Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03191396
Sponsor trial ID:	NN9535-4339
Official title of study:	Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1–3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes. (SUSTAIN 10)
Document date:	27 May 2019

16.1.1 Protocol and protocol amendments

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Redacted protocol
includes redaction of personal identifiable information.

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Protocol

Trial ID: NN9535-4339

SUSTAIN 10
Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1-3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes

Trial phase: 3b

Protocol originator

[redacted]

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
BG	blood glucose
BMI	body mass index
CRF	case report form
CV	cardio-vascular
DPP-4	ubiquitous dipeptidyl peptidase
DTSQ	Diabetes Treatment Satisfaction Questionnaire, short form
DUN	dispensing unit number
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FSFV	first subject first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IWRS	interactive web response system
LDL	low-density lipoprotein

LLOQ	lower limit of qualification
LSFV	last subject first visit
LSLV	last subject last visit
MACE	major adverse cardiovascular events
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
PG	plasma glucose
PP	per protocol
PRO	patient reported outcome
SAE	serious adverse event
SAS	safety analysis set
s.c.	subcutaneous(ly)
SF-36v2™	Short Form health survey
SIF	safety information form
SGLT-2	sodium-glucose co-transporter-2
SMPG	self-measured plasma glucose
SU	Sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
T2D	Type 2 diabetes mellitus
UNL	upper normal level

1 Summary

Objective(s) and endpoint(s)

The primary objective
To compare the effect of semaglutide subcutaneous (s.c.) 1.0 mg once-weekly versus liraglutide s.c. 1.2 mg once-daily on glycaemic control after 30 weeks of treatment in subjects with type 2 diabetes.

The secondary objectives
To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus liraglutide s.c. 1.2 mg once-daily after 30 weeks of treatment on body weight, efficacy parameters, safety and tolerability in subjects with type 2 diabetes.

Primary endpoint
Change from baseline to week 30 in $HbA_{1c.}$

Key secondary endpoints
Change from baseline to week 30 in

- Body weight (kg)
- Fasting plasma glucose (FPG)
- Systolic and diastolic blood pressure

Trial design
This is a 30-week, confirmatory, randomised, multicentre, multinational, active-controlled, parallel groups, open label, 2-armed trial.

Subjects with type 2 diabetes inadequately controlled on 1-3 oral anti-diabetic drugs will be randomised in a 1:1 manner to receive either semaglutide s.c. 1.0 mg once-weekly or liraglutide s.c. 1.2 mg once-daily.

The trial includes a treatment period of 30 weeks and a follow-up period of 5 weeks. Total trial duration for the individual subjects will be approximately 37 weeks, including a 2-week screening period.

Trial population
A planned total number of 576 subjects will be randomised.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus.
- HbA_{1c} of 7.0-11.0 % (53 - 97 mmol/mol) (both inclusive).
- Stable daily dose(s) including any of the following anti-diabetic drug(s) or combination regimens 90 days prior to the day of screening:
  a) Biguanides (metformin ≥ 1500 mg or maximum tolerated dose documented in the subject's medical record).
  b) Sulphonylureas (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).
  c) SGLT-2 inhibitors (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).

Key exclusion criteria

- Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
- History or presence of pancreatitis (acute or chronic).
- History of diabetic ketoacidosis.
- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
- Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 30 ml/min/1.73 m^2 as defined by KDIGO 2012 classification[1].
- Impaired liver function, defined as ALT ≥ 2.5 times upper normal limit at screening.
- Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.

Key assessments

- Glucose metabolism (HbA_{1c}, FPG)
- Body weight
- Blood pressure and pulse rate

Trial product(s)

Investigational medicinal products:

- Test product: Semaglutide 1.34 mg/mL, 1.5 mL PDS290 pre-filled pen-injector) for s.c. injection.
- Reference therapy: Liraglutide 6 mg/mL, 3.0 mL pre-filled pen-injector approved as Victoza® for the EU market for s.c. injection.

2 Flow chart

Trial Periods	Protocol section	Screening	Randomisation	Treatment						End of treatment	Follow-up	End of treatment - Premature discontinuation	Follow-up - Premature discontinuation
Visit(V)/Phone contact(P)		V1	V2	P3	V4	V5	V6	V7	P8	V9	P10	V9A	P10A
Timing of visit (weeks)		-2	0	1	4	8	12	16	23	30	35		
Visit window (days)		±7		+7	±3	±3	±3	±3	±3	±7	+7		
SUBJECT RELATED INFO/ASSESMENTS													
Informed consent	18.3	X											
In/exclusion criteria	6.2, 6.3	X	X										
Randomisation			X										
Medical history	8.2.3	X											
Concomitant illness	8.2.3	X											
Concomitant medication	8.2.4	X	X	X	X	X	X	X	X	X	X	X	X
Demography	8.2.1	X											
Diabetes history/diabetes	8.2.2	X											
Rescue criteria	6.4					X	X	X	X	X		X	
Premature discontinuation criteria	6.5			X	X	X	X	X	X	X		X	
Tobacco use	8.2.6	X											
EFFICACY													
Height	8.3.1		X										
Body weight	8.3.1		X		X	X	X	X		X		X	
BMI	8.3.1		X		X	X	X	X		X		X	
Waist circumference	8.3.2		X					X		X		X	

Trial Periods	Protocol section	Screening	Randomisation	Treatment						End of treatment	Follow-up	End of treatment - Premature discontinuation	Follow-up - Premature discontinuation
Visit(V)/Phone contact(P)		V1	V2	P3	V4	V5	V6	V7	P8	V9	P10	V9A	P10A
Timing of visit (weeks)		-2	0	1	4	8	12	16	23	30	35		
Visit window (days)		±7		+7	±3	±3	±3	±3	±3	±7	+7		
Blood pressure and pulse rate	8.3.3		X		X	X	X	X		X		X	
Fasting plasma glucose	8.5.1		X		X	X	X	X		X		X	
HbA_{1c}	8.5.1	X	X		X	X	X	X		X		X	
Lipids	8.5.1		X					X		X		X	
7-point profile	8.3.5		X					X		X		X	
PRO questionnaires	8.6.2		X							X		X	
SAFETY													
Hypoglycaemic episodes	8.4.5		X	X	X	X	X	X	X	X	X	X	X
ECG	8.4.2		X							X		X	
Eye examination	8.4.3	X[a]								X[a]		X[a]	
Physical examination	8.4.1	X								X		X	
Haematology	8.5.2		X		X	X		X		X		X	
Calcitonin	8.5.2		X					X		X		X	
Pregnancy test[b]	8.5.2	X	X							X		X	

[a] Fundus photography/dilated fundoscopy performed within 90 days prior to randomisation is acceptable if results are available for evaluation at V2, unless worsening of visual function since last examination.
Fundus photography/dilated fundoscopy must be performed again:

- at V9 or 5 weeks prior to this. Results should be available at V9.
- at V9A or within 5 weeks thereafter, and again at or within 5 weeks prior to V9, for subjects who have prematurely discontinued trial product

Trial Periods	Protocol section	Screening	Randomisation	Treatment						End of treatment	Follow-up	End of treatment - Premature discontinuation	Follow-up - Premature discontinuation
Visit(V)/Phone contact(P)		V1	V2	P3	V4	V5	V6	V7	P8	V9	P10	V9A	P10A
Timing of visit (weeks)		-2	0	1	4	8	12	16	23	30	35		
Visit window (days)		±7		+7	±3	±3	±3	±3	±3	±7	+7		
Biochemistry	8.5.2	X	X		X	X		X		X		X	
Adverse events	12		X[c]	X	X	X	X	X	X	X	X	X	X
TRIAL MATERIAL													
Dispensing visit			X			X		X					
Drug accountability	9.4					X		X		X		X	
IWRS call	10	X	X			X		X		X		X	
REMINDERS													
End of treatment										X		X	
End of trial											X[d]		
Attend visit fasting	8.1.5		X		X	X	X	X		X		X	
Schedule of eye examination for next visit	8.4.3								X			X[e]	
Training in trial product and pen	8.6.3		X		X								

[b] Only applicable for women of childbearing potential. At V2, urine pregnancy test will be taken. At V1 and V9/V9A, serum pregnancy test will be taken.
[c] Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF
[d] If premature discontinuation, End of Treatment form must be filled-in when the discontinuation happens and End of Trial form at scheduled visit P10. If a subject completes both the treatment and the trial at scheduled time, the End of Treatment form must be filled at V9 and End of Trial form to be filled in at P10. 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
[e] Fundus photography/dilated fundoscopy must be performed again at V9A or within 5 weeks thereafter, and again at or within 5 weeks prior to V9, for subjects who have prematurely discontinued trial product

Trial Periods	Protocol section	Screening	Randomisation	Treatment						End of treatment	Follow-up	End of treatment - Premature discontinuation	Follow-up - Premature discontinuation
Visit(V)/Phone contact(P)		V1	V2	P3	V4	V5	V6	V7	P8	V9	P10	V9A	P10A
Timing of visit (weeks)		-2	0	1	4	8	12	16	23	30	35		
Visit window (days)		±7		+7	±3	±3	±3	±3	±3	±7	+7		
Handout direction for use	8.6.3		X										
Handout and instruct in diary	8.6.1	X	X		X	X	X	X		X		X	
Handout and instruct in BG meter use	8.6.4	X											
Handout ID card	8.1.2	X											

3 Background information and rationale for the trial

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

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

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 β-cell function and abnormal glucose metabolism in the liver[4].

Optimal glycaemic control is the treatment goal in subjects with T2D in order to prevent long-term complications associated with chronic hyperglycaemia[5-8]. While an increasing number of agents to treat diabetes exist, data collected from 2007−2010 demonstrate that close to 50% of all patients treated for their T2D do not achieve the recommended blood glucose target of an HbA_{1c} <7% and are thus at increased risk of T2D-related complications[9].

3.1.2 Glucagon-like peptide-1 (GLP-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[10, 11]. Subjects with T2D have a decreased incretin effect[12-14] , but can respond to the blood glucose lowering effect of GLP-1 when administered at supraphysiological levels [15]. In addition, supraphysiological levels of GLP-1 reduce body weight by lowering energy intake by inducing feelings of satiety and fullness and lowering feelings of hunger. GLP-1 is also a neuropeptide produced in the brain and GLP-1 receptors are present in several areas of the brain involved in appetite regulation[16-18]. These mechanisms of action make glucagon-like peptide-1 receptor agonists (GLP-1 RAs) an attractive pharmacological treatment for T2D[19-21].

3.1.3 Semaglutide

Semaglutide is a potent human GLP-1 RA with a pharmacokinetics profile suitable for once-weekly subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza®), an once-daily GLP-1 RA 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 increased albumin binding, 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[22]: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone to increase stability against dipeptidyl peptidase-4 (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 whereto the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group[22, 23]. The spacer and the fatty acid both contribute to increased albumin binding, which slows the degradation of semaglutide in plasma and results in decreased renal clearance prolonging the half-life of semaglutide to around 1 week, making it suitable for once-weekly s.c. administration.

3.1.4 Nonclinical data - semaglutide

The nonclinical programme for semaglutide was designed according to the ICH M3[24] 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 RA. The finding in rodents is caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. As the GLP-1 receptor is not expressed in the normal human thyroid the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low[25]. C-cell neoplasia corresponds to medullary thyroid carcinoma in humans, which has not been reported in the completed phase 3a clinical trials.

Embryo−foetal development toxicity

In rats, semaglutide adversely affected embryo-foetal development, causing foetal mortality, reduced growth, and skeletal and visceral malformations. More specifically, the embryo−foetal

development was affected 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. However, this mechanism is not likely to be of relevance to humans due to the fact that in primates, the yolk sac does not invert to fully enclose the embryo. So it does not come in direct contact with the uterine wall to form a placenta as it does in rodents. In rabbits and cynomolgus monkeys, pregnancy losses and foetal abnormalities were observed at exposures below (rabbit) or 3–5 fold above (monkey) the maximum recommended human dose. These observations might be either incidental or related to the reduced maternal body weight, but a direct effect of semaglutide for subcutaneous administration could not be excluded.

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide for subcutaneous administration (NN9535) investigator's brochure (IB)[26], or any updates hereof.

3.1.5 Clinical data – semaglutide

More than 4,500 subjects have been exposed to once-weekly s.c. semaglutide in the 16 clinical pharmacology trials, the phase 2 trial and the 8 phase 3a trials completed so far (please see the current edition of the IB for s.c. administration of semaglutide (NN9535), or any updates thereto for details[26]).

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 anti-diabetic 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 (CV) outcomes trial in a T2D population at high risk of CV events.

Pharmacokinetics

The results from the completed clinical pharmacology trials confirm that semaglutide has pharmacokinetic properties compatible with once-weekly administration, with a median time to maximum concentration (tmax) of 1−3 days post dosing and a t½ of around 1 week. Overall, the pharmacokinetics properties of semaglutide appear comparable between healthy subjects, subjects with T2D and subjects with renal failure.

Results from drug-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.

Efficacy

Based on results from the clinical pharmacology trials, semaglutide treatment reduced both fasting and postprandial glucose compared to placebo, by improving multiple aspects of β-cell function and by reducing both fasting and postprandial glucagon concentrations, all in a glucose-dependent manner. The 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 RA, semaglutide caused a minor delay of early postprandial gastric emptying.

Both as monotherapy and as combination therapy, semaglutide significantly reduced glycosylated haemoglobin (HbA_{1c}) and body weight in all phase 3a trials when compared with the trial-specific comparator, including the active comparators sitagliptin, exenatide ER and insulin glargine. In the 5 global phase 3a trials (3623, 3624, 3625, 3626 and 3627), reductions in HbA_{1c} 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 American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE)-defined treatment target of an HbA_{1c} <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 HbA_{1c} were substantiated by improvements in secondary glycaemia-related supportive endpoints[27-30].

Safety

Data from the 6 global phase 3a clinical trials (3623, 3624, 3625, 3626, 3627, 3744) 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-1 RAs. The most frequent AEs leading to premature treatment discontinuation were nausea, diarrhoea and vomiting. The escalation regimen utilized was associated with good tolerability and low numbers of discontinuation due to AEs. Hypoglycaemia occurred infrequently in subjects receiving semaglutide and the events were mainly non-severe. No episodes of severe hypoglycaemia were observed when semaglutide was used as monotherapy. Hypoglycaemic episodes have most frequently been observed when semaglutide is combined with sulphonylurea (SU) or insulin. In line with findings for other GLP-1 RAs, an increase in pulse 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; CV death, non-fatal myocardial infarction and non-fatal stroke) versus placebo was evaluated in a T2D population at high risk for CV events, in the CV outcomes trial, SUSTAIN 6 (NN9535-3744)[31]. The SUSTAIN 6

trial achieved its primary objective by showing non-inferiority of semaglutide versus placebo on CV outcomes by ruling out an 80% increased risk. Moreover, semaglutide significantly reduced the risk of MACEs by 26% vs placebo[32].

The overall safety profile of semaglutide in the SUSTAIN 6 trial was consistent with previous semaglutide clinical trials. However, in this trial, there was a higher frequency of confirmed events of diabetic retinopathy complications in semaglutide-treated subjects compared with placebo.

Further details will soon be available in the semaglutide s.c. (NN9535) IB edition 12.

3.1.6 Liraglutide

The selected active comparator in this trial is liraglutide, an injectable once-daily human GLP-1 RA developed by Novo Nordisk and approved for the treatment of T2D in the European Union, US and Japan under the brand name Victoza®. Victoza® was first approved for marketing in the EU on 30 Jun 2009. Up until 30 Jun 2016, Victoza® has been approved in 106 countries and launched in 81 countries worldwide, including the major countries/regions Australia, Brazil, Canada, China, EU, Japan, Mexico and the U.S. In the EU, Victoza® is indicated for the treatment of adults with T2D to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control. For further details, please see the current EU summary of product characteristics (SmPC) for Victoza®[33].

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

3.2 Rationale for the trial

The current available treatment modalities for T2D are still not satisfactory, as a large proportion of patients do not reach their HbA_{1c} treatment targets. Furthermore, there is a segment of patients, who either has difficulties adhering to once-daily treatments, or has a wish for more convenient treatment regimens such as once-weekly treatments.

Liraglutide and semaglutide are both human GLP-1 RAs with a prolonged half-life compared to native GLP-1, making them suitable for once-daily and once-weekly s.c. injections, respectively.

Based on the phase 3a results, semaglutide is expected to be marketed with two treatment doses (0.5 mg and 1.0 mg). Dose-dependent reductions in both HbA_{1c} and body weight were observed in these trials with significantly more patient reaching treatment targets of $HbA_{1c} < 7\%$ and $\leq 6.5\%$ with semaglutide 1.0 mg compared with semaglutide 0.5 mg. Hence, 1.0 mg is expected to be the most frequently used dose when semaglutide is marketed. For liraglutide (Victoza®)), 1.2 mg and 1.8 mg are approved treatment doses for treatment of type 2 diabetes. However, in most European countries

the 1.2 mg dose of Victoza® is the most commonly used dose[34, 35]. Therefore, the aim for the current trial is to demonstrate the efficacy and safety of once-weekly 1.0 mg semaglutide versus once-daily 1.2 mg liraglutide [36].

4 Objectives and endpoints

4.1 Objectives

The primary objective

To compare the effect of semaglutide s.c. 1.0 mg once-weekly versus liraglutide s.c. 1.2 mg once-daily on glycaemic control after 30 weeks of treatment in subjects with type 2 diabetes.

The secondary objectives

To compare the effect of semaglutide s.c. 1.0 mg once-weekly versus liraglutide s.c. 1.2 mg once-daily after 30 weeks of treatment on body weight, efficacy parameters, safety and tolerability in subjects with type 2 diabetes.

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline to week 30 in HbA_{1c}

4.2.2 Secondary endpoints

Confirmatory secondary endpoints

Change from baseline to week 30 in body weight (kg)

Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline to week 30 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 (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides)
- Body Mass Index (BMI)
- Waist circumference
- Systolic and diastolic blood pressure
- Body weight (%)

Subjects who after 30 weeks of treatment achieve:

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

Supportive secondary endpoints for selected patient-reported outcomes (PRO)

Change from baseline to week 30 in:

- SF-36v2™ Short Form health survey. Total summary scores (physical component and mental component) and scores from the 8 domains
- Diabetes Treatment Satisfaction Questionnaire (DTSQ). Treatment satisfaction summary score (sum of 6 of 8 items) and the 8 items separately upportive secondary safety endpoints

Supportive secondary safety endpoints

- Number of treatment-emergent adverse events
- 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 30 in:

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

5 Trial design

5.1 Type of trial

This is a 30-week, confirmatory, randomised, multicentre, multinational, active-controlled, parallel groups, open label, 2-armed trial.

Subjects with T2D inadequately controlled on 1-3 oral anti-diabetic drug(s) (OAD) will be randomised in a 1:1 manner to receive either semaglutide s.c. 1.0 mg once-weekly or liraglutide s.c. 1.2 mg once-daily. The randomisation will be stratified based on subjects background medication of SU and sodium-glucose cotransporter-2 (SGLT-2) inhibitors:

- SU (+/- metformin)
- SGLT-2 inhibitors (+/- metformin)
- SU + SGLT-2 inhibitors (+/- metformin)
- No SU and no SGLT-2 inhibitors (metformin monotherapy)

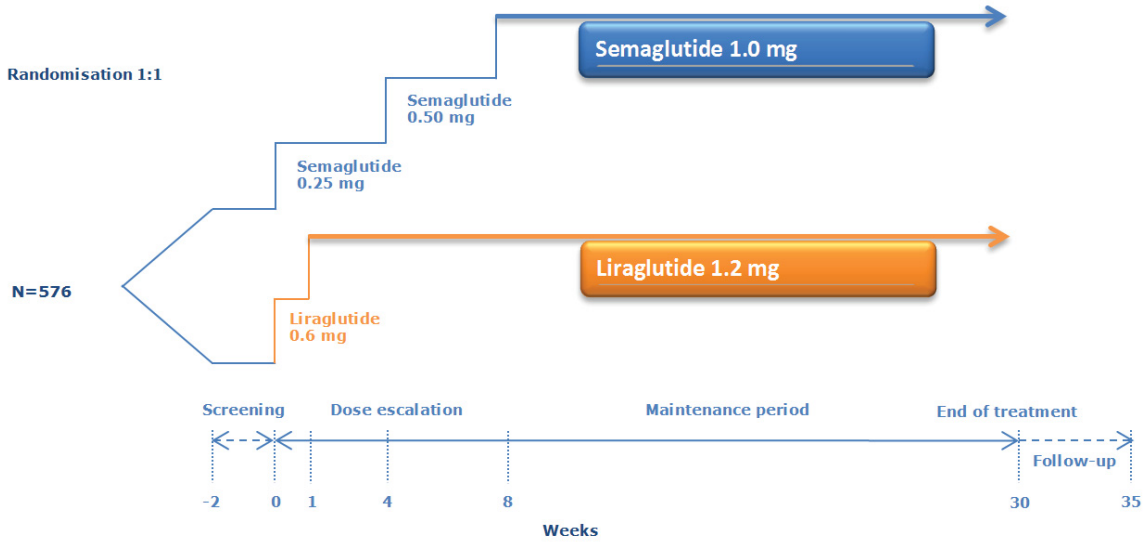

Figure 5–1 Trial design

5.2 Rationale for trial design

This trial has been designed as an open-label, two-arm, parallel-group, randomised trial to secure a direct comparison between s.c. semaglutide once-weekly and s.c. liraglutide once-daily. The treatment period will be 30 weeks to ensure adequate time to compare the full effect of both treatments on glycaemic control and body weight. The reason for designing the trial as an open-label trial is to enable comparison of patient satisfaction with once-weekly versus once-daily administration and to limit the number of injections in participating subjects.

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

5.3 Treatment of subjects

Treatment of subjects is summarised schematically in Table 5–1.

Semaglutide will be administered once-weekly and liraglutide once-daily, both as s.c. injections. After randomisation, all subjects will follow a fixed dose escalation for semaglutide and liraglutide. The maintenance dose of 1.0 mg for semaglutide will be reached after an 8-week escalation period. This period will consist of 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg, while the period of maintenance will be 22 weeks. Thus, a total treatment duration of 30 weeks.

The maintenance daily dose of 1.2 mg for liraglutide will be reached after 1 week of 0.6 mg daily dosing. In case of unacceptable gastrointestinal AEs, escalation from 0.6 mg to 1.2 mg of liraglutide can be extended over 2 weeks at the discretion of the investigator.

Once the maintenance dose of semaglutide (1.0 mg) and liraglutide (1.2 mg) has been reached, doses must not be changed during the trial. After the end of the treatment period, there will be a 5-week follow-up period for safety data collection.

Table 5–1 Treatment of subjects

Trial periods		**Screening**	**Treatment period 1**	**Treatment period 2**	**Treatment period 3**	**Treatment period 4**	**Follow-up**
Alias for trial period		Screening	Dose escalation	Dose escalation/ Maintenance	Dose escalation/ Maintenance	Maintenance	Follow-up
Visits in each period		V1	V2	P3	V4	V5-V9	P10
Duration of each period		2 weeks	1 week	3 weeks	4 weeks	22 weeks	5 weeks
Treatment arm	**N**						
Semaglutide s.c. 1.0 mg	288	Screening	Semaglutide 0.25 mg	Semaglutide 0.25 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Follow-up
Liraglutide s.c. 1.2 mg	288	Screening	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.2 mg	Liraglutide 1.2 mg	Follow-up
All subjects on background medication of 1−3 OADs							

5.3.1 Trial Products/Investigational medicinal Products supplied by Novo Nordisk

- Semaglutide 1.34 mg/mL, 1.5 mL PDS290 pre-filled pen-injector for s.c. injection.
- Liraglutide 6 mg/mL, 3.0 mL pre-filled pen-injector approved as Victoza® for the EU market for s.c. injection.

5.3.2 Background medication

After screening (V1), subjects must continue their anti-diabetic pre-trial background medication throughout the entire trial. The background medication must be maintained at the stable, pre-trial dose during the entire treatment period unless rescue criteria are met (see Section 6.4) or a safety concern related to the background medication arises e.g. acute renal impairment on a background of metformin or SGLT-2 inhibitors and unacceptable hypoglycaemia on a background of SUs.

All locally available metformin, SGLT-2 inhibitors and SUs are allowed for background medication.

In addition, the background medication:

1. Is considered to be a non-investigational medicinal product (NIMP)
2. Will not be supplied by Novo Nordisk A/S. However, the background medication will be reimbursed if allowed by the countries regulatory authority or independent ethics committee (IEC)
3. Should be used in accordance with standard of care or local label in the individual country

4. Should not exceed the maximum approved dose in the individual country

5.4 Injection site

Semaglutide and liraglutide are administered s.c. by injections in the thigh, abdomen or upper arm, any time of the day and irrespective of meals. Injections should not be administered intravenously or intramuscularly. For semaglutide, injections should be administered once weekly on the same weekday. For liraglutide, injections should be administered daily and the time of injection is recommended to be consistent from one day to another.

5.5 Missed dose

Semaglutide

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). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer the missed dose but rather wait for the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.

Liraglutide

If a liraglutide dose is missed, it should be taken as soon as noticed; however, if it is more than 12 hours since subject should have taken liraglutide, the missed dose should be skipped, and next dose should be taken as usual the following day.

5.6 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of treatment visit (V9) or if trial product is discontinued prematurely, the subject should be switched to a suitable marketed product at the discretion of the investigator. The long half-life of semaglutide must be taken into consideration when selecting anti-diabetic treatment after discontinuation of trial product.

5.7 Rationale for treatment

Semaglutide has been developed for s.c. administration. A three dose level escalation of semaglutide (0.25, 0.5 and 1.0 mg), has been chosen based on data from the phase 2 dose-finding trial (NN9535-1821)[22]. This regimen has shown a good benefit-risk profile across the phase 3a programme[26].

Liraglutide is approved for the treatment of T2D in doses of 1.2 mg and 1.8 mg. As the 1.2 mg daily dose is currently used as part of standard-of-care in most European countries, a two dose level escalation from 0.6 mg to 1.2 mg daily is needed[34] [35].

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

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised: **576**

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age ≥18 years at the time of signing informed consent.
3. Diagnosed with T2D .
4. HbA_{1c} of 7.0-11.0% (53−97 mmol/mol) (both inclusive).
5. Stable daily dose(s) including any of the following anti-diabetic drug(s) or combination regimens 90 days prior to the day of screening:
   a) Biguanides (metformin ≥1500 mg or maximum tolerated dose documented in the subject's medical record).
   b) SU (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).
   c) SGLT-2 inhibitors (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

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 or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository). (Not applicable for Sweden).
  Vasectomised partner (where partner is sole partner of subject) and where vasectomy has been confirmed by medical assessment
  True sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.

  For Germany only: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner.

4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
5. Any condition, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
7. History or presence of pancreatitis (acute or chronic).
8. History of diabetic ketoacidosis.
9. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
10. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
11. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
12. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of <30 ml/min/1.73 m^2 as defined by KDIGO 2012 classification[1].
13. Impaired liver function, defined as alanine aminotransferase (ALT) ≥2.5 times upper normal limit 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 and previous insulin treatment for gestational diabetes 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 is allowed.

6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. If any of the FPG values (including protocol scheduled fasting SMPG) exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, the subject must be called in for a confirmatory FPG (at central laboratory):

- FPG $\geq$ 13.3 mmol/L (240 mg/dl) from week 8 (V5) to end of week 15 (up until V7)
- FPG $\geq$ 11.1 mmol/L (200 mg/dl) from week 16 (V7) 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. These subjects should continue to follow the protocol-specified visit schedule. Rescue medication should be prescribed at the investigator's discretion as add-on to the randomised treatment and according to ADA/European Association for the Study of Diabetes guidelines[37, 38] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Please note, that for subjects randomised to liraglutide, the dose of 1.2 mg must not be exceeded and if rescue medication is needed in these subjects, another anti-diabetic agent must be added or the dose of existing background therapy increased, at the investigator's discretion. The long half-life of semaglutide must be taken into consideration when prescribing rescue medication.

Considerations regarding rescue medication should be documented in the medical records and rescue medication and any changes hereto should be captured on the concomitant medication form in the electronic case report form (eCRF) (see Section 8.2.4). Rescue medication is considered to be NIMP and will not be provided by Novo Nordisk.

6.5 Criteria for premature discontinuation of trial product

All efforts should be made to keep the subject on trial product.

However, the subject may 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 6.6).

The subject must be prematurely discontinued from trial product, if one of 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. Calcitonin ≥100 ng/L (see Appendix A).

The primary reason for premature 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 the protocol-specified visit schedule.

See Section 8.1.4 for procedures to be performed for subjects discontinuing trial product prematurely.

6.6 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. Only subjects who withdraw consent should be considered as withdrawn from trial.

See Section 8.1.5 for procedures to be performed for subjects withdrawing consent.

6.7 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

6.8 Rationale for trial population

The trial population will include subjects treated with stable doses of 1−3 OAD(s) (see Section 5.3.2) for at least 90 days prior to screening.

The HbA_{1c} limits 7.0– 11.0% (53–97 mmol/mol) have been chosen to include subjects needing intensification of their anti-diabetic medication. FPG and HbA_{1c} will be monitored throughout the trial and rescue medication should be initiated in subjects with persistent, unacceptable hyperglycaemia according to the investigator.

Subjects with liver test abnormalities (ALT ≥2.5 × upper normal level) will be excluded to avoid potential confounding of liver safety assessments. As SGLT-2 inhibitors have been associated with euglycaemic diabetic ketoacidosis, subjects with a history of diabetic ketoacidosis will also be excluded from this trial.

Overall, the eligibility criteria allow for enrolment of a broad trial population resembling the target population in common practice.

7 Milestones

Planned duration of recruitment period (first subject first visit (FSFV) – last subject first visit (LSFV): 20 weeks

Planned date for FSFV: 27-June-2017

Planned date for last subject last visit (LSLV): 14-Aug-2018

End of trial is defined as LSLV (trial completion date).

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 and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[39], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[40], the Food and Drug Administration Amendment Act (FDAAA)[41], European Commission Requirements[42, 43] 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.

Primary Completion Date is the last assessment of the primary endpoint, and is for this protocol LSFV + 32 weeks corresponding to V9. If the last subject is withdrawn/dropout early the Primary Completion Date is the date when the last subject would have completed V9. The Primary Completion Date determines the deadline for results disclosure at Clinicaltrials.gov according to FDAAA.

8 Methods and assessments

8.1 Visit procedures

Timing of assessments and procedures are specified in the flow chart (see Section 2). This section includes a description of these assessments and procedures.

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

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.

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

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

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

8.1.3 Fasting visits

The subjects should attend site visits in a fasting state (see Section 2). 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.

8.1.4 Premature discontinuation of trial product

If a subject prematurely discontinues trial product, the investigator must undertake procedures described for V9A as soon as possible (preferably the same day), which are similar to those at V9. Phone contact 10A 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 V9A and trial procedures must be performed accordingly.

Subjects should continue with the originally scheduled site contacts after P10A and up to and including P10. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after P10A. However, all attempts should be made to ensure that V9 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 premature 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 8.1.5).

The primary reason for premature discontinuation of trial product must be specified in the end-of-treatment form in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS at V9A (see Section 10).

8.1.5 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake the procedures for V9A as soon as possible. If a subject has already prematurely discontinued from trial product and previously attended V9A and P10A, 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 premature treatment discontinuation session must be made in the IWRS, if not already done due to prior discontinuation from trial product. 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.

8.1.6 Investigator assessment

Review of diaries, patient reported outcomes questionnaire (PROs), laboratory reports, ECGs, eye and physical examinations must be documented with the dated signature of the investigator or delegated trial staff, either on the front page of the documents and/or in subject's medical record. The signed documents must be retained at the trial site as source documentation.

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

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

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 or delegate 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 and the PROs to ensure that AEs, including overall change in health and concomitant medication, are reported.

If clarification of entries or discrepancies in the diary or the PROs 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.

Laboratory report values:

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 or delegate on the day of evaluation. The signed laboratory report is retained at the trial site as source documentation.

8.2 Subject related information/assessments

8.2.1 Demography

Demography 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 consist of:

- Date of diagnosis of T2D
- Information regarding diabetes complications including date of onset
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease)

8.2.3 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial as described in Section 8.1.6. Procedures and assessments performed at visit 1 and/or visit 2 (prior to randomisation) are considered as screening procedures.

Medical history is a medical event that the subject has experienced in the past. Only relevant concomitant illness and medical history as judged by the investigator should be reported. Diabetes history and related complications should be reported separately in the diabetes history/complication form.

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 investigators own practice; the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.4 Concomitant medication

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

Changes in concomitant medication, including anti-diabetic treatment, must be recorded at each visit as they occur. The eCRF should be updated accordingly. GLP-1 RAs, DPP-4 inhibitors and amylin analogues must not be pre-prescribed as add-on to the randomised treatment.

The information collected for each concomitant medication includes:

- Trade name or generic name
- Primary 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.

8.2.5 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 (see Section 8.5.2). Female subjects of childbearing potential must be instructed to use adequate contraceptive methods (see Section 6.3) 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

8.2.6 Tobacco use

Details of tobacco use must be recorded at V1. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

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

8.3 Efficacy assessments

8.3.1 Height, body weight and body mass index

Height is measured without shoes in cm and recorded to nearest ½ cm.

Body weight should be measured in kilogram (kg), with one decimal, without shoes and only wearing light clothing.

BMI = body weight (kg)/(height (m) x height (m)) [kg/m^2 = lb/in^2 x 703] and will be calculated in the eCRF every time the weight is measured.

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 and will be measured using a non-stretchable measuring tape. The measurement of waist circumference should be performed and recorded in the eCRF to the nearest ½ cm 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 Blood pressure and pulse rate

Systolic and diastolic blood pressure and pulse rate (beats per minute) 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 (BG) meter including auxiliaries and instructions for use. The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display. Only the BG meter provided by Novo Nordisk must be used for the measurements required.

Subjects should be instructed in how to record the results of the SMPGs in the diaries. The record of each SMPG should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact.

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

8.3.5 7-point self-measured plasma glucose 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 minutes after start of lunch, before dinner, 90 min after start of dinner and at bedtime. For details on how to record SMPG, see Section 8.3.4.

8.4 Safety assessments

8.4.1 Physical examination

A physical examination includes 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 Electrocardiogram – 12 lead

A 12-lead ECG must be performed and interpreted locally by the investigator or delegate as described in Section 8.1.6.

It is allowed to perform the baseline ECG between the screening visit and the randomisation visit. The results must 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 a part of 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.

8.4.3 Eye examination

Fundus photography or dilated fundoscopy will be performed as per flow chart (see Section 2) by the investigator or according to local practise. Fundoscopy requires pharmacological dilation of both pupils. Results of the fundus photography or dilated fundoscopy will be interpreted by the investigator (see Section 8.1.6). Relevant findings as a result of the screening procedure must be recorded as concomitant illness/medical history or as diabetes history/diabetes complication in accordance with Section 8.2.3.

If the fundus photography or dilated fundoscopy has been performed within 90 days prior to randomisation, the procedure does not need to be repeated, unless worsening of visual function since the last examination. If the subject did not have 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 according to local practice. The results must be available 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, fundus photography/dilated fundoscopy must be performed at V9 or 5 weeks prior to this. Results should be available at V9. In the case of premature discontinuation, fundus photography/dilated fundoscopy must be performed both at V9A and at V9. At V9A the assessments can be performed in the period between V9A and P10A , but the results should be available and reviewed no later than at P10A.

8.4.4 Adverse events

AEs must be reported in accordance with the procedures outlined in Section 12.

8.4.4.1 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 AE(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.4.2 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:

- Hypersensitivity reaction
- Pancreatitis
- Renal event
- Hepatic event
- Diabetic retinopathy
- Acute gallstone disease

See Appendix B for details about the additional information to report.

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

8.4.5 Hypoglycaemic episodes

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

All PG values:

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

should be reported in the diary throughout the trial from visit V2 to P10 according to the instructions (see Section 8.6.1). All information must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial. For Novo Nordisk classification of hypoglycaemia, see Section 17.5.2.2.Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[44].

A SMPG value ≤3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms should 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 plasma glucose (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[44].

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 anti-diabetic 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)?[44]
  - 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[45, 46].

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. The central laboratory may utilise sub-contractors. 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.

Subjects will be asked to attend the site visits fasting for samples, except for screening samples (see Sections 2 and 8.1.3). 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.

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 according to Section 8.2.3 and 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 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.

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis.

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

8.5.1 Laboratory assessments for efficacy

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

- Glucose metabolism:
  - HbA_{1c}
  - 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 and subject must attend these visits fasting (see Section 8.1.3).

A central FPG result obtained at the central laboratory of ≤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 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:

- ALT
- Aspartate aminotransferase (AST)
- Albumin, bilirubin (total)
- Alkaline phosphatase
- Potassium
- Sodium
- Calcium (total)
- Amylase
- Lipase
- Calcitonin[a]
- Creatinine, including eGFR (per CKD-EPI)[a]

[a] In case any calcitonin value at any time of the trial is ≥10 ng/L, the algorithm in Appendix A should be followed

Haematology:

- Haemoglobin
- Haematocrit
- Erythrocytes
- Thrombocytes
- Leucocytes

Pregnancy test (females of childbearing potential):

- Serum beta-human chorionic gonadotropin (V1, V9/V9A)
- Urine dip stick (V2)

Pregnancy testing

Females of childbearing potential will have a serum pregnancy test performed at selected visits (see Section 2). 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 8.2.5).

8.6 Other assessments

8.6.1 Subject diary

At each site visit, the subject will be provided with a new paper diary. Entries in the diaries are only to be made by the subject, unless otherwise specified. The diary should be collected at the next site visit and retained at the site as source data in accordance with Section 14. However, the last diary collecting data from after V9 (End Treatment) will not be returned to the site by the subject, since the follow-up visit is a phone contact.

The diary recordings must be reviewed as described in Section 8.1.6 and transcribed to the eCRF.

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[a] Creatinine will be measured using a method traceable to isotope dilution mass spectrometry (IDMS) and eGFR calculated using the equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) as defined in KDIGO{National Kidney Foundation, 2012, KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update}

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

If hypoglycaemic events are reported at P10 or P10A, related information should be documented in the subject's medical record and will be considered source data. The information must be entered into the eCRF.

If a subject prematurely discontinues trial product, diaries should not be dispensed and completed by the subject after the follow-up-premature discontinuation visit (P10A).

8.6.2 Patient reported outcome questionnaires

The following PRO questionnaire will be used in the trial:

- SF-36v2™
- DTSQs

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. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The completed questionnaires must be reviewed for potential adverse events and missing data as described in Section 8.1.6, while the subject is still at the site. All results from the PROs must be transferred into the eCRF. Please refer to Appendix C for details on the PRO questions.

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 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).

8.6.3 Training in the pen-injector

An injection pen is used for s.c. administration of semaglutide/liraglutide. The subjects must be trained in how to handle the injection pen when handed out the first time. Training must be repeated at V4 and during the trial at regular intervals according to needs, in order to ensure correct use of the injection pen. 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 and instructed in how to use and handle the BG meter, in accordance with the flow chart (see Section 2). The instruction will be repeated 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 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.

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

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Semaglutide	1.34 mg/mL	solution for injection	s.c	1.5 mL pre-filled pen-injector[a]
Liraglutide , approved as Victoza®	6 mg/mL	solution for injection	s.c	3 mL pre-filled pen-injector[b]

SGLT-2 inhibitors, metformin and SUs are considered background medication (NIMPs) and will not be provided by Novo Nordisk.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[47], local regulations and trial requirements. Each box will be labelled with a unique dispensing unit number (DUN). Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial products will be distributed to the trial sites according to enrolment and randomisation.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time[c]
Semaglutide 1.34 mg/mL	Store in a refrigerator (2°C to 8°C) Protect from light Do not freeze	Store below 30°C Protect from light Do not freeze	Use within 8 weeks
Liraglutide 6 mg/mL	Store in a refrigerator (2°C to 8°C) Protect from light Do not freeze	Store below 30°C or in a refrigerator (2°C to8°C) Protect from light Do not freeze	Use within 1 month

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

[a] Semaglutide 1.34 mg/mL, 1.5 mL pre-filled pen-injector (0.25mg/0.5mg/1.0mg)
[b] Liraglutide 6 mg/mL, 3.0 mL pre-filled pen-injector (0.6mg/1.2mg/1.8mg)
[c] In-use time starts when first dose is taken

product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual.

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 according to Section 2 (drug accountability). 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 of investigational medicinal products should be performed at pen level.

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 Trial Materials Manual:

- Direction for use for each trial product
- Needles for pre-filled pen-injectors for trial products
- BG-meter and related auxiliaries

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

10 Interactive web response system

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Stratification (please see Section 5.1)
- Medication arrival
- Dispensing
- Dispensing Verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

A completion session must be performed in IWRS after completion of V9 (and for subjects attending V9A).

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

This is an open label, two-arm 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 treatments groups in a 1:1 manner:

- Semaglutide 1.0 mg once-weekly
- Liraglutide 1.2 mg once-daily

Randomisation will be stratified based on anti-diabetic background medication at screening (see Section 5.1) to ensure a 1:1 distribution of the two treatment arms within each stratum.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An 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: 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 8.4.5).

The following three definitions are used when assessing an AE:

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

- **Causality**

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

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

- **Final outcome**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.

- **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets 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 SAE is an experience that at any dose results in any of the following:

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

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

b. The term "hospitalisation" is used when a subject:

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

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

c. A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change,

impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

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

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

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug. Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- 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 8.4.4.1).

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

- Hypersensitivity reaction
- Pancreatitis
- Renal event

- Hepatic event
- Diabetic retinopathy
- Acute gallstone disease

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 until the end of the follow-up period (P10). 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 safety information form (SIF) must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

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

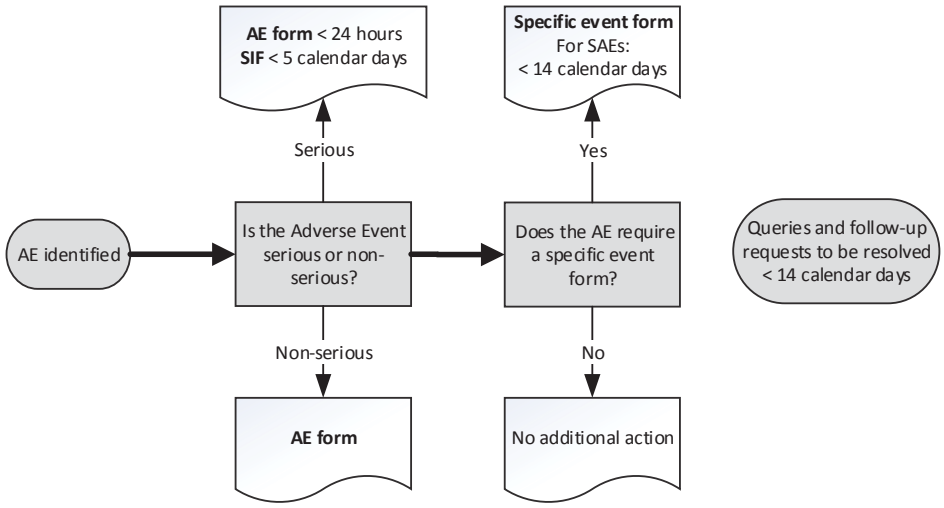
Timelines for initial reporting of AEs:

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

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

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

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



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

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

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

- Semaglutide: NN9535 IB, current version[26] and any updates thereto
- Company Core Data Sheet for Victoza® 6 mg/ml ; current versions and any updates thereto

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[2]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including European Medicines Agency (EMA), of trial product-related SUSARs. In addition, Novo Nordisk will inform the IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[2], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

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

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all

queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Semaglutide 1.34 mg/mL 1.5 mL prefilled PDS290 pen-injector
- Liraglutide 6 mg/mL 3.0 mL pre-filled pen-injector
- Novo Nordisk needles

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

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

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

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

The investigator must ensure that the technical complaint sample contains the batch, 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

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:

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.

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

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- 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.

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.

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

12.6 Precautions and/or overdose

Overdoses of up to 4 mg of semaglutide in a single dose/in one week have been reported in clinical trials. The most commonly reported adverse reaction was nausea, vomiting and headache.

For liraglutide, overdoses have been reported up to 40 times the recommended maintenance dose (72 mg). One case of a 10-fold overdose (18 mg daily) given for 7 months has been reported. Generally, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. For more information, please refer to the SmPC for Victoza® 6 mg/ml.

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

Novo Nordisk will constitute an internal semaglutide s.c. safety committee and perform ongoing safety surveillance on all reported safety data in the trial.

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

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

indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

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

13.1 Corrections to case report forms

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

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

Corrections to the data in the paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorized staff.

If corrections are made by the investigator's delegated staff after the date of the investigator's signature on the affirmation statement, the affirmation statement 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 investigator must ensure that data is recorded as soon as possible after the visit and the phone contact. At the end of the trial the investigator must ensure that all remaining data have been entered into then eCRF no later than 3 days after 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.

14 Monitoring procedures

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

The monitor must be given direct access to all source documents (original documents, data and records). 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/or PROs must not be removed from the trial site, unless they form part of the CRF/eCRF and a copy is kept at the site.

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

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

- Date for obtaining informed consent
- Reason for screening failure

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

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

15 Data management

Data management is the responsibility of Novo Nordisk.

Appropriate measures, including encryption of data files containing 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 data will be performed before the database is locked.

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

Results from a statistical analysis will be presented by the estimated treatment contrasts at week 30 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 liraglutide 1.2 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.

17.1.1 Primary estimand

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

- The treatment difference between semaglutide and liraglutide at week 30 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 liraglutide. 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.

17.1.2 Missing data considerations at week 30

The overall rate of missing data at week 30 is expected to be not more than 10% based on the rate of subjects with measurements of the primary and the confirmatory secondary endpoints in the s.c. semaglutide phase 3a clinical development programme. The frequency and reasons of missing data is expected to be similar in the semaglutide and the liraglutide groups.

When estimating the primary estimand, the combined rate of missing data and, subjects discontinuing treatment prematurely or initiating rescue medication on top of trial product, is expected to be maximum 20%. This is based on the results from the s.c. semaglutide phase 3a clinical development programme. Based on these data, premature treatment discontinuation due to gastrointestinal adverse events is expected to be low. Other possible reasons for premature discontinuing treatment are assumed to be unrelated to treatment and to therefore occur at similar rates between the two treatment groups. Thus, overall, the frequency of missing data or data not used at week 30 in the primary analysis is expected to be similar between the treatment groups.

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 for the primary and secondary endpoints will be presented by treatment group.

17.1.3 Confirmatory hypotheses

The mean treatment difference is defined as μ = (semaglutide minus liraglutide). Three confirmatory hypotheses are to be tested:

1. HbA_{1c} non-inferiority of semaglutide 1.0 mg vs. liraglutide 1.2 mg with a non-inferiority margin of 0.3

- H_0: $\mu \geq 0.3$%-point against Ha: $\mu < 0.3$%-point

2. Body weight superiority of semaglutide 1.0 mg vs. liraglutide 1.2 mg
    - H_0: $\mu \geq 0.0$ kg against Ha: $\mu < 0.0$ kg

3. HbA_{1c} superiority of semaglutide 1.0 mg vs.liraglutide 1.2 mg
    - H_0: $\mu \geq 0.0$%-point against Ha: $\mu < 0.0$%-point

The non-inferiority margin of 0.3 is chosen based on the diabetes guideline[48, 49]. The effect of liraglutide was investigated in various trials including the LEAD programme that included a series of six randomised controlled phase 3 trials. In these trials, a substantial and sustained reduction in HbA1c was obtained with liraglutide treatment across the continuum of care in patients with type 2 diabetes[50]. Based on the Lead 1 & Lead 4 studies, Liraglutide 1.2 mg showed HbA1c treatment difference to placebo of -1.3%[51] and -0.9% [52] respectively. Hence, based on these trials, and considering the LEAD programme results collectively that assures the effect of liraglutide, the chosen non-inferiority margin of 0.3 provides assurance that semaglutide has an effect greater than 0 with a clinically relevant size.With regards to the constancy assumption, controlled clinical trials have consistently established that liraglutide is an effective anti-diabetic drug. Therefore, lack of trial sensitivity with liraglutide as comparator is not anticipated to be an issue in this trial.

17.1.4 Multiplicity and criteria for confirming hypotheses

The Type-I error rate for testing the three confirmatory hypotheses related to the HbA1c and body weight endpoints will be preserved in the strong sense at an overall alpha (α) level of 2.5% using the closed testing procedure described in Bretz et al. The overall α-level of 2.5% is initially allocated to the HbA1c non-inferiority test. For this hypothesis, and in general, if a hypothesis is confirmed the local α-level (α-local) 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.

Each of the following hypotheses will be tested at their local α level. This process will be repeated until no further hypotheses can be confirmed.

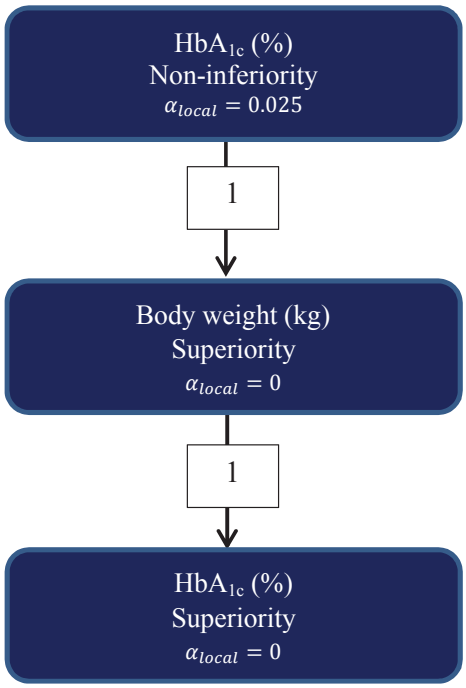


Figure 17–1 Graphical illustration of the closed testing procedure

17.2 Sample size calculation

The sample size calculation will assume a power of 90% for confirming all three confirmatory hypotheses (see Section 17.1.3) across efficacy and in-trial assumptions. Please see Table 17–2 for calculated powers for efficacy as estimated by the primary analysis for the primary estimand (see Section 17.4.1) and for the in-trial effect as estimated by the treatment policy sensitivity analysis (see Section 17.4.4)

The sample size assumptions for efficacy based on 'on-treatment without rescue medication' data and a treatment effect based on in-trial data (see Section 17.3.1.2) together with the standard are given in Table 17–1.These are based on the efficacy results and an observed reduction of up to 15% in the treatment effect based on in-trial data compared to efficacy based on 'on-treatment without rescue medication' data in the s.c. semaglutide phase 3a clinical development programme. A similar reduction in the in-trial treatment effect compared to efficacy is assumed with liraglutide as comparator.

Table 17–1 Assumptions used in the sample size calculation

Semaglutide vs. liraglutide	HbA_{1c}	Body weight
Efficacy (treatment difference)	-0.35%	-3.3 kg
In-trial treatment effect (treatment difference)	-0.30 %	-2.38 kg
Standard deviation	1.1%	4.0 kg

Tests statistics for treatment differences are assumed to follow normal distributions. The sample size is calculated using the calcPower function in the R package, gMCP[54], using 10,000 simulations. All of the three 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.
With the above assumptions, allocating 288 subjects to each of the semaglutide and liraglutide groups (576 subjects in total) provides at least 90% power to reject all three confirmatory hypotheses and thus confirm HbA_{1c} superiority and body weight superiority of semaglutide vs. liraglutide across efficacy and in-trial assumptions. Please see Table 17–2.

Table 17–2 Calculated powers for meeting individual hypotheses

Statistical test	HbA_{1c} non-inferiority	HbA_{1c} superiority	Body weight superiority	All
Efficacy power (%)	>99%	97%	>99%	97%
In-trial effect power (%)	>99%	90%	>99%	90%

17.3 Data definitions

17.3.1 Data selection

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

17.3.1.1 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".

17.3.1.2 Definition of observation periods

Definition of the observation periods:

In-trial: This observation period represents the time period after randomisation where subjects are considered to be in the trial, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in 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 (phone 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 exposed to 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 AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- The follow-up visit (P10)
- The premature discontinuation follow-up visit (P10A)
- 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 s.c. 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 AEs including hypoglycaemic episodes, 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 with a visit window of + 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 rescue medication. Specifically, the period starts at the date of first dose of trial product and ends at the first date of any of the following:

- The last dose of trial product with a visit window of +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. 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.

17.3.2 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 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).

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

17.3.3 Definition of baseline

For each assessment, the baseline assessment is defined as the latest available measurement at or prior to the randomisation visit (V2). 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.

17.3.4 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 (P10). Subjects completing the follow-up visit (P10) will be considered trial completers.

17.3.5 Treatment completion

Treatment period completion is defined as when the subject has received the required treatment, and attended the 'End of Treatment' (V9).

17.4 Primary endpoint

The primary endpoint is change from baseline to week 30 in HbA_{1c}.

17.4.1 Primary analysis

The primary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 30 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/liraglutide). 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 500 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 30. 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 the SU and SGLT-2 inhibitors anti-diabetic background medication stratification

factor (SU +/- metformin, SGLT-2 inhibitors +/- metformin, SU + SGLT-2 inhibitors +/- metformin, no SU and no SGLT-2 inhibitors (metformin monotherapy)) as categorical effects and the baseline and post-baseline HbA_{1c} values observed prior to the visit in question as covariates.

- An analysis of covariance (ANCOVA) with treatment and the SU and SGLT-2 inhibitors anti-diabetic background medication stratification factor (SU +/- metformin, SGLT-2 inhibitors +/- metformin, SU + SGLT-2 inhibitors +/- metformin, no SU and no SGLT-2 inhibitors (metformin monotherapy)) as categorical effects and baseline HbA_{1c} as a covariate will be used to analyse HbA_{1c} values at week 30 for each of the 500 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 liraglutide at week 30 will be presented together with the associated two-sided 95% confidence interval and unadjusted two sided p-values.

The one-sided non-inferiority and superiority hypotheses will be confirmed using the overall significance level of 2.5% in line with the closed testing procedure in Figure 17–1. Operationally, 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 (non-inferiority H0: $u=0.3$ vs. Ha: $u\neq0.3$, superiority H0: $u=0$ vs Ha: $u\neq0$ respectively), from the primary analysis of the primary estimand, is strictly below two times its local significance level resulting from the closed testing procedure.

17.4.2 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_{1c} hypotheses.

17.4.3 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 less beneficial 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 liraglutide 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 30 to imputed observations in the semaglutide group before applying ANCOVA on the 500 complete data sets.

17.4.4 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 30 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/ liraglutide) but also by the status of treatment completion (still on randomised treatment at week 30 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 30 are similar in terms of randomised treatment and treatment completion status. In addition in the imputation step stratification factor is not included in the model in order to avoid potential issues with sparse data. This analysis could be considered addressing an effectiveness estimand.
- Per protocol (PP) analysis based on the PP data set using the 'on-treatment without rescue medication' 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

The confirmatory secondary endpoint is change from baseline to week 30 in body weight (kg).

The primary estimand will be estimated for body weight using the same approach as described in Section 17.4.1. Body weight will be tested for superiority. Baseline and post-baseline body weight will be used as covariates instead of HbA1c.

The one-side hypothesis of superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the analysis of body weight is strictly below two times its local two-sided significance level resulting from the closed testing procedure inFigure 17–1.

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 30 in:

- FPG
- 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)
- BMI
- Waist circumference
- Systolic and diastolic blood pressure
- Body weight (%)

The above continuous endpoints will be analysed separately using a similar model approach as for the primary endpoint with the associated baseline value as covariates instead of HbA_{1c} 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, and divided by the measurement time.

Binary endpoints

The binary endpoints are subjects who after 30 weeks treatment achieve (yes/no):

- $HbA_{1c} < 7.0\%$ (53 mmol/mol), ADA target
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol), AACE target
- Weight loss $\geq 3\%$
- Weight loss $\geq 5\%$
- Weight loss $\geq 10\%$

- HbA_{1c} <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} reduction ≥ 1%
- HbA_{1c} reduction ≥ 1% and weight loss ≥ 3%
- HbA_{1c} reduction ≥ 1% and weight loss ≥ 5%
- HbA_{1c} 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 treatmentand the SU and SGLT-2 inhibitors anti-diabetic background medication stratification factor (SU +/- metformin, SGLT-2 inhibitors +/- metformin, SU + SGLT-2 inhibitors +/- metformin, no SU and no SGLT-2 inhibitors (metformin monotherapy)) as categorical effects and associated baseline and post-baseline response(s) (i.e. HbA_{1c} responses for HbA_{1c} endpoints, body weight responses for weight endpoints and both HbA_{1c} 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 (500) 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 500 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[55].

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 AEs is used to support the safety objective;

- Number of treatment emergent adverse events

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 AEs 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' AEs (i.e., AEs with onset date [or increase in severity] during the 'in-trial' observation period). AEs 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 AEs will be defined as preferred terms 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 observation period (see Section 17.3.1.2)

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

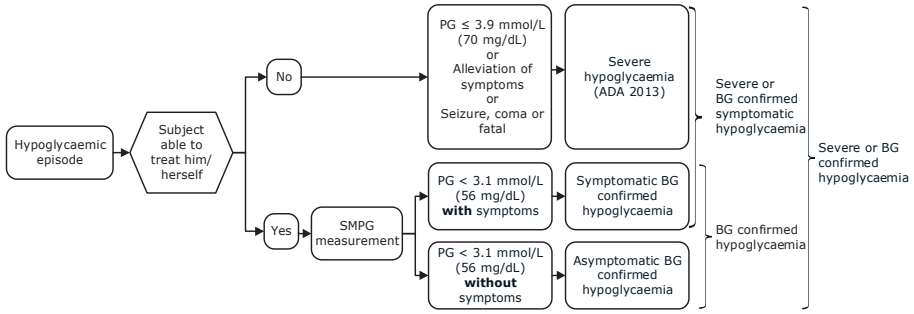
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–2) and the ADA classification of hypoglycaemia (see Figure 17–3).

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) [56]. 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[57] 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

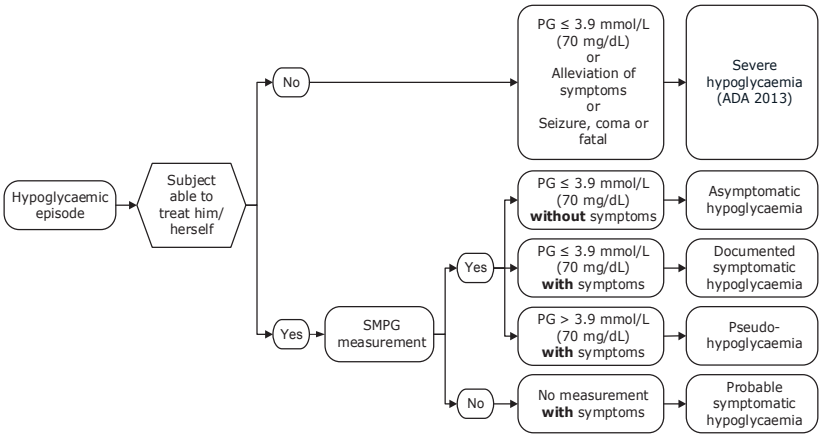
BG: blood glucose PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 Novo Nordisk classification of hypoglycaemia

ADA classification[57] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.

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



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–3 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 35 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 the SU and SGLT-2 inhibitors anti-diabetic background medication stratification factor (SU +/- metformin, SGLT-2 inhibitors +/- metformin, SU + SGLT-2 inhibitors +/- metformin, no SU and no SGLT-2 inhibitors (metformin monotherapy)) as categorical factors and baseline HbA_{1c} 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 the SU and SGLT-2 inhibitors anti-diabetic background medication stratification factor (SU +/- metformin, SGLT-2 inhibitors +/- metformin, SU + SGLT-2 inhibitors +/- metformin, no SU and no SGLT-2 inhibitors (metformin monotherapy))as categorical factors and baseline HbA_{1c} 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 30 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 value as covariates instead of HbA_{1c}. Lipase and amylase values will be log-transformed prior to the analysis.

Pulse rate

Change from baseline to week 30 in pulse rate will be analysed separately with the same model approach as for amylase and lipase but with the pulse rate value at baseline value as covariates instead of HbA_{1c}.

Categorical safety assessments

The categorical assessments supporting the safety objective are change from baseline to week 30 in:

- ECG category
- Physical examination category
- Eye examination category

The above assessments will be summarised descriptively

17.6 Health economics and/or PROs

Change from baseline to week 30 in:

- Scores for selected patient reported outcomes:
  - SF-36v2™ : Total summary scores (physical component and mental component) and scores from the 8 domains
  - DTSQs: Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately

The PRO questionnaires, SF-36v2™, DTSQs 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 using a similar model approach as for the primary endpoint with the associated baseline value as covariates.

17.7 Interim analysis

No interim analyses will be performed before the database is locked

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

Gastrointestinal adverse events
Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical trials with semaglutide and liraglutide have been gastrointestinal disorders (nausea, diarrhoea, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastro oesophageal reflux disease, eructation and flatulence). 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 steps have been implemented in the trial.

Gallstones
Events of gallstones (cholelithiasis) have been reported from clinical trials both with semaglutide and with liraglitide. These events may lead to hospitalisation and removal of the gallbladder. If cholelithiasis is suspected appropriate clinical follow-up should be initiated at the investigator's discretion.

Hypoglycaemia
Patients treated with semaglutide or liraglutide in combination with a SU or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of SU or insulin when initiating treatment with semaglutide/liraglutide.

Allergic reactions and injection site reaction
As in the case with all protein-based pharmaceuticals, treatment with semaglutide or liraglutide may evoke allergic reactions. These may include localized injection site reactions or generalized reactions, including urticaria, rash, and 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.

Acute renal impairment
In subjects treated with GLP-1 RAs, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary renal impairment and acute renal failure. 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, a background medication in this trial, 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-1 RAs 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.

Medullary thyroid cancer
The human relevance of the proliferative C-cell changes found in rodents treated with GLP-1 RAs is unknown, but data suggest that rodents are more sensitive to the mode of action of GLP-1 RAs for induction of C-cell tumours. However, as a precaution, subjects with a family or personal history of multiple endocrine neoplasticity 2 or Medullary thyroid cancer will not be enrolled in the trial. During the trial, calcitonin will be measured on V2, V7 and V9, and the guidance for investigators on further evaluation and action on elevated calcitonin concentrations is included in Appendix A.

Diabetic retinopathy
A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment[58]. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large

improvements in BG may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression[59] [60] even in intensively treated patients who experienced early worsening[61]. In a 2-year cardiovascular outcomes trial with semaglutide, results showed an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo, albeit the proportion of subjects with an EAC-confirmed event of diabetic retinopathy complications was low (semaglutide: 3%; placebo: 1.8%). As a precaution in this trial, all subjects are required to have a fundus photography or dilated fundoscopy 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[62].

Acute pancreatitis
Acute pancreatitis has been reported in subjects treated with GLP-1 RAs, including semaglutide and liraglutide. 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
While 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 classified as a potential class risk of GLP-1 RAs by EMA.

Other risks
Patients treated with semaglutide or liraglutide may also experience increased heart rate, increase lipase and amylase, fatigue, decreased appetite, headache, upper respiratory tract infections , malaise and cholecystitis.

18.1.2 Other safety considerations

Teratogenicity (embryo-foetal development toxicity)
Please see Section 3.1.4 for information on embryo−foetal development toxicity. 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 according to flowchart in Section 2 and at any time during the trial if a menstrual period is missed, or as required by local law.

General precautions

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

There are also strict glycaemic rescue criteria in place to ensure acceptable glycaemic control during the trial (see Section 6.4). If rescue medication is required, it should be in accordance with ADA/European Association for the Study of Diabetes[37, 38](excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues).

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2017 Standards of Medical Care in Diabetes[62].

Further details with regards to safety of trial product are described in the current edition of the IB for semaglutide (NN9535)[26] or any updates thereto.

Safety information on liraglutide can be found in the current SmPC for Victoza®[33]

18.1.3 Benefits

In this trial, subjects will be randomised in a 1:1 manner to either semaglutide s.c 1.0 mg once-weekly or liraglutide s.c 1.2 mg once-daily as add-on to their current background medication with 1−3 OADs (metformin, SU, SGLT-2 inhibitors). Subjects will therefore be treated with a regimen anticipated to be better than the treatment they receive at the time of entry into the trial. Based on the results of the phase 3a trials, semaglutide is expected to provide clinically relevant improvements in glycaemic control and body weight in subjects with T2D. Similarly, treatment with liraglutide is expected to provide significant improvements in glycaemic control.

In addition, it is expected that all subjects will benefit from participation through close contact with the study 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.

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

18.1.4 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. The phase 3a results indicate that semaglutide will provide clinically relevant improvements in glycaemic control and body weight.

Liraglutide is already a marketed drug approved for the use in subjects with T2D.

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

18.2 Informed consent

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

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

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 prematurely discontinue treatment with trial product.

18.3 Data handling

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

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

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

18.4 Information to subjects during trial

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

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the 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 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 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. 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 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 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 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 IB and 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)

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

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

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

22 Responsibilities

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

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

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

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

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[63]

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[39].

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 [63] (sometimes referred to as the Vancouver Criteria).

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

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

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation

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

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

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

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

The files from the trial site/institution must be retained for 15 years after end of trial 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 Independent Ethics Committees and regulatory authorities

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the 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 IEC.

The investigator must ensure submission of the clinical trial report synopsis to the 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 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 France only: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research.

For Germany only: German Drug Law dated 24 August 1976 in the version published on 12 Dec 2005 (BGBI. I S. 3394), last amended by Article 3 of the Law of 04 Apr 2016 (BGBI. I S. 569).

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Appendix A

Monitoring of calcitonin

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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_2-blockers and glucocorticoids)

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

2 Calcitonin monitoring

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

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

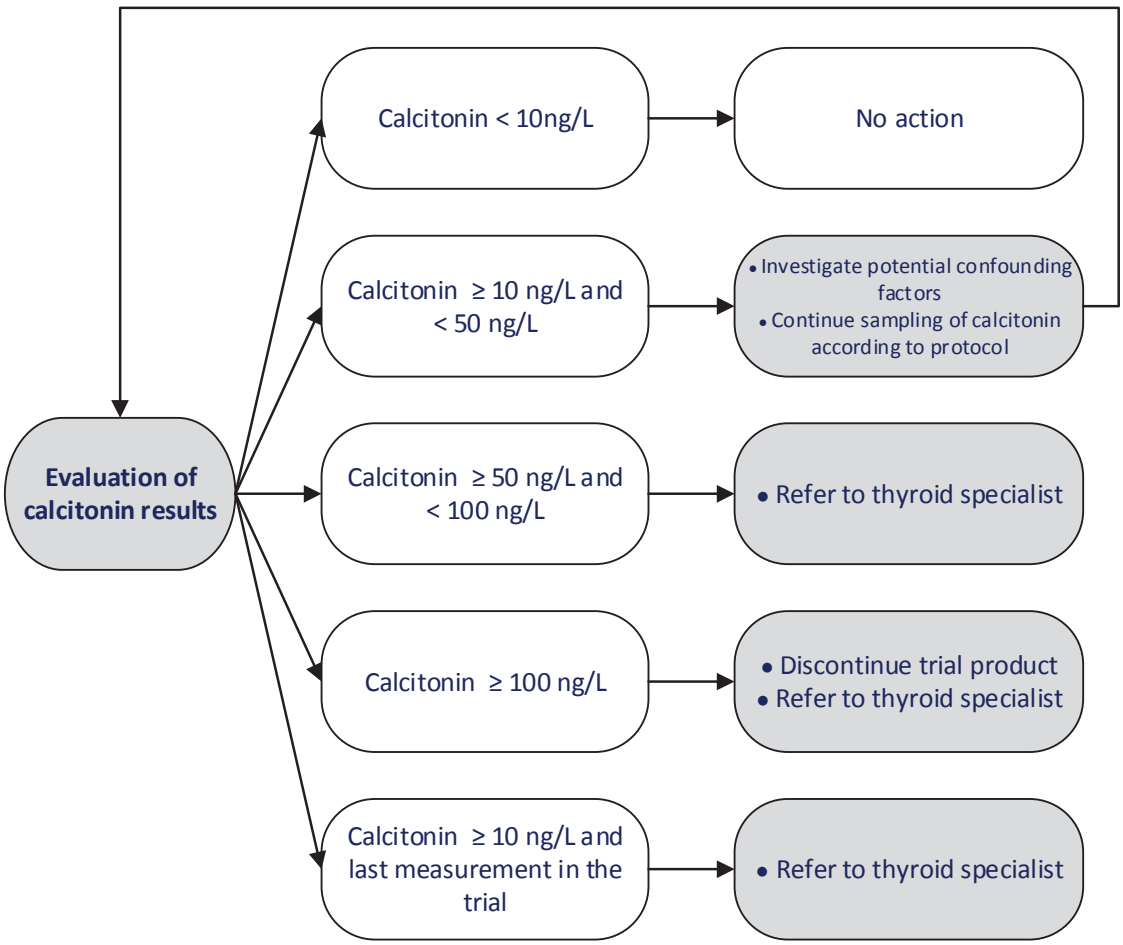

Figure 1 Flow of calcitonin monitoring

2.1 Calcitonin ≥100 ng/L

Action: The subject must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued . 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 [1]. All of these patients were diagnosed with medullary thyroid carcinoma (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 multiple endocrine neoplasia type 2 and perform a genetic test for RET proto-oncogene mutation.

2.2 Calcitonin ≥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 [1]. Two of these subjects were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available, and 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 ≥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 [1]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values between 10-20 ng/L Costante et al. [1] 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 [2, 3].

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Appendix B

Adverse events requiring additional data collection

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Table of Contents

1 Adverse events requiring additional data collection

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

- Hypersensitivity reaction
- Pancreatitis
- Renal event
- Hepatic event
- Diabetic retinopathy
- Acute gallstone disease

Additional information on a specific form is also required for hypoglycaemic episode and medication errors, which is described in the protocol.

1.1 Hypersensitivity reactions

All events of hypersensitivity reactions must be reported and the following additional information should 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[1] to the trial product, the subject must be discontinued from trial product but should remain in the trial. 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. Tryptase concentrations, if available, should be included in the specific event form when reporting the AE.

In case of suspicion of immune complex disease[1], the subject must be discontinued from trial product but should remain in the trial. 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.

1.2 Pancreatitis

For all confirmed events of pancreatitis the following additional information should 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[2]. 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[2]. 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 should be performed, including measurement of amylase and lipase.

The diagnosis of acute pancreatitis requires two of the following three features[3]:

- 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.

1.3 Renal event

If a renal event is observed during the trial, the following additional information should 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

1.4 Hepatic event

- ALT or AST > 5 × UNL and total bilirubin ≤ 2 × UNL
- ALT or AST > 3 × UNL and total bilirubin > 2 × UNL*
- Hepatic event leading to trial product discontinuation

If one of the above events is observed during the trial, the following additional information should 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 × UNL and total bilirubin > 2 × UNL, where no alternative aetiology exits (Hy's law), should also be reported as a SAE.

1.5 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 associated with the event
- Results of the eye examination
- Treatment for and complications of the event
- Contributing conditions

1.6 Acute gallstone disease

If an event of gallstone is observed during the trial the following additional information should be reported if available:

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

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Appendix C

SF-36v2™ and DTSQ

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Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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(SF-36v2® Health Survey Standard, United States (English))

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

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DTSQs © Prof Clare Bradley 9/93 Standard UK English (rev. 7/94)
Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

There are no more questions.

Thank you for carefully answering all the questions.

Please check that you have answered all the questions and once you are done, hand the questionnaire to the study coordinator.

Thank you very much for your help.

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1-Fr
to Protocol, final version 2.0
dated 03 february 2017

Trial ID:NN9535-4339

SUSTAIN 10
Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1-3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes

Trial phase: 3b

Applicable to France

Amendment originator:

[redacted]
[redacted]

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Table of Tables

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1 Introduction including rationale for the protocol amendment

Following the submission of the NN9535-4339 on the 22 March 2017, the French Health Authority requested the changes below to be included in the protocol:

- The IMPD to be modified in order to comply with the European guidance CPMP/QWP/159/96 corr for the in-use shelf life limited to 4 weeks at a temperature below 30 °C consequently the protocol is updated with an in-use period for semaglutide drug product of 28 days

- The protocol to be modified in order to specify that the trial will include patients with type 2 diabetes in whom treatment with diet and physical exercise alone should have been attempted and deemed not sufficient to achieve glycaemic control and who subsequently are treated with stable doses of 1-3 OAD(s).

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

2 Changes

2.1 Page 30, Section 6.8 Rationale for trial population

The trial population will include subjects *in whom treatment with diet and physical exercise alone should have been attempted and deemed not sufficient to achieve glycaemic control, and who subsequently are* treated with stable doses of 1−3 OAD(s) (see Section 5.3.2) for at least 90 days prior to screening.

2.2 Page 48, Section 9.3 Storage

Table 9–2 Storage conditions

Trial product	**Storage conditions (not-in-use)**	**In-use conditions**	**In-use time[1]**
Semaglutide 1.34 mg/mL	Store in a refrigerator (2°C to 8°C)	Store below 30°C Protect from light	Use within ~~8 weeks~~ *28 days*
Liraglutide 6 mg/mL	Store in a refrigerator (2°C to 8°C)	Store below 30°C or in a refrigerator (2°C to8°C)	Use within 1 month

Protocol Amendment

No. 2-IT
to Protocol, final version 2.0
dated 03 february 2017

Trial ID:NN9535-4339

SUSTAIN 10
Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1-3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes

Trial phase: 3b

Applicable to Italy

Amendment originator:

[redacted]

[redacted]

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1 Introduction including rationale for the protocol amendment

Following the submission of the NN9535-4339 trial on the 10 Mar 2017, the Italian Health Authority (AIFA) requested further clarifications regarding information about diet and the level of physical activity based on the SmPC for liraglutide. In the Smpc, it is stated that liraglutide can be used in combination with other oral anti-diabetic drugs (OADs) and /or basal insulin if these drugs, associated to diet and physical activity, are not sufficient to guarantee an adequate glycaemic control.

Subjects in this trial are required to be treated with stable doses of pre-defined anti-diabetic medications and should therefore have exhausted the option of diet and physical exercise only. However, to ensure that diet and exercise has been attempted before pharmacological therapy is initiated and that lifestyle modification is recommended as adjunct therapy to all subjects with type 2 diabetes, the following will be added to Sections 6.8 and 18.1.2 of the trial protocol.

In this protocol amendment:

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

2 Changes

2.1 Page 30, Section 6.8 Rationale for trial population

The trial population will include subjects *in whom treatment with diet and physical exercise alone should have been attempted and deemed not sufficient to achieve glycaemic control, and who subsequently are* treated with stable doses of 1−3 OAD(s) (see Section 5.3.2) for at least 90 days prior to screening.

2.2 Page 81, Section 18.1.2 Other safety considerations

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2017 Standards of Medical Care in Diabetes[62]. *This includes guidance on lifestyle modification as adjunct to therapy as per current local practice.*

62. Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. J Diabetes. 2017.

Protocol Amendment

No. 3-PL
to Protocol, final version 2.0
dated 03 february 2017

Trial ID:NN9535-4339

SUSTAIN 10
Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1-3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes

Trial phase: 3b

Applicable to Poland

Amendment originator:

[redacted]

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1 Introduction including rationale for the protocol amendment

Based on local regulations, below indemnity statement is added to section 26.

In this protocol amendment:

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

2 Changes

2.1 Section 26 Indemnity statement

Novo Nordisk accepts liability in accordance with:

For Poland only:

Novo Nordisk carries liability for the Trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigator are covered by the Insurance Policy issued according to applicable Polish law.

Local Substantial Amendment

no 1.0_BG

Trial ID: 9535-4339

SUSTAIN 10

Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1-3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes

Trial phase: 3b

Applicable to Bulgaria

Amendment originator:

Name: [redacted]

Department: [redacted]

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1 Changes

This is an amendment to patients' material "Overview of visit activities in the SUSTAIN 10 study". A mistake has been identified in the master of the document "Overview of visit activities in the SUSTAIN 10 study", version 2.0, dated 08-Feb-2017 - a physical exam icon was present at visit 2, however according to the protocol there is no physical exam at visit 2. The master document was updated to version 3.0, dated 03-July-2017. The local translation of this document was changed in accordance with the master document and version updated.

Local Substantial Amendment

no 2.0_BG

Trial ID: 9535-4339

SUSTAIN 10

Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1-3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes

Trial phase: 3b

Applicable to Bulgaria

Amendment originator:

Name: [redacted]

Department: [redacted]

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1 Changes

IB for Semaglutide (subcutaneous administration) updated to new edition 13, version 1.0, dated 08 March 2018 and this update is considered as Substantial amendment due to change in Reference Safety Information (RSI).

Local Substantial Amendment

no 3.0_BG

Trial ID: 9535-4339

SUSTAIN 10

Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1-3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes

Trial phase: 3b

Applicable to Bulgaria

Amendment originator:

Name: [redacted]

Department: [redacted]

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1 Changes

The RSI section in IB Liraglutide (Victoza®), edition 20, dated 05 April 2018 has been changed to reflect the requirements set forth by the new Clinical Trial Facilitation Group (CTFG) guidance on the Reference safety information (RSI).

Going forward, the RSI contained in the IB section RSI will be used for assessment of expectedness of serious adverse reactions instead of the CCDS as included now in the protocol for NN9535-4339 section 12.