17–1 Graphical illustration of the closed testing procedure.**

The overall significance level of  $\alpha = 0.05$  (two-sided) is initially allocated to the HbA<sub>1c</sub> non-inferiority test. The local significance level ( $\alpha$ -local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses). The total fat mass superiority test will receive the overall significance of  $\alpha = 0.05$  (two-sided) if and only if both HbA<sub>1c</sub> and body weight superiority are confirmed at their respective local significance levels.

The overall significance level of  $\alpha = 0.05$  (two-sided) is initially allocated to the HbA<sub>1c</sub> non-inferiority test. The local significance level ( $\alpha$ -local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses). The total fat mass superiority test will receive the overall significance of  $\alpha = 0.05$  (two-sided) if and only if both HbA<sub>1c</sub> and body weight superiority are confirmed at their respective local significance levels.

### 17.2.1 Sample size for the sub-study (DXA scan)

For the sub-study on body composition assuming an efficacy treatment difference of 1.8 kg and a SD of 3.5 kg, 174 subjects (87 subjects in each arm) will provide 92% power to establish a statistical significant difference resulting in 91% power for confirming superiority in the testing strategy in terms of fat mass loss (kg) at week 52 using a two-sided significance level of 5%.

### 17.3 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 majority of the period they were on treatment. This will be referred to as contributing to the evaluation “as treated”.

**Per protocol (PP) analysis set:** includes all subjects in the FAS who fulfil the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have a non-missing HbA<sub>1c</sub> measurement at screening and/or randomisation
- Is on trial product at week 28 and have at least one non-missing HbA<sub>1c</sub> measurement at or after week 28

Subjects in the PP analysis set will contribute to the analysis “as treated” as defined for the SAS.

#### 17.3.1 Data selections and observation periods

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 after randomisation, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in IWRS) and ends at the date of:

- The last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up visit
- 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 dies before any of the above

For subjects not randomised but exposed to trial product the in-trial period starts at the date of first dose of trial product

**On-treatment:** This observation period represents the time period where subjects are considered treated with trial product. The observation period is a sub-set of the in-trial observation period. It starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately according to the flow chart. For adjudicated events, ECG's and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- the follow-up visit (P11)
- the follow-up prematurely discontinuation visit (P11A)
- the last date on trial product + 42 days
- the end-date for the in-trial observation period

The follow-up visit is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of subcutaneous semaglutide. The visit window for the follow-up visit is + 7 days, which is the reason for the 42 days specified in the bullet above. Hence, for those assessments this period reflects the period in which subjects are exposed.

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product + 7 days. This ascertainment window corresponds to the dosing interval and will be used to avoid attenuation of a potential treatment effect on endpoints for which the effect is reversible shortly after treatment discontinuation. Hence, for those assessments this period reflects the period in which subjects are treated.

**On-treatment without rescue medication:** This observation period is a sub-set 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 any of the following:

- the last dose of trial product +7 days
- initiation of rescue medication

The 'on-treatment without rescue medication' observation period will be the primary observation period for efficacy evaluations. The in-trial observation period will be considered supportive for efficacy evaluation. Safety will be evaluated based on the in-trial and the on-treatment observation periods unless otherwise specified.

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. For adjudicated events, the onset date will be the EAC adjudicated onset date.

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility

of the members of the Novo Nordisk study group.

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 will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

## **17.4 Primary endpoint**

The primary endpoint is change from baseline to week 52 in HbA<sub>1c</sub>.

### **17.4.1 Primary analysis for the primary estimand**

The primary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the 'on-treatment without rescue medication' observation period. Imputation of missing data will be handled using multiple imputation assuming that missing data is missing at random (MAR). Missing data will be imputed using observed data within the same group defined by the randomised treatment (semaglutide/canagliflozin). 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 receive the same treatment.

Technically missing values will be imputed as follows:

- Intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 200 copies of the dataset will be generated
- A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 52. A model used to impute missing values at each planned visit will be fitted for each of the treatment groups using observed data. The model will include stratification factor (sub-study, non-sub-study) and region as categorical effects and baseline and post-baseline HbA<sub>1c</sub> values observed prior to the visit in question as covariates.
- An ANCOVA with treatment, stratification factor (sub-study, non-sub-study) and region as categorical effects and baseline HbA<sub>1c</sub> as a covariate will be used to analyse HbA<sub>1c</sub> values at week 52 for each of the 200 complete data sets generated as part of the imputation of missing values. Rubin's rule will be used to combine the analysis results in order to draw inference.

From this analysis, the estimated treatment difference between semaglutide and canagliflozin at week 52 will be presented together with the associated two-sided 95% confidence interval and unadjusted two sided p-values for testing non-inferiority and superiority.

### 17.4.2 Primary hypotheses

For the primary HbA<sub>1c</sub> endpoint the following confirmatory one-sided hypotheses are planned to be tested for semaglutide versus canagliflozin. Let the mean treatment difference be defined as  $\mu =$  (semaglutide minus canagliflozin):

- Non-inferiority, using a non-inferiority margin of 0.3%
  - H<sub>0</sub>:  $\mu \geq 0.3\%$  against H<sub>a</sub>:  $\mu < 0.3\%$
- Superiority
  - H<sub>0</sub>:  $\mu \geq 0.0\%$  against H<sub>a</sub>:  $\mu < 0.0\%$

Operationally the hypotheses will be evaluated by two-sided tests.

The non-inferiority margin of 0.3 is chosen based on the diabetes guideline<sup>56,57</sup> and the effect of canagliflozin on glycaemic effect seen in a similar trial (DIA3006) where canagliflozin was used as add on to metformin. In this trial canagliflozin showed an HbA<sub>1c</sub> treatment difference to placebo of -0.77%. Hence, based on this trial, the chosen margin of 0.3 provides assurance that semaglutide has an effect compared to placebo greater than 0 with a clinically relevant size. With regards to the constancy assumption, controlled clinical trials have consistently established that canagliflozin is an effective anti-diabetic drug. Therefore, lack of trial sensitivity with canagliflozin as comparator is not anticipated to be an issue in this trial.

### 17.4.3 Multiplicity and criteria for confirming hypotheses

The Type-I error for testing the four confirmatory hypotheses related to the HbA<sub>1c</sub>, body weight, and fat mass endpoints will be preserved in the strong sense at 5% (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et. al.<sup>46</sup> and outlined in [Figure 17-1](#). The first hypothesis to be tested is non-inferiority of HbA<sub>1c</sub>. It will be tested at the overall significance level (5%) while allocating 0% local significance level to the remaining three hypotheses. For this hypothesis, and in general, if a hypothesis is confirmed the significance level will be reallocated according to the weight and the direction of the edges going from the confirmed hypothesis to the next hypotheses as specified in [Figure 17-1](#). Total fat mass will be tested at the overall significance level if each of the other 3 hypotheses is confirmed, otherwise its local significance level will remain 0%. Each of the following hypotheses will be tested at their local significance level ( $\alpha$ -local). This process will be repeated until no further hypotheses can be confirmed.

Non-inferiority and subsequent superiority will be considered confirmed if the mean treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below its local two-sided significance level as defined by the closed testing procedure in [Figure 17-1](#). This is equivalent to using a one-sided p-

value (nominal  $\alpha = 0.025$ ) and a one-sided 2.5% overall significance level in the closed testing procedure.

#### **17.4.4 Statistical subgroup analyses of HbA<sub>1c</sub>**

Five subgroups based on baseline HbA<sub>1c</sub> values are defined as follows:

1.  $\leq 7.5\%$
2.  $> 7.5\%$  to  $8.0\%$  (inclusive)
3.  $> 8.0\%$  to  $8.5\%$  (inclusive)
4.  $> 8.5\%$  to  $9.0\%$  (inclusive)
5.  $> 9.0\%$

Change from baseline in HbA<sub>1c</sub> at week 52 for subgroups based on baseline HbA<sub>1c</sub> values will be analysed for the primary estimand using a similar multiple imputation approach as described in section [17.4.1](#). The complete data sets from the primary analysis will be reused. However the ANCOVA model used to analyse the 200 complete data sets will additionally include the interaction effect of subgroup and treatment as a categorical effect. Rubin's rule will then be used to combine the results and the p-value for the interaction effect and estimated treatment differences at 52 weeks with corresponding two-sided 95% confidence intervals for each subgroup will be presented.

#### **17.4.5 Sensitivity analyses**

In order to investigate the robustness of the conclusions from the primary analysis and to stress test the MAR assumption for missing data tipping point sensitivity analyses will be performed for the primary estimand both for the sensitivity of the non-inferiority and the superiority HbA<sub>1c</sub> hypotheses.

##### **17.4.5.1 Sensitivity analyses for the primary estimand**

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

- Tipping-point analysis (pattern mixture model based) based on the FAS using the 'on-treatment without rescue medication' observation period. In this analysis, subjects from the semaglutide group with missing observations will be given a penalty, i.e., it is assumed that subjects with missing observations who are randomised to semaglutide will receive a treatment that is worse than subjects with observed values who are randomised to semaglutide. The idea is to gradually increase the penalty to evaluate at which level the superiority conclusion of the analyses in terms of statistical significance is changed. The tipping point is the penalty level, at which the magnitude of efficacy reduction in subjects with missing data creates a shift in the treatment effect of semaglutide from being statistically significantly better than canagliflozin to being non-statistically significantly better for the superiority test and similarly for the non-inferiority test. Technically, this analysis will be implemented by replicating the primary analysis including

the assumption of MAR but subsequently adding increasing penalty values at week 52 to imputed observations in the semaglutide group before applying ANCOVA on the 200 complete data sets.

#### **17.4.5.2 Other sensitivity analyses**

The following additional sensitivity analyses are specified:

- In-trial treatment policy analysis based on the FAS using post-baseline measurements up to and including week 52 from the in-trial observation period. Missing data will be imputed using the same approach as described for the primary analysis of the primary estimand. However the imputation will be done within the same group defined not only by the randomised treatment (semaglutide/canagliflozin) but also by the status of treatment completion (still on randomised treatment at week 52 yes/no) (4 groups in total). 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 52 are similar in terms of randomised treatment and treatment completion status. In addition in the imputation step stratification factor and region is not included in the model in order to avoid potential issues with sparse data. This analysis could be considered addressing an effectiveness estimand.
- PP analysis based on the PP data set using the ‘on-treatment without rescue’ observation period. This analysis will be carried out for non-inferiority testing only. The statistical analysis will be the same as the primary analysis for the primary estimand.

### **17.5 Secondary endpoints**

#### **17.5.1 Confirmatory secondary endpoints**

Change from baseline to week 52 in body weight (kg) and change from baseline to week 52 in total fat mass (kg) will be confirmatory secondary endpoints.

The primary estimand will be estimated using the same approach as described for the primary HbA<sub>1c</sub> endpoint. Body weight and total fat mass will be tested for superiority. Baseline and post-baseline body weight or total fat mass will be used as covariates instead of HbA<sub>1c</sub> for their respective analyses.

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below its local two-sided significance level resulting from the closed testing procedure in [Figure 17-1](#).

The tipping point sensitivity analysis pre-specified to evaluate the robustness of the conclusions from the primary analysis of HbA<sub>1c</sub> will also be performed to evaluate the robustness of the

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date: 17 October 2016  
Version: 2.0  
Status: Final  
Page: 90 of 118

**Novo Nordisk**

conclusions from the body weight and total fat mass superiority tests. In addition, the in-trial sensitivity analysis will also be performed for both body weight and total fat mass.

## **17.5.2 Supportive secondary endpoints**

No sensitivity analyses are planned for the supportive secondary endpoints.

### **17.5.2.1 Efficacy endpoints**

#### **Continuous endpoints**

The continuous endpoints are change from baseline to week 52 in:

- Fasting Plasma Glucose (FPG)
- Self-Measured Plasma Glucose (SMPG), 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)
- Body Mass Index (BMI) and waist circumference
- Systolic and diastolic blood pressure
- Body weight (%)
- Total fat mass (%)
- Total lean mass (kg)
- Total lean mass (%)
- Visceral fat mass (kg)
- Visceral fat mass (%)
- Ratio between total fat mass and total lean mass

The above continuous endpoints will be analysed for the primary estimand separately using a similar model approach as for the primary endpoint with the associated baseline and post-baseline responses as covariates instead of HbA1c for their respective analyses.

Fasting lipid profile endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

#### **Mean 7-point profile (SMPG) definition**

Subjects will be asked to perform SMPG measurements before and 90 minutes after breakfast, lunch, dinner, and at bedtime.

Mean of the 7-point profile is defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time.

## Binary endpoints

The binary endpoints are subjects who after 52 weeks treatment achieve (yes/no):

- HbA<sub>1c</sub> <7.0% (53 mmol/mol), American Diabetes Association (ADA) target
- HbA<sub>1c</sub> ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists (AACE) target
- Weight loss ≥3%
- Weight loss ≥5%
- Weight loss ≥10%
- HbA<sub>1c</sub> <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA<sub>1c</sub> reduction ≥1%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥3%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥5%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥10%

The above 10 endpoints will be analysed for the primary estimand. The analyses for the primary estimand for all 10 endpoints will be based on the 'on-treatment without rescue medication' observation period. They will be analysed separately using the same type of logistic regression model with treatment, stratification factor (sub-study, non- sub-study), region and associated baseline and post-baseline response(s) (i.e. HbA<sub>1c</sub> responses for HbA<sub>1c</sub> endpoints, body weight responses for weight endpoints and both HbA<sub>1c</sub> and body weight responses for the binary endpoints that combine both parameters) as covariates. To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- Multiple imputed data sets (200) will be created in which missing values for the underlying continuous assessments are imputed by treatment group assuming MAR similar to the approach described for the primary analysis in section [17.4.1](#).
- The binary endpoint will be created for each of the 200 complete data sets
- Each of the created complete data sets will be analysed with the logistic regression model. Estimated odds ratios will be log transformed and inference will be drawn using Rubin's rule<sup>58</sup>.

The results after applying Rubin's rule will be back-transformed and described by the odds ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### 17.5.2.2 Safety endpoints

The safety endpoints will be evaluated based on SAS using the on-treatment observation period and the in-trial observation period unless otherwise stated.

## **Adverse Events**

The following endpoint related to adverse events is used to support the safety objective;

- Number of treatment emergent adverse events (TEAEs)

A treatment-emergent AE is an event that has onset date (or increase in severity) during the on-treatment observation period. These will therefore be referred to as ‘on-treatment AEs’ hereafter. On-treatment adverse events are summarised descriptively in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). These summaries are replicated by outputs including all ‘in-trial’ adverse events (i.e., adverse events with onset date [or increase in severity] during the ‘in-trial’ observation period). Adverse events with onset after the end of the ‘in-trial’ observation period will be reported in a listing. The development over time in gastrointestinal AEs will be presented graphically.

The most frequent adverse events will be defined as preferred terms (PTs) that are experienced by at least 5% of the subjects in any of the treatment arms.

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

## **Hypoglycaemic episodes**

The following two endpoints related to hypoglycaemic episodes are used to support the safety objective:

- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes (yes/no)

Data on treatment-emergent hypoglycaemic episodes are 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 years of exposure. Summaries of treatment-emergent hypoglycaemic episodes will be presented as an overview including all episodes and episodes by severity.

### **Classification of Hypoglycaemia:**

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset is in the on-treatment period (see definition of observation period in section [17.3.1](#))

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

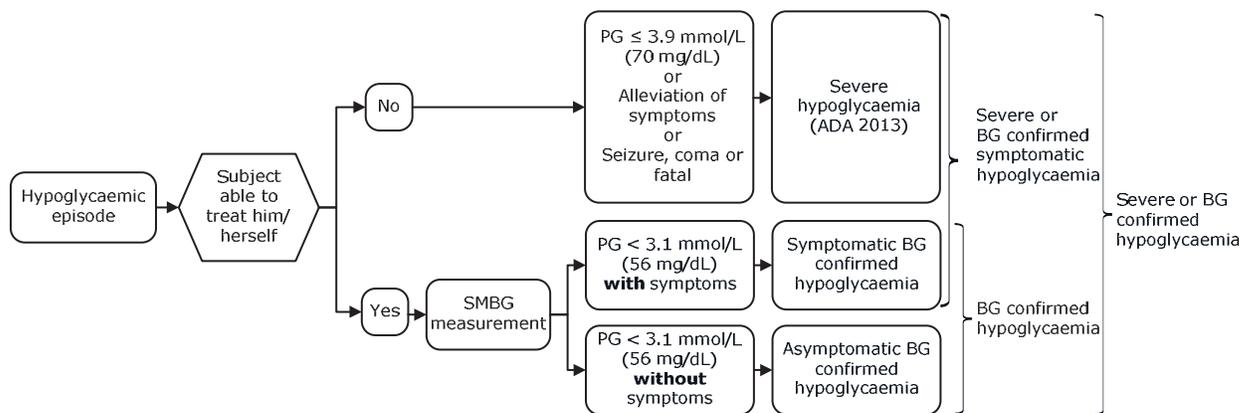
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 17-2](#)) and the ADA classification of hypoglycaemia (see [Figure 17-3](#)).

### Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)<sup>59</sup>. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

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

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification<sup>60</sup> or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

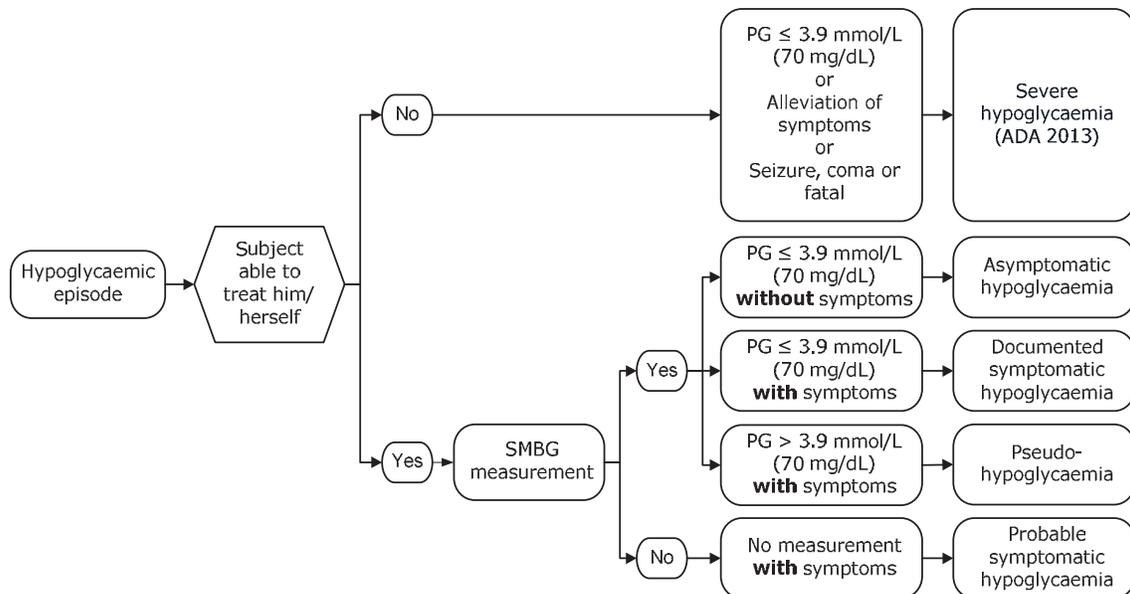


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

**Figure 17-2 Novo Nordisk classification of hypoglycaemia**

### ADA classification<sup>60</sup> 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  $\leq 3.9$  mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration  $\leq 3.9$  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  $\leq 3.9$  mmol/L (70 mg/dL).



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

Figure 17–3 ADA classification of hypoglycaemia

### **Number of treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes**

Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 56 weeks will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period, from the randomisation and up to the time point in which an occurrence of a hypoglycaemic episode is considered treatment emergent as offset assuming MAR. The model will include factors for treatment and stratification factor (sub-study, non- sub-study) as categorical factors and baseline HbA<sub>1c</sub> as covariate. The SAS will be used for the analysis.

The results will be described by the rate ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### **Treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes (yes/no)**

The binary endpoint indicating whether a subject has no treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes or at least one will be analysed using a logistic regression model. The model will include factors for treatment and stratification factor (sub-study, non- sub-study) as categorical factors and baseline HbA<sub>1c</sub> as covariate. The SAS will be used for the analysis.

The results will be described by the odds ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### **Laboratory assessments**

The laboratory assessments supporting the safety objective are change from baseline to week 52 in:

- Haematology
- Biochemistry
- Calcitonin

The above continuous laboratory assessments will be summarised and evaluated by descriptive statistics.

In addition amylase and lipase will be analysed separately using an analysis similar to the primary analysis of the primary endpoint. However this analysis will be based on SAS using the on-treatment observation period.

Both analyses will use the associated baseline and post-baseline responses as covariates instead of HbA<sub>1c</sub>. Lipase and amylase values will be log-transformed prior to the analysis.

## **Pulse**

Change from baseline to week 52 in pulse will be analysed separately with the same model approach as for amylase and lipase but with the pulse value at baseline and post-baseline as covariates instead of HbA<sub>1c</sub>.

## **Categorical safety assessments**

The categorical assessments supporting the safety objective are change from baseline to week 52 in:

- Electrocardiogram (ECG) category
- Physical examination
- Eye examination category

The above assessments will be summarised descriptively

## **17.6 Health economics and/or patient reported outcomes (PROs)**

Change from baseline to week 52 in:

- Scores for selected patient reported outcomes:
  - SF-36v2™ Short Form health survey: Total scores (physical component and mental component) and scores from the 8 domains
  - Diabetes Treatment Satisfaction Questionnaire (DTSQ): Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately
  - Control of Eating Questionnaire (CoEQ): Scores from the 4 domains and scores from 19 individual items

The PRO questionnaires, SF-36v2™, DTSQ and CoEQ will be used to evaluate the objective regarding Quality of Life. Each of the PRO endpoints will be analysed separately as the other continuous efficacy endpoints for the primary estimand using a similar model approach as for the primary endpoint with the associated baseline and post-baseline responses as covariates.

## 18 Ethics

### 18.1 Benefit-risk assessment of the trial

#### 18.1.1 Risk and precautions

The nonclinical safety programme of semaglutide has not revealed any safety issues precluding use in humans.

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

#### 18.1.2 Identified risk

##### **Gastrointestinal adverse events**

Consistent with findings with other GLP-1RAs, the most frequently reported AEs in clinical trials with semaglutide have been gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). Clinical trials have indicated that a low starting dose and gradual dose escalation mitigates the risk of gastrointestinal AEs. Consequently, a low starting dose and dose escalation with 4 week dose-escalation steps have been implemented in the trial.

#### 18.1.3 Potential risks

##### **Medullary thyroid cancer**

The human relevance of the proliferative C-cell changes found in rodents treated with GLP-1RAs is unknown, but data suggest that rodents are more sensitive to the mode of action of GLP-1RAs for induction of C-cell tumours. However, as a precaution, subjects with a family or personal history of Multiple Endocrine Neoplasia type 2 (MEN 2) or Medullary thyroid cancer will not be enrolled in the trial. During the trial, calcitonin will be measured at randomisation visit, visit 8 and at V10/V10A, and the guidance for investigators on further evaluation and action on elevated calcitonin concentrations is included in [appendix A](#).

##### **Acute pancreatitis**

Acute pancreatitis has been reported in subjects treated with GLP-1RAs including semaglutide. As a precaution, subjects with a history of acute or chronic pancreatitis will not be enrolled in the trial. Also, subjects will be informed about the symptoms of acute pancreatitis and serum levels of lipase and amylase will be monitored throughout the trial.

##### **Pancreatic cancer**

Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical studies or clinical trials or post marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been

included as a separate potential risk due to the scientific debate surrounding a potential association to GLP-1-based therapies and the unknown long-term effects of stimulation of  $\beta$ -cells and suppression of  $\alpha$ -cells. Pancreatic cancer has been classified as a potential class risk of GLP-1RAs by EMA.

### **Allergic reactions and injection site reaction**

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

### **Hypoglycaemia**

Based on current knowledge about the GLP-1RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when semaglutide is combined with SU or insulin.

### **Acute kidney injury**

In subjects treated with GLP-1RAs, including semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute kidney injury. Subjects with gastrointestinal AEs are recommended to drink plenty of fluids to avoid volume depletion. Also, serum creatinine and other markers of kidney function will be monitored throughout the trial.

SGLT-2 inhibitors have also been associated with volume depletion. It is recommended to monitor renal function and for signs and symptoms of fluid loss during therapy. Severe dehydration may be a risk factor for ketoacidosis.

Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1RAs are co-administered with metformin. As a precaution, serum creatinine 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. The use of the background medication should be in accordance with the current, approved labels.

## **18.1.4 Other safety considerations**

### **Teratogenicity (embryo-foetal development toxicity)**

Semaglutide caused embryo-foetal malformations in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans. However, as a precaution, females who are pregnant, breast-feeding

or intend to become pregnant or are of childbearing potential and not using an adequate contraceptive method will not be enrolled in the trial. In addition, pregnancy tests will be performed at all visits, including screening and follow-up and at any time during the trial if a menstrual period is missed, or as required by local law.

### **Diabetic retinopathy**

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment<sup>61-63</sup>. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression<sup>5, 64</sup> even in intensively treated patients who experienced early worsening<sup>62</sup>. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo. As a precaution in this trial, all subjects are required to have a fundus photography or dilated funduscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial<sup>65</sup>.

### **General precautions**

All subjects will be included after a thorough evaluation with regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment.

There are also strict glycaemic rescue criteria in place to ensure acceptable glycaemic control during the trial. If rescue medication is required, it should be in accordance with ADA/European Association for the Study of Diabetes<sup>33, 34</sup> (excluding GLP-1RAs, DPP-4 inhibitors, amylin analogues and SGLT-2).

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2016 Standards of Medical Care in Diabetes<sup>65</sup>.

Further details with regards to safety of trial product are described in the current edition of the IB for semaglutide (NN9535)<sup>25</sup> or any updates thereto or in the current approved label of the relevant SGLT-inhibitors.

### **Canagliflozin**

Subjects should be considered suitable for treatment with canagliflozin and the use of canagliflozin should be in accordance with the current, approved label. It is important to monitor renal function and for signs and symptoms of volume depletion during therapy. Serum creatinine will be measured regularly for monitoring of renal function.

The most common adverse reactions reported with canagliflozin are female genital mycotic infections, urinary tract infections and increased urination. Other events include hypoglycaemia

(with concomitant use of insulin or insulin secretagogues), hypotension, hyperkalemia, increased LDL-C levels and bone fracture. Canagliflozin and other SGLT-2 inhibitors have also been associated with a risk of urinary tract infections and ketoacidosis. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, general malaise and shortness of breath. Ketoacidosis associated with the use of SGLT-2 inhibitors can occur even if blood sugar levels are only relatively elevated or non-elevated. If ketoacidosis is suspected, canagliflozin or canagliflozin placebo should be discontinued and appropriate treatment should be instituted promptly.

### **18.1.5 Benefits**

In this trial, subjects will be randomised in a 1:1 manner to one of two treatment arms involving an active add-on treatment regimen anticipated to be more efficacious than the treatment they receive at the time of entry into the trial (metformin only).

Based on the results of the completed clinical trials, semaglutide is expected to provide clinically relevant improvements in glycaemic control and body weight in subjects with type 2 diabetes.

In addition, it is expected that all subjects, will benefit from participation through close contact with the trial site, with close follow-up of their T2D and a careful medical examination, all of which will most likely result in an intensified management of their T2D.

Finally, data from two cardiovascular outcomes trials investigating treatment with GLP-1RAs compared to placebo have indicated that there might be a potential beneficial effect of these drugs on cardiovascular outcomes when added to standard of care in subjects with T2D at high risk of cardiovascular events (see Section [3.1.5.3](#)).

All subjects in this trial will receive trial products and auxiliary supplies free of charge.

## **18.2 Risk and benefit conclusion**

The safety profile for semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of semaglutide in accordance with the planned clinical trial. Completed clinical trials with semaglutide provided clinically relevant improvements in glycaemic control and body weight.

Safety and efficacy will be monitored regularly and acceptable glycaemic control will be reinforced at all times during the trial.

In conclusion, the potential risk to the subjects in this trial is considered low and acceptable in view of the anticipated benefits semaglutide would provide to patients with T2D.

## **18.3 Informed consent**

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

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.

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.

In order to avoid missing data, the subjects will be informed about the importance of completing the trial also if the subjects discontinue treatment with trial product.

#### **18.4 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.

#### **18.5 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.

#### **18.6 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.

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 SmPC or similar labelling
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

### **Only applicable for US trial sites:**

- 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.

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date: 17 October 2016  
Version: 2.0  
Status: Final  
Page: 106 of 118

**Novo Nordisk**

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

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

## 22 Responsibilities

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

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

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

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

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

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

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

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

## 23 Reports and publications

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

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

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

One or two investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications<sup>66</sup>.

### 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<sup>35</sup>.

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<sup>66</sup> (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.

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date:	17 October 2016	<b>Novo Nordisk</b>
Version:	2.0	
Status:	Final	
Page:	110 of 118	

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 and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

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

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

## **25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities**

### **IRB/IEC:**

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

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

The investigator must ensure submission of the 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:

For Mexico only:

- a) *Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.*
- b) *If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the 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.*
- c) *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.*
- d) *By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.*

## 27 References

1. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis.* 2012;60(5):850-86.
2. International Conference of Harmonisation. ICH Harmonised Tripartite Guideline E6(R1): Guideline for Good Clinical Practice. 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. 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.
6. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care.* 2013;36(8):2271-9.
7. Kilpatrick ES, Das AK, Orskov C, Berntorp K. Good glycaemic control: an international perspective on bridging the gap between theory and practice in type 2 diabetes. *Current Medical Research and Opinion.* 2008;24(9):2651-61.
8. Holst JJ, Vilsboll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. *Mol Cell Endocrinol.* 2009;297(1-2):127-36.
9. Kieffer TJ, Habener JF. The glucagon-like peptides. *Endocr Rev.* 1999;20(6):876-913.
10. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsboll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2011;96(3):737-45.
11. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia.* 1986;29(1):46-52.
12. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia.* 2011;54:10-8.
13. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. *J Clin Invest.* 1967;46(12):1954-62.
14. Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia.* 2009;52(2):199-207.
15. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol.* 2012;8(12):728-42.
16. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest.* 1998;101(3):515-20.
17. Nauck MA, Niedereichholz U, Ettl R, Holst JJ, Orskov C, Ritzel R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol.* 1997;273(5 Pt 1):E981-8.

18. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36(8):741-4.
19. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. *Am J Med*. 2011;124(1 Suppl):S3-18.
20. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86(8):3717-23.
21. Nauck MA, Petrie JR, Sesti G, Mannucci E, Courrèges, J.P., et al. A Phase 2, Randomized, Dose-Finding Study of the Novel Once-Weekly Human GLP-1 Analog, Semaglutide, Compared With Placebo and Open-Label Liraglutide in Patients With Type 2 Diabetes. *Diabetes Care*. 2016;39(2):231-41.
22. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. *J Med Chem*. 2015;58(18):7370-80.
23. ICH Harmonised Tripartite Guideline. Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2). 2009.
24. Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. *Mod Pathol*. 2015;28(3):391-402.
25. Investigator's Brochure for s.c. Semaglutide (NN9535), Edition 11 or any updates hereof. 2016.
26. Sorli C HS, Tsoukas G, Unger J, Derving Karsbol J, Hansen T, Bain S. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in subjects with type 2 diabetes (SUSTAIN 1). ENDO 2016 - 98th Annual Meeting of the Endocrine Society 2016.
27. Ahrén B CL, Kumar H, Sargin M, Derving Karsbøl J, Jacobsen SH, Chow F. Efficacy and Safety of Once-weekly Semaglutide vs Sitagliptin as add-on to Metformin and/or Thiazolidinediones After 56 Weeks in Subjects With Type 2 Diabetes (SUSTAIN 2). *Diabetes*. 2016.
28. Ahmann A CM, Charpentier G, Dotta F, Henkel E, Lingvay I, Gaarsdal Holst A, Chang D, Aroda V. Efficacy and Safety of Once-weekly Semaglutide vs Exenatide ER After 56 Weeks in Subjects With Type 2 Diabetes (SUSTAIN 3). *Diabetes*. 2016.
29. Aroda V BS, Cariou B, Piletic M, Rose L, Axelsen MB, Everton R, de Vries JH. Efficacy and safety of once-weekly semaglutide vs once-daily insulin glargine in insulin-naïve subjects with type 2 diabetes (SUSTAIN 4). *Endocrine practice*. 2016.
30. Novo Nordisk A/S. Company Announcement: SUSTAIN 6. 2016.
31. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016.
32. Janssen-Cilag International N.V. Invokana (canagliflozin) EU prescribing information (SmPC). January 2016.
33. 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.

34. 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.
35. Novo Nordisk A/S. <http://www.novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx>.
36. 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.
37. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007.
38. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. *Official Journal of the European Communities*. 01 May 2001.
39. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.
40. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care*. 1995;18(4):517-22.
41. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. *Diabet Med*. 2001;18(9):690-705.
42. Center USDoHaHSFaDACfDEaRCCfBEaRC. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.
43. 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.
44. 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). 03 Feb 2010.
45. Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Strockbridge NL, et al. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials (Draft). 20 Aug 2014.
46. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biometrical Journal*. 2011;53(6):894-913.
47. Rohmeyer K, Klinglmueller F. gMCP: Graph Based Multiple Test Procedures. R package version 0.8-8. 3 Oct 2014.

48. Novo Nordisk successfully completes fourth phase 3a trial with semaglutide in people with type 2 diabetes. Company official announcement, Dec. 2015. Available at <http://www.novonordisk.com/media/news-details.1974382.html>.
49. Novo Nordisk successfully completes second phase 3a trial with semaglutide in people with type 2 diabetes. Company official announcement, Sept. 2015. Available at [http://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en\\_gb/home/media/news-details.1954507.html](http://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.1954507.html).
50. Novo Nordisk successfully completes first phase 3a trial with semaglutide in people with type 2 diabetes. Company official announcement, July 2015. Available at [http://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en\\_gb/home/media/news-details.1934243.html](http://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.1934243.html).
51. Results from the SUSTAIN 4 trial comparing once-weekly subcutaneous administration of the GLP-1 analogue semaglutide with once-daily insulin glargine. In 'Highlights to be presented at Novo Nordisk's Capital Markets Day 2015' - Company official announcement, Nov. 2015. Available at [http://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en\\_gb/home/media/news-details.1967802.html](http://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.1967802.html).
52. Novo Nordisk successfully completes fifth phase 3a trial with semaglutide in people with type 2 diabetes. Company official announcement, Feb 2016. Available at <http://www.novonordisk.com/media/news-details.1988465.html>. 2016.
53. Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab.* 2012;97(3):1020-31.
54. Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab.* 2014;16(2):159-69.
55. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet.* 2013;382(9896):941-50.
56. Administration FaD. Guidance for Industry. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 12/1/2008 2008.
57. 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.
58. Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.
59. 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.
60. 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.

61. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *Br Med J (Clin Res Ed)*. 1985;290(6471):811-5.
62. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol*. 1998;116(7):874-86.
63. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. *Diabetes Res Clin Pract*. 2014;103(3):e37-9.
64. The Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. *Diabetes Care*. 2016;39(7):1089-100.
65. American Diabetes Association. Standards of medical care in diabetes -2016. *Diabetes Care*. 2016;39 (Suppl. 1):S1-S109.
66. 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](http://www.icmje.org).

Protocol - Appendix A  
Trial ID: NN9535-4270  
UTN: U1111-1180-3651  
EudraCT No.: 2016-000989-35

~~CONFIDENTIAL~~

Date:	21 September 2016	<b>Novo Nordisk</b>
Version:	1.0	
Status:	Final	
Page:	1 of 6	

## Appendix A

# Monitoring of Calcitonin

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

## 1 Background

Treatment with GLP-1 receptor agonists has been shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with semaglutide.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) as likely indicative of C-cell neoplasia, the interpretation of values between upper normal range (5.0 and 8.4 ng/L for women and men, respectively) and 100 ng/L is less clear with regards to indication of disease.

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

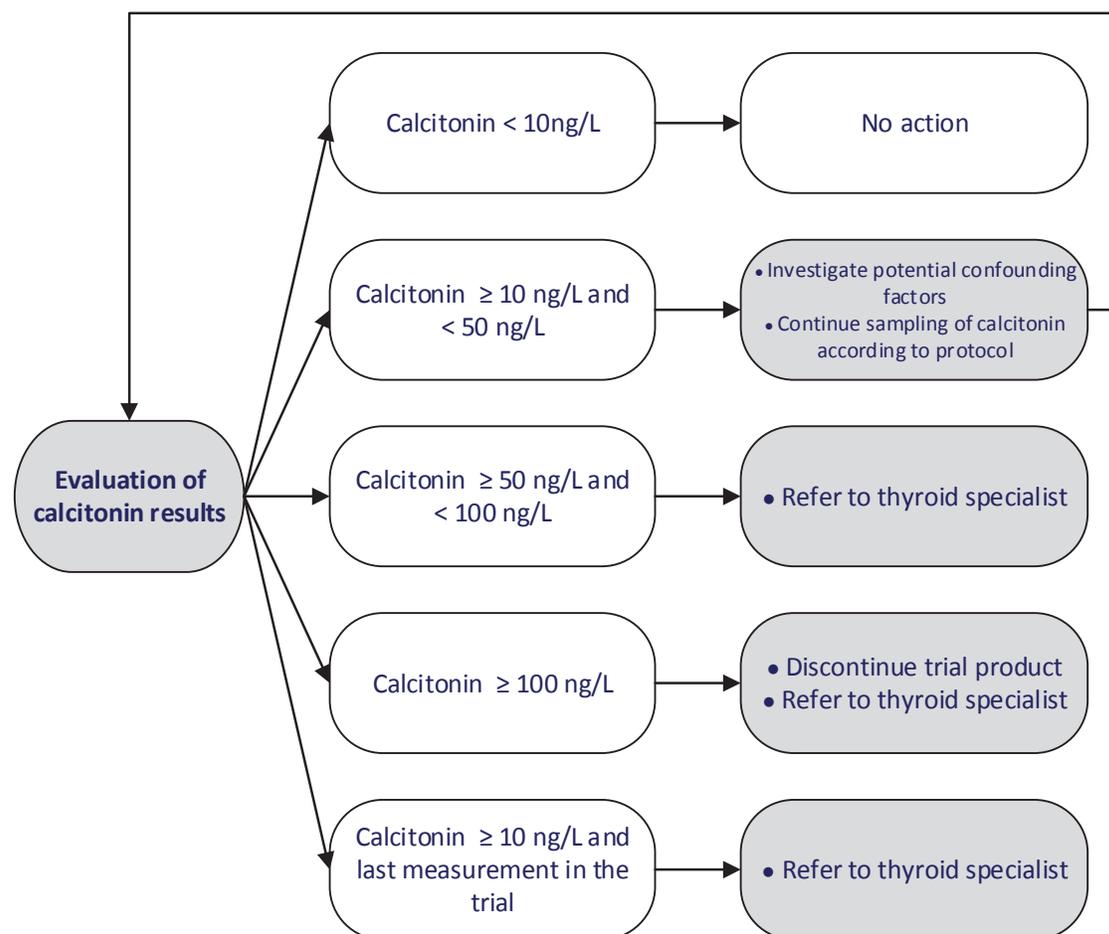
- renal dysfunction
- smoking
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H<sub>2</sub>-blockers and glucocorticoids)

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

## 2 Calcitonin monitoring

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

In case a subject has a calcitonin value  $\geq 10$  ng/L, the algorithm outlined in [Figure 1](#) and described below should be followed. The algorithm applies for all calcitonin values in the trial.



**Figure 1** Flow of calcitonin monitoring

### 2.1 Calcitonin $\geq 100$ ng/L

**Action:** The subject must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see protocol section [6.5](#) premature discontinuation of trial

product). The subject should remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

**Background:** These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease<sup>1</sup>. All of these patients were diagnosed with MTC, resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

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

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

## 2.2 Calcitonin $\geq 50$ and $< 100$ ng/L

**Action:** The subject should be referred to a thyroid specialist for further evaluation. The subject should remain in the trial and continuation on trial product should be based on the evaluation done by the thyroid specialist.

**Background:** These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease<sup>1</sup>. Two of these subjects were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

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

## 2.3 Calcitonin $\geq 10$ and $< 50$ ng/L

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

If the value is from the last sample taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

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

For calcitonin values between 10-20 ng/L Costante et al.<sup>1</sup> identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin value of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions<sup>2,3</sup>.

### 3 References

1. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. *J Clin Endocrinol Metab.* 2007;92(2):450-5.
2. Scheuba C, Kaserer K, A m, drosten R. Sporadic hypercalcitoninemia: clinica and therapeutic consequences. *Endocrine Related Cancer.* 2009;16(1):243-53.
3. Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M, et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? *Endocr Relat Cancer.* 2007;14(2):393-403.

Protocol - Appendix B  
Trial ID: NN9535-4270  
UTN: U1111-1180-3651  
EudraCT no.: 2016-000989-35

~~CONFIDENTIAL~~

Date:	21 September 2016	<b>Novo Nordisk</b>
Version:	1.0	
Status:	Final	
Page:	1 of 9	

## Appendix B

### Adverse events requiring additional data collection



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

<b>Table of Contents.....</b>	<b>2</b>
<b>1 Adverse events requiring additional data collection.....</b>	<b>3</b>
1.1 Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina).....	3
1.2 Cerebrovascular event (stroke or TIA).....	4
1.3 Heart failure.....	4
1.4 Hypersensitivity reactions.....	4
1.5 Neoplasm.....	5
1.6 Pancreatitis.....	5
1.7 Renal event.....	6
1.8 Thyroid disease.....	7
1.9 Hepatic event.....	7
1.10 Diabetic retinopathy.....	8
1.11 Laboratory outlier.....	8
<b>2 References.....</b>	<b>9</b>

## 1 Adverse events requiring additional data collection

For the following AEs, additional data collection is required and specific event forms must be completed in addition to the AE form. In case any of these events fulfil the criteria for an SAE, please report accordingly, see Section 12.1.2.

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack [TIA])
- Heart failure
- Hypersensitivity reaction
- Neoplasm (excluding thyroid neoplasm)
- Pancreatitis
- Renal event
- Thyroid disease (including thyroid neoplasm)
- Hepatic event
- Diabetic retinopathy
- Laboratory outlier

Additional information on a specific form is also required for hypoglycaemic episode and medication errors. The hypoglycaemia form is described in protocol section 8.4.6 and medication errors are described in protocol section 8.4.5.1. and 12.1.4.

### 1.1 Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)

If an event of acute coronary syndrome (ranging from unstable angina pectoris to myocardial infarction) is observed during the trial, the following additional information must be reported if available:

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Revascularisation procedures

## 1.2 Cerebrovascular event (stroke or TIA)

If a cerebrovascular event (e.g. TIA, stroke) is observed during the trial, the following additional information must be reported if available:

- Type of event (e.g. TIA, stroke)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the condition
- Treatment given for the condition

## 1.3 Heart failure

If an event of heart failure is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms of heart failure
- NYHA class
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

## 1.4 Hypersensitivity reactions

All events of hypersensitivity reactions must be reported and the following additional information must be reported if available:

- Signs and symptoms associated with the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed
- Treatment given for the reaction
- Previous history of similar reactions
- Risk or confounding factors identified

Assessments in case of suspicion of hypersensitivity reactions

In case of suspicion of a severe immediate systemic hypersensitivity reaction<sup>1</sup> to the trial product, the subject must be discontinued from trial product but should remain in the trial (see protocol section 6.5 and 8.1.6).

If suspicion of a hypersensitivity reaction occurs, the subjects should be instructed to contact the site staff as soon as possible for further guidance.

To assist in the diagnostic evaluation it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of onset of the hypersensitivity reaction, and if this is achieved, a tryptase sample should also be drawn 2 weeks after the event.

Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies should be drawn after 2 weeks and sent to central laboratory (see [attachment I](#)). Tryptase concentrations, if available, should be included in the specific event form when reporting the AE.

In case of suspicion of immune complex disease<sup>1</sup>, the subject must be discontinued from trial product but should remain in the trial (see Section 6.5 and 8.1.6). It is recommended to draw a blood sample for local assessment of complement levels (C3 and C4) to assist in the diagnostic evaluation. Complement level results should be included in the specific event form when reporting the AE.

## 1.5 Neoplasm

All events of neoplasms (excluding thyroid neoplasms, which will be reported under thyroid disease) must be reported during the trial and the following additional information must be reported if available:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated with the event

## 1.6 Pancreatitis

For all confirmed events of pancreatitis the following additional information must be reported if available:

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

## Assessments in case of suspicion of acute pancreatitis

Most patients with acute pancreatitis experience severe abdominal pain that is located generally in the epigastrium and radiates to the back. The onset of the pain may be swift, reaching maximum intensity within 30 min, is frequently unbearable, and characteristically persists for more than 24 hours without relief<sup>2</sup>. The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding.

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The level of the serum amylase and/or lipase does not correlate with the severity of acute pancreatitis<sup>2</sup>. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.

In case of suspicion of acute pancreatitis, the trial product should promptly be interrupted (no treatment discontinuation call should be made in IWRS before diagnosis of acute pancreatitis is confirmed). Appropriate additional examinations must be performed, including local measurement of amylase and lipase.

The diagnosis of acute pancreatitis requires two of the following three features<sup>3</sup>:

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

If acute pancreatitis is ruled out, trial product should be re-initiated.

If acute pancreatitis is confirmed, appropriate treatment and careful monitoring of the subject should be initiated. The subject must be discontinued from trial product (treatment discontinuation call in IWRS), but should remain in the trial (see Section 6.5 and 8.1.6).

### 1.7 Renal event

If a renal event is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms of renal failure
- Specific laboratory tests supporting the diagnosis
- Imaging performed supporting the diagnosis
- Kidney biopsy results

Risk or confounding factors identified including exposure to nephrotoxic agents

## 1.8 Thyroid disease

If an event of thyroid disease, including any thyroid neoplasms, is observed during the trial, the following additional information must be reported if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

## 1.9 Hepatic event

- ALT or AST  $> 5 \times$  UNL and total bilirubin  $\leq 2 \times$  UNL
- ALT or AST  $> 3 \times$  UNL and total bilirubin  $> 2 \times$  UNL\*
- Hepatic event leading to trial product discontinuation

If one of the above events is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms associated with the event
- Risk factors
- Relevant laboratory test results
- Diagnostic imaging performed
- Possible cause(s) of the event
- Assessments in case of increased levels of aminotransferases

The above mentioned hepatic events should prompt repeat testing (at the central laboratory) including ALT, AST, ALP and total bilirubin, and discontinuation of trial product should be considered. Thereafter, repeat testing (at the central laboratory) of ALT, AST, ALP and total bilirubin should be done regularly until the abnormalities return to normal or baseline state. Additional clinical information such as related symptoms, risk factors and contributing conditions (e.g. viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatobiliary or pancreatic disorders) should be gathered to seek a possible cause of the observed laboratory test abnormalities.

\*Please note that risk of liver injury defined as ALT or AST  $> 3 \times$  UNL and total bilirubin  $> 2 \times$  UNL, where no alternative aetiology exists (Hy's law), should also be reported as a SAE (important medical event, according to section 12.1.2).

### 1.10 Diabetic retinopathy

If an event of diabetic retinopathy (new onset or worsening of) is observed during the trial the following additional information should be reported if available on the diabetic retinopathy form:

- Signs and symptoms of diabetic retinopathy
- Fundoscopy/fundus photography supporting the diagnosis
- Verification of diagnosis
- Treatment given for the event
- Relevant risk factors associated with the event

### 1.11 Laboratory outlier

As a minimum but not limiting to the specified cut-offs for the following laboratory parameters a value above or below are considered to be clinically significant<sup>4</sup> and should be reported as a laboratory outlier by completing both an AE and a laboratory outlier form. Furthermore, repeated laboratory assessments should be obtained at the central laboratory until the value is within the normal range or back to baseline values.

- Alkaline phosphatase: > 20x ULN
- Total bilirubin: > 10x ULN
- Serum creatinine: > 6x ULN
- Leucocyte count: < 1000/mm<sup>3</sup> or 1x10<sup>9</sup>/L
- Thrombocyte count: < 25000/mm<sup>3</sup> or 25x10<sup>9</sup>/L
- Total calcium (serum corrected): <1.5 mmol/L or > 3.4 mmol/L
- Potassium: < 2.5 mmol/L or > 7 mmol/L
- Sodium: < 120 mmol/L or > 160 mmol/L

## 2 References

1. Food and Drug Administration. Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. 8/2015 2015.
2. Banks PA, Freeman ML, Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol.* 2006;101(10):2379-400.
3. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013;62(1):102-11.
4. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.03 (NIH publication # 09-7473). [http://evsncinihgov/ftp1/CTCAE/CTCAE\\_403\\_2010-06-14\\_QuickReference\\_5x7pdf](http://evsncinihgov/ftp1/CTCAE/CTCAE_403_2010-06-14_QuickReference_5x7pdf). 2010.

**Protocol Amendment**  
**no 1**  
**to Protocol, final version 2**  
**dated 17 Oct 2016**

**Trial ID:NN9535-4270**

**SUSTAIN 8 – semaglutide versus canagliflozin**

**Efficacy and safety of semaglutide versus canagliflozin as add-on to metformin in subject with type 2 diabetes**

**Trial phase: 3b**

**Applicable to all countries**

Amendment originator:



## Table of Contents

	<b>Page</b>
<b>Table of Contents</b> .....	<b>2</b>
<b>Table of Figures (N/A)</b> .....	<b>2</b>
<b>Table of Tables (N/A)</b> .....	<b>2</b>
<b>1 Introduction including rationale for the protocol amendment</b> .....	<b>3</b>
1.1 Risk-mitigation strategy for the risk of lower limb amputations potentially associated with canagliflozin, currently under review by the FDA and the EMA. This strategy includes additional exclusion and premature discontinuation criteria, physical examination of legs and feet at every site visits and description of this potential risk.....	3
1.2 Updates of identified risks for semaglutide .....	4
1.3 Other minor corrections and clarifications.....	4
<b>2 Changes</b> .....	<b>5</b>
2.1 Section 1 Summary.....	5
2.2 Section 2 Flowchart .....	6
2.3 Section 5.3 Treatment of subjects (Canagliflozin treatment arm) .....	6
2.4 Section 6.1 Number of subjects .....	7
2.5 Section 6.3 Exclusion criteria .....	7
2.6 Section 6.6 Criteria for premature discontinuation of trial product.....	9
2.7 Section 7 Milestones.....	9
2.8 Section 8.4.1 Physical examination .....	10
2.9 Section 12.2 Reporting of adverse events (Novo Nordisk assessment of AE expectedness) .....	10
2.10 Section 18.1.2 Identified risks .....	10
2.11 Section 18.1.4 Other safety considerations.....	11
2.12 References.....	12

## Table of Figures (N/A)

**Page**

**No table of figures entries found.**

## Table of Tables (N/A)

**Page**

**No table of figures entries found.**

# 1 Introduction including rationale for the protocol amendment

This protocol amendment introduces:

1. Risk-mitigation strategy for the risk of lower limb amputations potentially associated with canagliflozin, currently under review by the FDA and the EMA. This strategy includes additional exclusion and premature discontinuation criteria, physical examination of legs and feet at every site visits and description of this potential risk.
2. Update of identified risks for semaglutide
3. Other minor corrections and clarifications

## 1.1 Risk-mitigation strategy for the risk of lower limb amputations potentially associated with canagliflozin, currently under review by the FDA and the EMA. This strategy includes additional exclusion and premature discontinuation criteria, physical examination of legs and feet at every site visits and description of this potential risk.

Protocol sections updated: 1, 2, 6.3, 6.6, 8.4.1, and 18.1.4.

The European Medicines Agency (EMA)<sup>1</sup> and The U.S. Food and Drug Administration (FDA)<sup>2</sup> have started a review of the diabetes medicine canagliflozin after an increase in amputations, mostly affecting toes, based on data emerged from the ongoing clinical trial called Canagliflozin Cardiovascular Assessment Study (CANVAS) sponsored by Janssen Research & Development, LLC.

In the CANVAS trial an increased risk of leg and foot amputations have been identified. The amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo. An interim analysis showed that over a year's time, the risks of amputation for patients in the trial were equivalent to:

- 7 out of every 1,000 patients treated with 100 mg daily of canagliflozin
- 5 out of every 1,000 patients treated with 300 mg daily of canagliflozin
- 3 out of every 1,000 patients treated with placebo

Based on feedback from several National Health Authorities (HAs) for trial NN9535-4270, a full risk-mitigation strategy has been implemented in this trial, which includes:

- an additional exclusion criterion
- a premature discontinuation criterion
- legs and feet examinations at every clinic visit
- additional information on this potential new risk associated with canagliflozin
- Information to this potential new risk is added to the Subject Information/Informed Consent (SI/IC).

## **1.2 Updates of identified risks for semaglutide**

### **Identified risks**

Protocol section updated: 18.1.2

This protocol section is updated in order to reflect the recent IB amendment (amendment 1, to IB V 11, dated 18-Oct-2016) describing diabetic retinopathy complications as an identified risk. In addition, a new paragraph describing the new identified risk of cholelithiasis has been added, based on recent analyses of the SUSTAIN phase 3a development program.

## **1.3 Other minor corrections and clarifications**

### **Canagliflozin treatment arm**

Protocol section updated: 5.3

This protocol section is updated to align with section below.

### **Number of subjects**

Protocol section updated: 6.1

This protocol section is updated due to a subject re-allocation between countries participating in this trial. The number of subjects to be randomised for Mexico has increased by 5 subjects, hence a total number of 50 subjects are planned to be randomised in Mexico.

### **Milestones**

Protocol section updated: 7.0

This protocol section is updated to accommodate for the potential delay in approving this amendment and thereby the trial start in some countries.

### **Reporting of adverse event (Novo Nordisk assessment of AE expectedness)**

Protocol section updated: 12.2

This protocol section is updated to align with the current process in place in Novo Nordisk.

### **References**

Protocol section updated: 27

This protocol section is updated with 2 references added for the EMA and FDA safety announcements on the increased risk of small limb amputation.

## 2 Changes

In this protocol amendment:

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

### 2.1 Section 1 Summary

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).
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days prior to the day of screening.
5. Any disorder which in the investigator’s opinion might jeopardise subject’s safety or compliance with the protocol.
6. Subjects with ALT >2.5 x upper normal limit (UNL).
7. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
8. History or presence of pancreatitis (acute or chronic).
9. History of diabetic ketoacidosis (DKA).
10. Any of the following: myocardial infarction (MI), stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
13. Renal impairment measured as eGFR <60 ml/min/1.73 m<sup>2</sup> as defined by Kidney Disease Improving global outcomes (KDIGO 2012) classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening. .
14. 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 prior to the day of screening is allowed.
15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.
16. 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.

17. Medical history of diabetes-related lower limb amputations or signs of critical lower limb ischemia, (e.g. skin ulcer, osteomyelitis, or gangrene) within the last 26 weeks prior to screening.

## 2.2 Section 2 Flowchart

Trial Periods	Screening	Randomisation	Treatment							End of Treatment	Follow-up	End of treatment, Premature discontinuation	Follow-up
			V3	V4	P5	V6	V7	V8	V9				
Visit (V)/ phone contact (P)	V1	V2	V3	V4	P5	V6	V7	V8	V9	V10	P11	V10A	P11A
Timing of visit (weeks)	-2	0	4	8	10	12	16	28	40	52	57		
Visit window (days)	±7		±3	±3	±3	±7	±7	±7	±7	±7	+7		
<b>SUBJECT RELATED INFO/ASSESSMENTS</b>													
<b>TRIAL MATERIAL</b>	<b>Section</b>												
<b>SAFETY</b>													
Physical examination	8.4.1	x						x		x			
- Legs and Feet examination	8.4.1	x	x	x		x	x	x	x	x		x	

## 2.3 Section 5.3 Treatment of subjects (Canagliflozin treatment arm)

### Canagliflozin treatment arm

Treatment with canagliflozin, once-daily must follow a fixed dose escalation. The maintenance dose of canagliflozin 300 mg is reached after 56 doses (8 weeks) of 100 mg. After the maintenance dose of 300 mg is reached the dose must not be changed during the course of the trial unless the eGFR falls  $<45-60$  mL/min/1.73 m<sup>2</sup>, see below. In addition, all subjects randomised to canagliflozin will receive semaglutide placebo once-weekly.

Treatment with canagliflozin must be in compliance with current local prescribing information. Canagliflozin should be taken orally once a day, preferably before the first meal of the day. Tablets should be swallowed whole. Treatment with canagliflozin or canagliflozin placebo should be temporarily stopped in subjects who are hospitalized for major surgical procedures or acute serious medical illnesses. In subjects whose eGFR falls persistently  $<60$  mL/min/1.73 m<sup>2</sup>, the dose of canagliflozin or canagliflozin placebo should be reduced to 100 mg once-daily. The dose can be re-escalated to 300 mg once-daily in case the renal function improves (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>) during the trial. If the eGFR falls  $<45$  mL/min/1.73 m<sup>2</sup>, treatment with all trial products should be discontinued (see section 2.6)<sup>1</sup>.

## 2.4 Section 6.1 Number of subjects

Number of subjects planned to be screened (meaning the number of subjects providing informed consent):	1307
Number of subjects planned to be randomised in a 1:1 manner:	784
Number of subjects planned to be randomised in sub-study on body composition:	174
Number of subjects planned to complete the trial on randomised trial product without rescue medication.	549

*For Mexico only: Approximately 7583 subjects are planned to be screened and 4550 subject are planned to be randomised in Mexico.*

## 2.5 Section 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.

*For Brazil Only: 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.*

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).

*For Brazil only: 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.*

*For EU countries only:*

*The following contraceptive measures are considered adequate:*

- *Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
- *Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)*
- *Bilateral tubal occlusion*
- *Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository). (Not applicable for Sweden and the UK).*

- *Vasectomised partner (where partner is sole partner of subject) and that the vasectomised partner has received medical assessment of the surgical success.*
  - *True sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days prior to the day of screening.
  5. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
  6. Subjects with ALT >2.5 x upper normal limit (UNL).
  7. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
  8. History or presence of pancreatitis (acute or chronic).
  9. History of diabetic ketoacidosis (DKA).
  10. Any of the following: myocardial infarction (MI), stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
  11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
  12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
  13. Renal impairment measured as eGFR <60 ml/min/1.73 m<sup>2</sup> as defined by Kidney Disease Improving global outcomes (KDIGO 2012) classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.
  14. 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 prior to the day of screening is allowed.
  15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.
  16. 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.
  17. *Medical history of diabetes-related lower limb amputations or signs of critical lower limb ischemia, (e.g. skin ulcer, osteomyelitis, or gangrene) within the last 26 weeks prior to screening.*

## 2.6 Section 6.6 Criteria for premature discontinuation of trial product

All efforts should be made to keep the subject on trial product. However, the subject might be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

If so, all efforts must be made to ensure the subjects attend and complete all scheduled visit procedures. Subjects 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 6.7).

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Safety concern related to trial product or unacceptable intolerability at the discretion of the investigator
3. Pregnancy\*
4. Intention of becoming pregnant\*
5. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
6. If the eGFR falls persistently  $<45$  mL/min/1.73m<sup>2</sup>, treatment with any trial product should be discontinued (see section 5.3)
7. Calcitonin  $\geq 100$  ng/L (see appendix A)
8. *Lower limb amputations or signs of critical lower limb ischemia, (e.g. skin ulcer, osteomyelitis, or gangrene)*

\*No DXA scans can be performed on these subjects.

See Section 8.1.8 for procedures to be performed for subjects discontinuing trial product prematurely.

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 subjects should continue with protocol-specified visit schedule.

## 2.7 Section 7 Milestones

Planned duration of recruitment period ~~24~~28 weeks.

Planned date for FPFV: 15-Mar-2017

Planned date for LPLV: ~~24-Oct-2018~~ 21-Nov-2018

End of trial (P11) is defined as LPLV.

## 2.8 Section 8.4.1 Physical examination

A physical examination must be performed at V1, V8 and V10/V10A (*or as specified below*) and include the following:

- General appearance
- Skin
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Central and peripheral nervous system
- Lymph node palpation
- *Legs and feet\**

*\*Physical examination of legs and feet must be performed at every site visit.*

## 2.9 Section 12.2 Reporting of adverse events (Novo Nordisk assessment of AE expectedness)

Novo Nordisk assessment of AE expectedness is performed according to the following reference documents:

- Semaglutide: NN9535 IB current version and any updates thereto
- Canagliflozin: Current version of the Invokana SmPC and any updates thereto. ~~EU PI and U.S. Food and Drug Administration (FDA) prescribing information and any updates thereto.~~

## 2.10 Section 18.1.2 Identified risks

The section below on Diabetic retinopathy complications has been moved from section 18.1.4 Other safety considerations to section 18.1.2 Identified risks

### **Diabetic retinopathy complications**

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment<sup>61-63</sup>. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression<sup>5, 64</sup> even in intensively treated patients who experienced early worsening<sup>62</sup>. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo. As a

precaution in this trial, all subjects are required to have a fundus photography or dilated funduscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial<sup>65</sup>.

### **Cholelithiasis**

*Events of gallstones (cholelithiasis) have been reported from clinical trials with semaglutide. These events may lead to hospitalisation and removal of the gallbladder. If cholelithiasis is suspected potential discontinuation of trial product and appropriate clinical follow-up should be considered at the investigator's discretion.*

### **2.11 Section 18.1.4 Other safety considerations**

The section below on Diabetic retinopathy complications has been moved from section 18.1.4 Other safety considerations to section 18.1.2 Identified risks

#### **Diabetic retinopathy**

~~A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment<sup>61-63</sup>. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression<sup>5,64</sup> even in intensively treated patients who experienced early worsening<sup>62</sup>. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo. As a precaution in this trial, all subjects are required to have a fundus photography or dilated funduscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial<sup>65</sup>.~~

#### **Canagliflozin**

Subjects should be considered suitable for treatment with canagliflozin and the use of canagliflozin should be in accordance with the current, approved label. It is important to monitor renal function and for signs and symptoms of volume depletion during therapy. Serum creatinine will be measured regularly for monitoring of renal function.

The most common adverse reactions reported with canagliflozin are female genital mycotic infections, urinary tract infections and increased urination. Other events include hypoglycaemia (with concomitant use of insulin or insulin secretagogues), hypotension, hyperkalemia, increased

LDL-C levels and bone fracture. Canagliflozin and other SGLT-2 inhibitors have also been associated with a risk of urinary tract infections and ketoacidosis. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, general malaise and shortness of breath. Ketoacidosis associated with the use of SGLT-2 inhibitors can occur even if blood sugar levels are only relatively elevated or non-elevated. If ketoacidosis is suspected, canagliflozin or canagliflozin placebo should be discontinued and appropriate treatment should be instituted promptly.

*A signal of increased risk of lower limb amputations has been associated with the use of canagliflozin and is currently under investigation by the EMA<sup>1</sup> and the FDA<sup>2</sup>. While the review of this risk by the Health Authorities is ongoing, subjects at risk are excluded from participation in this clinical trial and assessment of leg and foot is required at every site visit. The investigators should instruct the subjects enrolled about the importance of regular leg and foot care and to further notify the investigator in case they notice any new pain or tenderness, sores or ulcers, or infections in legs or feet.*

## **2.12 References**

1. Agency EMA. EMA reviews diabetes medicine canagliflozin Review follows data on toe amputations in ongoing study 2016 [cited 2016 15 Apr].
2. U.S. Food and Drug Administration. Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate 2016 [cited 2016 18 May].

Semaglutide s.c.  
Trial ID: NN9535-4270  
Clinical Trial Report  
Appendix 16.1.1

~~CONFIDENTIAL~~

Date:  
Version:  
Status:

03 June 2019  
1.0  
Final

**Novo Nordisk**

## **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